Download Signaling Networks And Cell Cycle Control The Molecular Basis Of Cancer And Other Diseases Cancer Drug Discovery And Development

Right here, we have countless book **signaling networks and cell cycle control the molecular basis of cancer and other diseases cancer drug discovery and development** and collections to check out. We additionally meet the expense of variant types and in addition to type of the books to browse. The within acceptable limits book, fiction, history, novel, scientific research, as well as various other sorts of books are readily straightforward here.

As this signaling networks and cell cycle control the molecular basis of cancer and other diseases cancer drug discovery and development, it ends up living thing one of the favored book signaling networks and cell cycle control the molecular basis of cancer and other diseases cancer drug discovery and development collections that we have. This is why you remain in the best website to look the incredible books to have.

Signaling Networks and Cell Cycle Control - J. Silvio Gutkind - 2000-04-14
Leading scientists summarize the latest findings on signal transduction and cell cycle regulation and describe the effort to design and synthesize inhibiting molecules, as well as to evaluate their biochemical and biological activities. They review the relevant cell surface receptors, their ligands, and their downstream pathways. Also examined are the latest findings on the components of novel signaling networks controlling the activity of nuclear transcription factors and cell cycle regulatory molecules. Cutting-edge and highly suggestive, Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases presents a wealth of information on the emerging principles of the field, as well as an invaluable guide for all experimental and clinical investigators of cell regulation and its rapidly emerging pharmacological opportunities today.

Signaling Networks and Cell Cycle Control - J. Silvio Gutkind - 2000-04-14
Leading scientists summarize the latest findings on signal transduction and cell cycle regulation and describe the effort to design and synthesize inhibiting molecules, as well as to evaluate their biochemical and biological activities. They review the relevant cell surface receptors, their ligands, and their downstream pathways. Also examined are the latest findings on the components of novel signaling networks controlling the activity of nuclear transcription factors and cell cycle regulatory molecules. Cutting-edge and highly suggestive, Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases presents a wealth of information on the emerging principles of the field, as well as an invaluable guide for all experimental and clinical investigators of cell regulation and its rapidly emerging pharmacological opportunities today.

Signaling Networks and Cell Cycle Control - J. Silvio Gutkind - 2000-04-14
Leading scientists summarize the latest findings on signal transduction and cell cycle regulation and describe the effort to design and synthesize inhibiting molecules, as well as to evaluate their biochemical and biological activities. They review the relevant cell surface receptors, their ligands, and their downstream pathways. Also examined are the latest findings on the components of novel signaling networks controlling the activity of nuclear

transcription factors and cell cycle regulatory molecules. Cutting-edge and highly suggestive, Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases presents a wealth of information on the emerging principles of the field, as well as an invaluable guide for all experimental and clinical investigators of cell regulation and its rapidly emerging pharmacological opportunities today.

Signaling Networks and Cell Cycle Control - J. Silvio Gutkind - 2000-04-14
Leading scientists summarize the latest findings on signal transduction and cell cycle regulation and describe the effort to design and synthesize inhibiting molecules, as well as to evaluate their biochemical and biological activities. They review the relevant cell surface receptors, their ligands, and their downstream pathways. Also examined are the latest findings on the components of novel signaling networks controlling the activity of nuclear transcription factors and cell cycle regulatory molecules. Cutting-edge and highly suggestive, Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases presents a wealth of information on the emerging principles of the field, as well as an invaluable guide for all experimental and clinical investigators of cell regulation and its rapidly emerging pharmacological opportunities today.

Mathematical Modelling of the Cell Cycle Stress Response - Elahe Radmaneshfar - 2013-10-08
The cell cycle is a sequence of biochemical events that are controlled by complex but robust molecular machinery. This enables cells to achieve accurate self-reproduction under a broad range of conditions. Environmental changes are transmitted by molecular signaling networks, which coordinate their actions with the cell cycle. This work presents the first description of two complementary computational models describing the influence of osmotic stress on the entire cell cycle of S. cerevisiae. Our models condense a vast amount of experimental evidence on the interaction of the cell cycle network components with the osmotic stress pathway. Importantly, it is only by considering the entire cell cycle that we are able to make a series of novel predictions which emerge from the coupling between the molecular components of different cell cycle phases. The model-based predictions are supported by experiments in S. cerevisiae and, moreover, have recently been observed in other eukaryotes. Furthermore our models reveal the mechanisms that emerge as a result of the interaction between the cell cycle and stress response networks.

Mathematical Modelling of the Cell Cycle Stress Response - Elahe Radmaneshfar - 2013-10-08
The cell cycle is a sequence of biochemical events that are controlled by complex but robust molecular machinery. This enables cells to achieve accurate self-reproduction under a broad range of conditions. Environmental changes are transmitted by molecular signaling networks, which coordinate their actions with the cell cycle. This work presents the first description of two complementary computational models describing the influence of osmotic stress on the entire cell cycle of S. cerevisiae. Our models condense a vast amount of experimental evidence on the interaction of the cell cycle network components with the osmotic stress pathway. Importantly, it is only by considering the entire cell cycle that we are able to make a series of novel predictions which emerge from the coupling between the molecular components of different cell cycle phases. The model-based predictions are supported by experiments in S. cerevisiae and, moreover, have recently been observed in other eukaryotes. Furthermore our models reveal the mechanisms that emerge as a result of the interaction between the cell cycle and stress response networks.

Signaling Networks, Cell Cycle Control, and Human Cancer - James Turkson - 2008-07-01
The past few decades have witnessed scientists gaining a considerable understanding of the molecular pathogenesis of human diseases, especially of cancer. Studies of the molecular basis of carcinogenesis have led to the realization that cancer is fundamentally a disease of genetic alterations. The multiple genetic changes in cancer are predominantly the result of accumulating mutations that have occurred in the genome over time. These genetic changes lead to the production of gene products with upreguated, repressed, or loss of function, which in turn produce aberrant signal transduction pathways and dysregulated cellular functions. The bulk of evidence demonstrates that dysregulated signal transduction pathways promote malignant transformation and support the formation, maintenance and progression of tumors.

Signaling Networks, Cell Cycle Control, and Human Cancer - James

Turkson - 2008-07-01
The past few decades have witnessed scientists gaining a considerable understanding of the molecular pathogenesis of human diseases, especially of cancer. Studies of the molecular basis of carcinogenesis have led to the realization that cancer is fundamentally a disease of genetic alterations. The multiple genetic changes in cancer are predominantly the result of accumulating mutations that have occurred in the genome over time. These genetic changes lead to the production of gene products with upreguated, repressed, or loss of function, which in turn produce aberrant signal transduction pathways and dysregulated cellular functions. The bulk of evidence demonstrates that dysregulated signal transduction pathways promote malignant transformation and support the formation, maintenance and progression of tumors.

Interrogation of Kinase-mediated Signaling Pathways to Decode Human Cell Division - Amber Lynn Lasek - 2016
Protein interactions within a living cell are complex and are necessary for transmitting signals quickly and accurately. Kinases provide an important source of regulation and communication and play important roles for triggering and maintaining signaling cascades. These processes are themselves restrained so that they occur at the correct time and place. Due to the complexity of these processes and the need for improved methods, there remain many unresolved questions regarding the interconnectedness of signaling pathways and the extent that posttranslational modifications on kinases play for regulating kinase activity and function. Many kinases are known to be activated by phosphorylation within its catalytic loop; however, these proteins have multiple sites of modification including additional sites of phosphorylation and ubiquitination. Whether and how much these sites influence the activity and function of the kinase is unresolved. Using analog-specific kinases, I have discovered that Plk1 is not only regulated by the activating phosphorylation within the catalytic loop, T210, but also requires a neighboring site, T214. Additionally, other phosphorylation sites within the catalytic domain, but not in the C-terminal localization domain, redundantly control mitotic functions of Plk1 and cell cycle progression. These results demonstrate the intricacy of signaling to control and regulate Plk1. Further analysis of the complexity of signaling within a cell is demonstrated by comparing the pathways of two proteins. For a cellular process, involved proteins can act in parallel or overlapping pathways. If they overlap, can moderately perturbing a pathway from multiple directions simultaneously cause a greater response than each individual assault? This idea was used to design a screen between differing therapeutic agents. Many of the drugs include those that directly target proteins key to signaling pathways, kinases, while others were agents that would activate signaling pathways through error induction, such as mitotic checkpoint signaling activation with nocodazole treatment. Aurora A inhibition was found to potentiate the effect of a Plk1 inhibitor, a pan-Cdk inhibitor, and DNA damage response inducer, IUdR. Overall, this work expands the knowledge of and provides insight into the way that signaling networks function within the cell.

Interrogation of Kinase-mediated Signaling Pathways to Decode Human Cell Division - Amber Lynn Lasek - 2016
Protein interactions within a living cell are complex and are necessary for transmitting signals quickly and accurately. Kinases provide an important source of regulation and communication and play important roles for triggering and maintaining signaling cascades. These processes are themselves restrained so that they occur at the correct time and place. Due to the complexity of these processes and the need for improved methods, there remain many unresolved questions regarding the interconnectedness of signaling pathways and the extent that posttranslational modifications on kinases play for regulating kinase activity and function. Many kinases are known to be activated by phosphorylation within its catalytic loop; however, these proteins have multiple sites of modification including additional sites of phosphorylation and ubiquitination. Whether and how much these sites influence the activity and function of the kinase is unresolved. Using analog-specific kinases, I have discovered that Plk1 is not only regulated by the activating phosphorylation within the catalytic loop, T210, but also requires a neighboring site, T214. Additionally, other phosphorylation sites within the catalytic domain, but not in the C-terminal localization domain, redundantly control mitotic functions of Plk1 and cell cycle progression. These results demonstrate the intricacy of signaling to control and regulate Plk1. Further analysis of the complexity of signaling within a cell is demonstrated by comparing the pathways of two proteins. For a cellular process, involved proteins can act in parallel or overlapping pathways. If they overlap, can moderately perturbing a pathway from multiple directions simultaneously cause a greater response than each individual assault? This

idea was used to design a screen between differing therapeutic agents. Many of the drugs include those that directly target proteins key to signaling pathways, kinases, while others were agents that would activate signaling pathways through error induction, such as mitotic checkpoint signaling activation with nocodazole treatment. Aurora A inhibition was found to potentiate the effect of a Plk1 inhibitor, a pan-Cdk inhibitor, and DNA damage response inducer, IUdR. Overall, this work expands the knowledge of and provides insight into the way that signaling networks function within the cell.

Systems Biology of Metabolic and Signaling Networks - Miguel A. Aon - 2013-10-22
Systems Biology represents a new paradigm aiming at a whole-organism-level understanding of biological phenomena, emphasizing interconnections and functional interrelationships rather than component parts. The study of network properties, and how they control and regulate behavior from the cellular to organism level, constitutes a main focus of Systems Biology. This book addresses from a novel perspective a major unsolved biological problem: understanding how a cell works and what goes wrong in pathology. The task undertaken by the authors is in equal parts conceptual and methodological, integrative and analytical, experimental and theoretical, qualitative and quantitative, didactic and comprehensive. Essentially, they unravel the spatio-temporal unfolding of interacting mass-energy and information networks at the cellular and organ levels, as well as its modulation through activation or repression by signaling networks to produce a certain phenotype or (patho)physiological response. Starting with the historical roots, in thirteen chapters this work explores the Systems Biology of signaling networks, cellular structures and fluxes, organ and microorganism functions. In doing so, it establishes the basis of a 21st century approach to biological complexity.

Systems Biology of Metabolic and Signaling Networks - Miguel A. Aon - 2013-10-22
Systems Biology represents a new paradigm aiming at a whole-organism-level understanding of biological phenomena, emphasizing interconnections and functional interrelationships rather than component parts. The study of network properties, and how they control and regulate behavior from the cellular to organism level, constitutes a main focus of Systems Biology. This book addresses from a novel perspective a major unsolved biological problem: understanding how a cell works and what goes wrong in pathology. The task undertaken by the authors is in equal parts conceptual and methodological, integrative and analytical, experimental and theoretical, qualitative and quantitative, didactic and comprehensive. Essentially, they unravel the spatio-temporal unfolding of interacting mass-energy and information networks at the cellular and organ levels, as well as its modulation through activation or repression by signaling networks to produce a certain phenotype or (patho)physiological response. Starting with the historical roots, in thirteen chapters this work explores the Systems Biology of signaling networks, cellular structures and fluxes, organ and microorganism functions. In doing so, it establishes the basis of a 21st century approach to biological complexity.

Cancer Signaling - Christoph Wagener - 2016-12-12
Cancer, which has become the second-most prevalent health issue globally, is essentially resulting from a malfunction of cell signaling. Understanding how the intricate signaling networks of cells and tissues allow a cancer to thrive - and how these networks can be turned into potent weapons against it - is the key to managing cancer in the clinic and improving the outcome of cancer therapies. In their ground-breaking textbook, the authors tell a compelling story of how cancer works at the molecular level, and how targeted therapies - using kinase inhibitors and other modulators of signaling pathways - can contain and eventually cure it. The first part of the book gives an introduction into the cell and molecular biology of cancer, focusing on the key mechanisms of cancer formation. The second part of the book introduces the main signaling transduction mechanisms responsible for carcinogenesis and compares their functions in healthy versus cancer cells. Coloured figures and the text which is written in plain style make the complex topic easy to understand. Specially prepared teaching videos on key concepts and pathways in cancer signaling illustrate the most relevant aspects and are available online.

Cancer Signaling - Christoph Wagener - 2016-12-12
Cancer, which has become the second-most prevalent health issue globally, is essentially resulting from a malfunction of cell signaling. Understanding how the intricate signaling networks of cells and tissues allow a cancer to thrive - and how these networks can be turned into potent weapons against

it - is the key to managing cancer in the clinic and improving the outcome of cancer therapies. In their ground-breaking textbook, the authors tell a compelling story of how cancer works at the molecular level, and how targeted therapies - using kinase inhibitors and other modulators of signaling pathways - can contain and eventually cure it. The first part of the book gives an introduction into the cell and molecular biology of cancer, focusing on the key mechanisms of cancer formation. The second part of the book introduces the main signaling transduction mechanisms responsible for carcinogenesis and compares their functions in healthy versus cancer cells. Coloured figures and the text which is written in plain style make the complex topic easy to understand. Specially prepared teaching videos on key concepts and pathways in cancer signaling illustrate the most relevant aspects and are available online.

Relating Topology and Dynamics in Cell Signaling Networks - Jared Emanuel Toettcher - 2009

Cells are constantly bombarded with stimuli that they must sense, process, and interpret to make decisions. This capability is provided by interconnected signaling pathways. Many of the components and interactions within pathways have been identified, and it is becoming clear that the precise dynamics they generate are necessary for proper system function. However, our understanding of how pathways are interconnected to drive decisions is limited. We must overcoming this limitation to develop interventions that can fine tune a cell decision by modulating specific features of its constituent pathway's dynamics. How can we quantatively map a whole cell decision process? Answering this question requires addressing challenges at three scales: the detailed biochemistry of protein-protein interactions, the complex, interlocked feedback loops of transcriptionally regulated signaling pathways, and the multiple mechanisms of connection that link distinct pathways together into a full cell decision process. In this thesis, we address challenges at each level. We develop new computational approaches for identifying the interactions driving dynamics in protein-protein networks. Applied to the cyanobacterial clock, these approaches identify two coupled motifs that together provide independent control over oscillation phase and period. Using the p53 pathway as a model transcriptional network, we experimentally isolate and characterize dynamics from a core feedback loop in individual cells. A quantitative model of this signaling network predicts and rationalizes the distinct effects on dynamics of additional feedback loops and small molecule inhibitors. Finally, we demonstrated the feasibility of combining individual pathway models to map a whole cell decision: cell cycle arrest elicited by the mammalian DNA damage response. By coupling modeling and experiments, we used this combined perspective to uncover some new biology. We found that multiple arrest mechanisms must work together in a proper cell cycle arrest, and identified a new role for p21 in preventing G2 arrest, paradoxically through its action on G1 cyclins. This thesis demonstrates that we can quantitatively map the logic of cellular decisions, affording new insight and revealing points of control.

Relating Topology and Dynamics in Cell Signaling Networks - Jared Emanuel Toettcher - 2009

Cells are constantly bombarded with stimuli that they must sense, process, and interpret to make decisions. This capability is provided by interconnected signaling pathways. Many of the components and interactions within pathways have been identified, and it is becoming clear that the precise dynamics they generate are necessary for proper system function. However, our understanding of how pathways are interconnected to drive decisions is limited. We must overcoming this limitation to develop interventions that can fine tune a cell decision by modulating specific features of its constituent pathway's dynamics. How can we quantatively map a whole cell decision process? Answering this question requires addressing challenges at three scales: the detailed biochemistry of protein-protein interactions, the complex, interlocked feedback loops of transcriptionally regulated signaling pathways, and the multiple mechanisms of connection that link distinct pathways together into a full cell decision process. In this thesis, we address challenges at each level. We develop new computational approaches for identifying the interactions driving dynamics in protein-protein networks. Applied to the cyanobacterial clock, these approaches identify two coupled motifs that together provide independent control over oscillation phase and period. Using the p53 pathway as a model transcriptional network, we experimentally isolate and characterize dynamics from a core feedback loop in individual cells. A quantitative model of this signaling network predicts and rationalizes the distinct effects on dynamics of additional feedback loops and small molecule inhibitors. Finally, we demonstrated the feasibility of combining individual pathway models to map a whole cell decision: cell cycle arrest elicited by

the mammalian DNA damage response. By coupling modeling and experiments, we used this combined perspective to uncover some new biology. We found that multiple arrest mechanisms must work together in a proper cell cycle arrest, and identified a new role for p21 in preventing G2 arrest, paradoxically through its action on G1 cyclins. This thesis demonstrates that we can quantitatively map the logic of cellular decisions, affording new insight and revealing points of control.

Cellular Signal Transduction in Toxicology and Pharmacology - Jonathan W. Boyd - 2019-03-21
Covering a key topic due to growing research into the role of signaling mechanisms in toxicology, this book focuses on practical approaches for informatics, big data, and complex data sets. Combines fundamentals / basics with experimental applications that can help those involved in preclinical drug studies and translational research Includes detailed presentations of study methodology and data collection, analysis, and interpretation Discusses tools like experimental design, sample handling, analytical measurement techniques

Cellular Signal Transduction in Toxicology and Pharmacology - Jonathan W. Boyd - 2019-03-21
Covering a key topic due to growing research into the role of signaling mechanisms in toxicology, this book focuses on practical approaches for informatics, big data, and complex data sets. Combines fundamentals / basics with experimental applications that can help those involved in preclinical drug studies and translational research Includes detailed presentations of study methodology and data collection, analysis, and interpretation Discusses tools like experimental design, sample handling, analytical measurement techniques

Quantitative Measurement and Modeling of the DNA Damage Signaling Network - Andrea Ruth Tentner - 2009
DNA double-strand breaks (DSB) are one of the major mediators of chemotherapy-induced cytotoxicity in tumors. Cells that experience DNA damage can initiate a DNA damage-mediated cell-cycle arrest, attempt to repair the damage and, if successful, resume the cell-cycle (arrest/repair/resume). Cells can also initiate an active cell-death program known as apoptosis. However, it is not known what "formula" a cell uses to integrate protein signaling molecule activities to determine which of these paths it will take, or what protein signaling-molecules are essential to the execution of that decision. A better understanding of how these cellular decisions are made and mediated on a molecular level is essential to the improvement of existing combination and targeted chemotherapies, and to the development of novel targeted and personalized therapies. Our goal has been to gain an understanding of how cells responding to DSB integrate protein signaling-molecule activities across distinct signaling networks to make and execute binary cell-fate decisions, under conditions relevant to tumor physiology and treatment. We created a quantitative signal-response dataset, measuring signals that widely sample the response of signaling networks activated by the induction of DSB, and the associated cellular phenotypic responses, that together reflect the dynamic cellular responses that follow the induction of DSB. We made use of mathematical modeling approaches to systematically discover signal-response relationships within the DSB-responsive protein signaling network. The structure and content of the signal-response dataset is described, and the use of mathematical modeling approaches to analyze the dataset and discover specific signal-response relationships is illustrated. As a specific example, we selected a particularly strong set of identified signal-response correlations between ERK1/2 activity and S phase cell-cycle phenotype, identified in the mathematical data analysis, to posit a causal relationship between ERK1/2 and S phase cell cycle phenotype. We translated this posited causal relationship into an experimental hypothesis and experimentally test this hypothesis. We describe the validation of an experimental hypothesis based upon model-derived signal response relationships, and demonstrate a dual role for ERK1/2 in mediating cell-cycle arrest and apoptosis following DNA damage. Directions for the extension of the signal-response dataset and mathematical modeling approaches are outlined.

Quantitative Measurement and Modeling of the DNA Damage Signaling Network - Andrea Ruth Tentner - 2009
DNA double-strand breaks (DSB) are one of the major mediators of chemotherapy-induced cytotoxicity in tumors. Cells that experience DNA damage can initiate a DNA damage-mediated cell-cycle arrest, attempt to repair the damage and, if successful, resume the cell-cycle (arrest/repair/resume). Cells can also initiate an active cell-death program known as apoptosis. However, it is not known what "formula" a cell uses to

integrate protein signaling molecule activities to determine which of these paths it will take, or what protein signaling-molecules are essential to the execution of that decision. A better understanding of how these cellular decisions are made and mediated on a molecular level is essential to the improvement of existing combination and targeted chemotherapies, and to the development of novel targeted and personalized therapies. Our goal has been to gain an understanding of how cells responding to DSB integrate protein signaling-molecule activities across distinct signaling networks to make and execute binary cell-fate decisions, under conditions relevant to tumor physiology and treatment. We created a quantitative signal-response dataset, measuring signals that widely sample the response of signaling networks activated by the induction of DSB, and the associated cellular phenotypic responses, that together reflect the dynamic cellular responses that follow the induction of DSB. We made use of mathematical modeling approaches to systematically discover signal-response relationships within the DSB-responsive protein signaling network. The structure and content of the signal-response dataset is described, and the use of mathematical modeling approaches to analyze the dataset and discover specific signal-response relationships is illustrated. As a specific example, we selected a particularly strong set of identified signal-response correlations between ERK1/2 activity and S phase cell-cycle phenotype, identified in the mathematical data analysis, to posit a causal relationship between ERK1/2 and S phase cell cycle phenotype. We translated this posited causal relationship into an experimental hypothesis and experimentally test this hypothesis. We describe the validation of an experimental hypothesis based upon model-derived signal response relationships, and demonstrate a dual role for ERK1/2 in mediating cell-cycle arrest and apoptosis following DNA damage. Directions for the extension of the signal-response dataset and mathematical modeling approaches are outlined.

Future Aspects of Tumor Suppressor Gene - Yue Cheng - 2013-04-10
Tumor suppressor genes (TSGs) and their signaling networks are fast growing areas in current biomedical science. These groups of genes, which are not limited to tumor suppression, play critical roles in many cellular activities. This book, "Future Aspects of Tumor Suppressor Genes", contains some fascinating fields, from basic to translational researches, in recent TSG studies. For example, several TSG signaling pathways are addressed in this book, and both mouse and Drosophila models used for the exploration of these genes are described based on the experimental evidence. A detailed review for current knowledge of microRNA studies in the regulation of tumor growth is introduced. Additionally, how natural compounds interfere with the progression of cancer development via TSG pathways is systemically summarized. Recent progresses in cell reprogramming and stemness transition processes regulated by TSG pathways are also included in this book.

Future Aspects of Tumor Suppressor Gene - Yue Cheng - 2013-04-10
Tumor suppressor genes (TSGs) and their signaling networks are fast growing areas in current biomedical science. These groups of genes, which are not limited to tumor suppression, play critical roles in many cellular activities. This book, "Future Aspects of Tumor Suppressor Genes", contains some fascinating fields, from basic to translational researches, in recent TSG studies. For example, several TSG signaling pathways are addressed in this book, and both mouse and Drosophila models used for the exploration of these genes are described based on the experimental evidence. A detailed review for current knowledge of microRNA studies in the regulation of tumor growth is introduced. Additionally, how natural compounds interfere with the progression of cancer development via TSG pathways is systemically summarized. Recent progresses in cell reprogramming and stemness transition processes regulated by TSG pathways are also included in this book.

Advances in Systems Biology - Igor I. Goryanin - 2011-12-09
The International Society for Systems Biology (ISSB) is a society aimed at advancing world-wide systems biology research by providing a forum for scientific discussions and various academic services. The ISSB helps coordinate researchers to form alliances for meeting the unique needs of multidisciplinary and international systems biology research. The annual International Conference on Systems Biology (ICSB) serves as the main meeting for the society and is one of the largest academic and commercial gatherings under the broad heading of ‘Systems Biology’.

Advances in Systems Biology - Igor I. Goryanin - 2011-12-09
The International Society for Systems Biology (ISSB) is a society aimed at advancing world-wide systems biology research by providing a forum for scientific discussions and various academic services. The ISSB helps

coordinate researchers to form alliances for meeting the unique needs of multidisciplinary and international systems biology research. The annual International Conference on Systems Biology (ICSB) serves as the main meeting for the society and is one of the largest academic and commercial gatherings under the broad heading of ‘Systems Biology’.

Coordination and Integration of Signaling and Resources Allocation in the Yeast Stress Response - - 2015
Proper stress responses are pivotal for cells to survive and adapt to new environments. Stressed cells coordinate a multi-faceted response spanning many levels of physiology involving growth and cell cycle arrest, metabolites changes, translation arrest and a large fraction of transcriptomic change, which includes the common environmental stress response (ESR). Yet knowledge of the complete stress-activated regulatory network, principles for signal integration as well as the rationale of ESR activation upon stress remains elusive. To decipher complicated signaling networks, we developed an experimental and computational approach to integrate available protein interaction data with gene fitness contributions, mutant transcriptome profiles, and phospho-proteome changes in cells responding to salt stress, to infer the salt-responsive signaling network in yeast. The inferred subnetwork presented many novel predictions by implicating new regulators, uncovering unrecognized crosstalk between known pathways, and pointing to previously unknown 'hubs' of signal integration. We exploited these predictions to show that Cdc14 phosphatase is a central hub in the network and that modification of RNA polymerase II coordinates ESR activation: induction of stress-defense genes with reduction of growth-related transcripts. Additionally, we show that the yeast ESR cannot be simply explained as a byproduct of altered cell-cycle distribution or arrested growth upon stress, given that arrest of growth and cell cycle progression did not trigger strong ESR activation. Furthermore, ESR transcripts did not fluctuate with cell cycle phase in dividing cells and did not respond to arrest points as proposed previously. We also show that activation of the ESR is an active response to stress as arrested cells show robust, dose-dependent ESR activation in response to stress. We propose that ESR activation helps reallocate transcription and translation capacity to stress defense genes upon stresses.

Coordination and Integration of Signaling and Resources Allocation in the Yeast Stress Response - - 2015
Proper stress responses are pivotal for cells to survive and adapt to new environments. Stressed cells coordinate a multi-faceted response spanning many levels of physiology involving growth and cell cycle arrest, metabolites changes, translation arrest and a large fraction of transcriptomic change, which includes the common environmental stress response (ESR). Yet knowledge of the complete stress-activated regulatory network, principles for signal integration as well as the rationale of ESR activation upon stress remains elusive. To decipher complicated signaling networks, we developed an experimental and computational approach to integrate available protein interaction data with gene fitness contributions, mutant transcriptome profiles, and phospho-proteome changes in cells responding to salt stress, to infer the salt-responsive signaling network in yeast. The inferred subnetwork presented many novel predictions by implicating new regulators, uncovering unrecognized crosstalk between known pathways, and pointing to previously unknown 'hubs' of signal integration. We exploited these predictions to show that Cdc14 phosphatase is a central hub in the network and that modification of RNA polymerase II coordinates ESR activation: induction of stress-defense genes with reduction of growth-related transcripts. Additionally, we show that the yeast ESR cannot be simply explained as a byproduct of altered cell-cycle distribution or arrested growth upon stress, given that arrest of growth and cell cycle progression did not trigger strong ESR activation. Furthermore, ESR transcripts did not fluctuate with cell cycle phase in dividing cells and did not respond to arrest points as proposed previously. We also show that activation of the ESR is an active response to stress as arrested cells show robust, dose-dependent ESR activation in response to stress. We propose that ESR activation helps reallocate transcription and translation capacity to stress defense genes upon stresses.

Maintenance of Genome Integrity: DNA Damage Sensing, Signaling, Repair and Replication in Plants - Alma Balestrazzi - 2016-05-06
Environmental stresses and metabolic by-products can severely affect the integrity of genetic information by inducing DNA damage and impairing genome stability. As a consequence, plant growth and productivity are irreversibly compromised. To overcome genotoxic injury, plants have evolved complex strategies relying on a highly efficient repair machinery that responds to sophisticated damage perception/signaling networks. The

DNA damage signaling network contains several key components: DNA damage sensors, signal transducers, mediators, and effectors. Most of these components are common to other eukaryotes but some features are unique to the plant kingdom. ATM and ATR are well-conserved members of PIKK family, which amplify and transduce signals to downstream effectors. ATM primarily responds to DNA double strand breaks while ATR responds to various forms of DNA damage. The signals from the activated transducer kinases are transmitted to the downstream cell-cycle regulators, such as CHK1, CHK2, and p53 in many eukaryotes. However, plants have no homologue of CHK1, CHK2 nor p53. The finding of Arabidopsis transcription factor SOG1 that seems functionally but not structurally similar to p53 suggests that plants have developed unique cell cycle regulation mechanism. The double strand break repair, recombination repair, postreplication repair, and lesion bypass, have been investigated in several plants. The DNA double strand break, a most critical damage for organisms are repaired non-homologous end joining (NHEJ) or homologous recombination (HR) pathway. Damage on template DNA makes replication stall, which is processed by translesion synthesis (TLS) or error-free postreplication repair (PPR) pathway. Deletion of the error-prone TLS polymerase reduces mutation frequencies, suggesting PPR maintains the stalled replication fork when TLS is not available. Unveiling the regulation networks among these multiple pathways would be the next challenge to be completed. Some intriguing issues have been disclosed such as the cross-talk between DNA repair, senescence and pathogen response and the involvement of non-coding RNAs in global genome stability. Several studies have highlighted the essential contribution of chromatin remodeling in DNA repair DNA damage sensing, signaling and repair have been investigated in relation to environmental stresses, seed quality issues, mutation breeding in both model and crop plants and all these studies strengthen the idea that components of the plant response to genotoxic stress might represent tools to improve stress tolerance and field performance. This focus issue gives researchers the opportunity to gather and interact by providing Mini-Reviews, Commentaries, Opinions, Original Research and Method articles which describe the most recent advances and future perspectives in the field of DNA damage sensing, signaling and repair in plants. A comprehensive overview of the current progresses dealing with the genotoxic stress response in plants will be provided looking at cellular and molecular level with multidisciplinary approaches. This will hopefully bring together valuable information for both plant biotechnologists and breeders.

Maintenance of Genome Integrity: DNA Damage Sensing, Signaling, Repair and Replication in Plants - Alma Balestrazzi - 2016-05-06
Environmental stresses and metabolic by-products can severely affect the integrity of genetic information by inducing DNA damage and impairing genome stability. As a consequence, plant growth and productivity are irreversibly compromised. To overcome genotoxic injury, plants have evolved complex strategies relying on a highly efficient repair machinery that responds to sophisticated damage perception/signaling networks. The DNA damage signaling network contains several key components: DNA damage sensors, signal transducers, mediators, and effectors. Most of these components are common to other eukaryotes but some features are unique to the plant kingdom. ATM and ATR are well-conserved members of PIKK family, which amplify and transduce signals to downstream effectors. ATM primarily responds to DNA double strand breaks while ATR responds to various forms of DNA damage. The signals from the activated transducer kinases are transmitted to the downstream cell-cycle regulators, such as CHK1, CHK2, and p53 in many eukaryotes. However, plants have no homologue of CHK1, CHK2 nor p53. The finding of Arabidopsis transcription factor SOG1 that seems functionally but not structurally similar to p53 suggests that plants have developed unique cell cycle regulation mechanism. The double strand break repair, recombination repair, postreplication repair, and lesion bypass, have been investigated in several plants. The DNA double strand break, a most critical damage for organisms are repaired non-homologous end joining (NHEJ) or homologous recombination (HR) pathway. Damage on template DNA makes replication stall, which is processed by translesion synthesis (TLS) or error-free postreplication repair (PPR) pathway. Deletion of the error-prone TLS polymerase reduces mutation frequencies, suggesting PPR maintains the stalled replication fork when TLS is not available. Unveiling the regulation networks among these multiple pathways would be the next challenge to be completed. Some intriguing issues have been disclosed such as the cross-talk between DNA repair, senescence and pathogen response and the involvement of non-coding RNAs in global genome stability. Several studies have highlighted the essential contribution of chromatin remodeling in DNA repair DNA damage sensing, signaling and repair have been investigated in relation to environmental stresses, seed quality issues, mutation breeding in

both model and crop plants and all these studies strengthen the idea that components of the plant response to genotoxic stress might represent tools to improve stress tolerance and field performance. This focus issue gives researchers the opportunity to gather and interact by providing Mini-Reviews, Commentaries, Opinions, Original Research and Method articles which describe the most recent advances and future perspectives in the field of DNA damage sensing, signaling and repair in plants. A comprehensive overview of the current progresses dealing with the genotoxic stress response in plants will be provided looking at cellular and molecular level with multidisciplinary approaches. This will hopefully bring together valuable information for both plant biotechnologists and breeders.

Role of the Mammalian Polo-like Kinase 3(Plk3) in Cell Cycle Regulation and DNA Damage Checkpoints - David Myer - 2006
In order for cell division to be completed with a high degree of fidelity, the cell division cycle is controlled by cell cycle promoting proteins, that promote a highly ordered step-wise progression through the cell cycle, and checkpoint proteins, that halt cell cycle progression in response to genotoxic stress. Deregulation of these two protein groups leads to malignant transformation. Recent evidence suggests that one family of proteins, the polo-like kinases (Plks), is comprised of members having both cell cycle promoting and checkpoint functions. These serine/threonine kinases are components of many signaling networks that regulate mitotic entry, centrosome maturation and separation, chromosome segregation, mitotic exit, and cytokinesis. Of the four mammalian Plk homologues, Plk3 is the only known Plk that is expressed throughout the entire cell cycle and after DNA damage. Plk3 appears to keep a constant vigil as a checkpoint protein that responds to a variety of genotoxic stress. Since Plk3 phosphorylates Chk2, Cdc25A, and Cdc25C, the goal of this study was to determine how Plk3 phosphorylation of a checkpoint protein, Chk2, and the checkpoint targets, Cdc25C and Cdc25A, affects their function and in turn affects cell cycle regulation. We demonstrated that Plk3 phosphorylates Chk2 on serine 62 and serine 73 to prime Chk2 for phosphorylation and activation by the ataxia-telangiectasia mutated (ATM) protein. We determined that Plk3 phosphorylates Cdc25C to promote its nuclear accumulation, and possible nuclear sequestration. Lastly, the results of these studies revealed that in vitro, Plk3 phosphorylates two residues (S513 and S519) on the Cdc25A proximal C-terminal domain. Interestingly, these two phosphorylation sites are adjacent to K514 and R520, two residues shown to be important in cyclin B binding to Cdc25A. In vivo, phospho-mimetics of S513 and S519 promote ionizing radiation (IR) mediated Cdc25A instability in asynchronous cells and constitutive binding of cyclin B1 in response to a spindle checkpoint activator, nocodazole. In support of these results, we have also shown that IR- treated Plk3 deficient mouse embryonic fibroblasts (MEFs) contain more Cdc25A than Plk3 proficient cells. Thus we have described pathways and demonstrated molecular mechanisms by which Plk3 serves as a checkpoint protein.

Role of the Mammalian Polo-like Kinase 3(Plk3) in Cell Cycle Regulation and DNA Damage Checkpoints - David Myer - 2006
In order for cell division to be completed with a high degree of fidelity, the cell division cycle is controlled by cell cycle promoting proteins, that promote a highly ordered step-wise progression through the cell cycle, and checkpoint proteins, that halt cell cycle progression in response to genotoxic stress. Deregulation of these two protein groups leads to malignant transformation. Recent evidence suggests that one family of proteins, the polo-like kinases (Plks), is comprised of members having both cell cycle promoting and checkpoint functions. These serine/threonine kinases are components of many signaling networks that regulate mitotic entry, centrosome maturation and separation, chromosome segregation, mitotic exit, and cytokinesis. Of the four mammalian Plk homologues, Plk3 is the only known Plk that is expressed throughout the entire cell cycle and after DNA damage. Plk3 appears to keep a constant vigil as a checkpoint protein that responds to a variety of genotoxic stress. Since Plk3 phosphorylates Chk2, Cdc25A, and Cdc25C, the goal of this study was to determine how Plk3 phosphorylation of a checkpoint protein, Chk2, and the checkpoint targets, Cdc25C and Cdc25A, affects their function and in turn affects cell cycle regulation. We demonstrated that Plk3 phosphorylates Chk2 on serine 62 and serine 73 to prime Chk2 for phosphorylation and activation by the ataxia-telangiectasia mutated (ATM) protein. We determined that Plk3 phosphorylates Cdc25C to promote its nuclear accumulation, and possible nuclear sequestration. Lastly, the results of these studies revealed that in vitro, Plk3 phosphorylates two residues (S513 and S519) on the Cdc25A proximal C-terminal domain. Interestingly, these two phosphorylation sites are adjacent to K514 and R520, two residues shown to be important in cyclin B binding to Cdc25A. In vivo, phospho-

mimetics of S513 and S519 promote ionizing radiation (IR) mediated Cdc25A instability in asynchronous cells and constitutive binding of cyclin B1 in response to a spindle checkpoint activator, nocodazole. In support of these results, we have also shown that IR- treated Plk3 deficient mouse embryonic fibroblasts (MEFs) contain more Cdc25A than Plk3 proficient cells. Thus we have described pathways and demonstrated molecular mechanisms by which Plk3 serves as a checkpoint protein.

A Novel High-throughput In-cell Western Assay for the Quantitative Measurement of Signaling Dynamics in DNA Damage Signaling Networks - Andrea Ruth Tentner - 2006
Following exposure to DNA damage, cells initiate a stress response involving multiple protein kinase signaling cascades. The DNA damage response results in one of several possible cell-fate decisions, or cellular responses: induction of cell-cycle arrest, initiation of DNA repair, activation of transcriptional programs, and either apoptosis, necrosis or cell senescence. The mechanisms by which cells make these decisions, and how cell fate depends upon variables such as DNA damage type and dose, and other environmental factors, is unknown. The process by which cells select among alternate fates following such stimuli, or "cues" is likely to involve a dynamic, multi-variate integration of signals from each of the kinase signaling components. A major goal of signal transduction research is to understand how information flows through signal transduction pathways downstream of a given cue, such as DNA damage, and how signals are integrated, in order to mediate cellular responses. Mathematical modeling approaches are necessary to advance our understanding of these processes.

A Novel High-throughput In-cell Western Assay for the Quantitative Measurement of Signaling Dynamics in DNA Damage Signaling Networks - Andrea Ruth Tentner - 2006
Following exposure to DNA damage, cells initiate a stress response involving multiple protein kinase signaling cascades. The DNA damage response results in one of several possible cell-fate decisions, or cellular responses: induction of cell-cycle arrest, initiation of DNA repair, activation of transcriptional programs, and either apoptosis, necrosis or cell senescence. The mechanisms by which cells make these decisions, and how cell fate depends upon variables such as DNA damage type and dose, and other environmental factors, is unknown. The process by which cells select among alternate fates following such stimuli, or "cues" is likely to involve a dynamic, multi-variate integration of signals from each of the kinase signaling components. A major goal of signal transduction research is to understand how information flows through signal transduction pathways downstream of a given cue, such as DNA damage, and how signals are integrated, in order to mediate cellular responses. Mathematical modeling approaches are necessary to advance our understanding of these processes.

Signal Transduction in Cancer - David A. Frank - 2006-04-18
One of the most exciting areas of cancer research now is the development of agents which can target signal transduction pathways that are activated inappropriately in malignant cells. The understanding of the molecular abnormalities which distinguish malignant cells from their normal counterparts has grown tremendously. This volume summarizes the current research on the role that signal transduction pathways play in the pathogenesis of cancer and how this knowledge may be used to develop the next generation of more effective and less toxic anticancer agents. Series Editor comments: "The biologic behavior of both normal and cancer cells is determined by critical signal transduction pathways. This text provides a comprehensive review of the field. Leading investigators discuss key molecules that may prove to be important diagnostic and/or therapeutic targets."

Signal Transduction in Cancer - David A. Frank - 2006-04-18
One of the most exciting areas of cancer research now is the development of agents which can target signal transduction pathways that are activated inappropriately in malignant cells. The understanding of the molecular abnormalities which distinguish malignant cells from their normal counterparts has grown tremendously. This volume summarizes the current research on the role that signal transduction pathways play in the pathogenesis of cancer and how this knowledge may be used to develop the next generation of more effective and less toxic anticancer agents. Series Editor comments: "The biologic behavior of both normal and cancer cells is determined by critical signal transduction pathways. This text provides a comprehensive review of the field. Leading investigators discuss key molecules that may prove to be important diagnostic and/or therapeutic targets."

Cell Cycle Control - Lecturer in Biological Sciences Department of Biological Sciences Christopher Hutchison - 1995
What makes a cell begin the complicated process of cell division? How does it stop? What happens when things go wrong? The use of developing technologies has revealed the extraordinary degree to which cell cycle control mechanisms have been conserved through eukaryotic evolution. This is thefirst book to cover the cell cycle field in the wake of groundbreaking research from the past five years. A historical look at cell cycle findings places this new knowledge into perspective and demonstrates the universality of cell cycle control, from the evolutionary process to cancer research andmitotic regulation. Cell cycle research is the most exciting area in contemporary biology, and anyone either interested or involved in the cell cycle field will find this an invaluable study.

Cell Cycle Control - Lecturer in Biological Sciences Department of Biological Sciences Christopher Hutchison - 1995
What makes a cell begin the complicated process of cell division? How does it stop? What happens when things go wrong? The use of developing technologies has revealed the extraordinary degree to which cell cycle control mechanisms have been conserved through eukaryotic evolution. This is thefirst book to cover the cell cycle field in the wake of groundbreaking research from the past five years. A historical look at cell cycle findings places this new knowledge into perspective and demonstrates the universality of cell cycle control, from the evolutionary process to cancer research andmitotic regulation. Cell cycle research is the most exciting area in contemporary biology, and anyone either interested or involved in the cell cycle field will find this an invaluable study.

The ras Superfamily of GTPases (1993) - Juan Carlos Lacal - 2017-11-22
The ras Superfamily of GTPases presents the most comprehensive compilation of information available regarding aspects of the putative function of small ras-related GTPases. The book's chapters were written by the world's most prominent scientists in this field and cover such topics as the structure and properties of ras proteins, ras function, the ras superfamily in general, and the functional regulation of ras and ras-related GTPases. The book will benefit cell biologists, oncologists, neurobiologists, molecular biologists, and others interested in the topic.

The ras Superfamily of GTPases (1993) - Juan Carlos Lacal - 2017-11-22
The ras Superfamily of GTPases presents the most comprehensive compilation of information available regarding aspects of the putative function of small ras-related GTPases. The book's chapters were written by the world's most prominent scientists in this field and cover such topics as the structure and properties of ras proteins, ras function, the ras superfamily in general, and the functional regulation of ras and ras-related GTPases. The book will benefit cell biologists, oncologists, neurobiologists, molecular biologists, and others interested in the topic.

Annual Plant Reviews, Intracellular Signaling in Plants - Zhenbiao Yang - 2009-01-22
Annual Plant Reviews, Volume 33 Intracellular Signaling in Plants An intriguing and important question in our understanding of plantdevelopmental programming and responses to the environment is whatkinds of strategies and mechanisms plant cells use for thetransmission and the integration of various developmental andenvironmental signals. This book provides insight into thisfundamental question in plant biology. Intracellular Signaling in Plants is an excellent new addition tothe increasingly well-known and respected Annual Plant Reviews andoffers the reader: * Chapters prepared by an esteemed team of internationalauthors * A consistent and well-illustrated approach to the subjectmatter * An invaluable resource for all researchers and professionals inplant biochemistry and biology This important volume also deals with major known signalingmechanisms and several representative intracellular signalingnetworks in plants, integrating comprehensive reviews and insightsfrom leading experts in the field. Libraries in all universities and research establishments wherebiological sciences are studied and taught should have copies ofthis essential work on their shelves. Also Available from Wiley-Blackwell Annual Plant Reviews, Volume 32 Cell Cycle Control and Plant Development Edited by Dirk Inzé Print: 9781405150439 Online: 9780470988923 DOI: 10.1002/9780470988923 Annual Plant Reviews, Volume 31 Plant Mitochondria Edited by David Logan Print: 9781405149396 Online: 9780470986592 DOI: 10.1002/9780470986592

Annual Plant Reviews, Intracellular Signaling in Plants - Zhenbiao Yang - 2009-01-22
Annual Plant Reviews, Volume 33 Intracellular Signaling in Plants An

intriguing and important question in our understanding of plantdevelopmental programming and responses to the environment is whatkinds of strategies and mechanisms plant cells use for thetransmission and the integration of various developmental andenvironmental signals. This book provides insight into thisfundamental question in plant biology. Intracellular Signaling in Plants is an excellent new addition tothe increasingly well-known and respected Annual Plant Reviews andoffers the reader: * Chapters prepared by an esteemed team of internationalauthors * A consistent and well-illustrated approach to the subjectmatter * An invaluable resource for all researchers and professionals inplant biochemistry and biology This important volume also deals with major known signalingmechanisms and several representative intracellular signalingnetworks in plants, integrating comprehensive reviews and insightsfrom leading experts in the field. Libraries in all universities and research establishments wherebiological sciences are studied and taught should have copies ofthis essential work on their shelves. Also Available from Wiley-Blackwell Annual Plant Reviews, Volume 32 Cell Cycle Control and Plant Development Edited by Dirk Inzé Print: 9781405150439 Online: 9780470988923 DOI: 10.1002/9780470988923 Annual Plant Reviews, Volume 31 Plant Mitochondria Edited by David Logan Print: 9781405149396 Online: 9780470986592 DOI: 10.1002/9780470986592

Signaling Crosstalk: A Live in Situ Analysis of the Temporal and Spatial Regulation of Key Pathways in Human Breast Cancer Progression - - 2007

Signal transduction networks such as the PI3K-AKT and EGFR pathways are important regulators of cell fate decisions, including cell proliferation, differentiation, apoptosis, and homeostasis. Furthermore, these pathways integrate and influence one another when cells are within an appropriate microenvironment. Using a proteomic approach, we identify stratifin, a protein which regulates AKT and EGFR signaling as well as the cell cycle, to be upregulated in T4-2 cells cultured in 3D lrECM. Expression of stratifin decreases to S1 levels upon phenotypic reversion; these effects were not seen when cells were cultured in 2D, supporting a possible role of stratifin in crosstalk. In the mouse mammary gland, stratifin expression was restricted to myoepithelial cells, and was expressed predominantly during periods of branching morphogenesis and ductal infiltration. Taken together, these data suggest a novel role of stratifin in epithelial cell proliferation and migration. The signaling networks regulated by stratifin will be assessed by shRNA knockdown in T4-2 cells.

Signaling Crosstalk: A Live in Situ Analysis of the Temporal and Spatial Regulation of Key Pathways in Human Breast Cancer Progression - - 2007

Signal transduction networks such as the PI3K-AKT and EGFR pathways are important regulators of cell fate decisions, including cell proliferation, differentiation, apoptosis, and homeostasis. Furthermore, these pathways integrate and influence one another when cells are within an appropriate microenvironment. Using a proteomic approach, we identify stratifin, a protein which regulates AKT and EGFR signaling as well as the cell cycle, to be upregulated in T4-2 cells cultured in 3D lrECM. Expression of stratifin decreases to S1 levels upon phenotypic reversion; these effects were not seen when cells were cultured in 2D, supporting a possible role of stratifin in crosstalk. In the mouse mammary gland, stratifin expression was restricted to myoepithelial cells, and was expressed predominantly during periods of branching morphogenesis and ductal infiltration. Taken together, these data suggest a novel role of stratifin in epithelial cell proliferation and migration. The signaling networks regulated by stratifin will be assessed by shRNA knockdown in T4-2 cells.

Identification of Signaling Pathways Coordinating Cell Growth and Division in Fission Yeast - Lin Deng - 2015

"Cell growth and division are coordinated to keep homeostasis of cell size. The components of the core machinery are conserved in a wide range of cell types. Fission yeast (S. pombe) has been an important model organism to study cell size control due to its regular rod-shape and constant division size. A two-component Pom1-Cdr2 system has been previously modeled as a "sizer" to measure cell size: the cell polarity kinase Pom1 forms protein gradients emanating from the cell ends to inhibit the cell cycle protein Cdr2 which organizes a band of nodes in the cell center. It has been unknown how Pom1 inhibits Cdr2, and how this regulation might connect to other forms of crosstalk between cell polarity and cell cycle progression. In this thesis I used genetic, biochemical approaches and live cell imaging to investigate the signaling pathways that coordinate cell growth and division in fission yeast. This work shows that Pom1 regulates cell polarity through complex networks and cell size exclusively through Cdr2. Phosphorylation

of the Cdr2 C-terminal domain by Pom1 prevents its T-loop activation by the CaMKK Ssp1; Cdr2 activity rather than protein level promotes mitotic entry. Ssp1 may be a master kinase in fission yeast to couple cell growth with nutrient availability. Beyond regulation of Cdr2. Ssp1 acts through AMPK in response to glucose starvation, which is counteracted by PP6 family phosphatase Ppe1. For crosstalk between cell polarity and cell cycle networks, I identified the cell polarity protein Skb1 as an important link. Skb1 inhibits mitotic entry through the Cdr1-Wee1 pathway. Skb1 and Cdr1 form different cortical nodes on the plasma membrane. Each Skb1 node represents a megadalton complex on the plasma membrane that is formed by the physical interaction of Skb1 with a membrane anchor protein Slf1. The compartmentalization of Cdr1 and Skb1 nodes act to prevent their inhibitory interactions and provide spatial cues for cell growth."

Identification of Signaling Pathways Coordinating Cell Growth and Division in Fission Yeast - Lin Deng - 2015
"Cell growth and division are coordinated to keep homeostasis of cell size. The components of the core machinery are conserved in a wide range of cell types. Fission yeast (S. pombe) has been an important model organism to study cell size control due to its regular rod-shape and constant division size. A two-component Pom1-Cdr2 system has been previously modeled as a "sizer" to measure cell size: the cell polarity kinase Pom1 forms protein gradients emanating from the cell ends to inhibit the cell cycle protein Cdr2 which organizes a band of nodes in the cell center. It has been unknown how Pom1 inhibits Cdr2, and how this regulation might connect to other forms of crosstalk between cell polarity and cell cycle progression. In this thesis I used genetic, biochemical approaches and live cell imaging to investigate the signaling pathways that coordinate cell growth and division in fission yeast. This work shows that Pom1 regulates cell polarity through complex networks and cell size exclusively through Cdr2. Phosphorylation of the Cdr2 C-terminal domain by Pom1 prevents its T-loop activation by the CaMKK Ssp1; Cdr2 activity rather than protein level promotes mitotic entry. Ssp1 may be a master kinase in fission yeast to couple cell growth with nutrient availability. Beyond regulation of Cdr2. Ssp1 acts through AMPK in response to glucose starvation, which is counteracted by PP6 family phosphatase Ppe1. For crosstalk between cell polarity and cell cycle networks, I identified the cell polarity protein Skb1 as an important link. Skb1 inhibits mitotic entry through the Cdr1-Wee1 pathway. Skb1 and Cdr1 form different cortical nodes on the plasma membrane. Each Skb1 node represents a megadalton complex on the plasma membrane that is formed by the physical interaction of Skb1 with a membrane anchor protein Slf1. The compartmentalization of Cdr1 and Skb1 nodes act to prevent their inhibitory interactions and provide spatial cues for cell growth."

Quantitative Analysis of Signaling Networks in Proneural Glioblastoma - Rebecca Susan Lescarbeau - 2015
Glioblastoma (GBM) is the most common malignant form of brain cancer. Even with treatment including surgery, radiation, and temozolomide chemotherapy, the 1 year survival rate is only 35%. To identify specific mediators of GBM progression in a genetically engineered murine model of proneural GBM, we quantified signaling networks using mass spectrometry. We identified oncogenic signaling associated with the GBM model, such as increased phosphorylation of ERK1/2, P13K, and PDGFRA, relative to murine brain. Phosphorylation of CDK1 Y15, which causes G2 /M cell cycle arrest, was measured to be the most differentially phosphorylated site, with a 14-fold increase in the tumors. We used syngeneic cell lines to investigate this checkpoint further and treated these cells with MK-1775, an inhibitor of Wee1, the kinase responsible for phosphorylation of CDK1 Y15. MK-1775 treatment resulted in mitotic catastrophe of these cells, as measured by increased DNA damage, abnormal percentages of cells in cell cycle phases, and death by apoptosis. This response was abrogated by inhibiting CDK1 with roscovitine, a CDK inhibitor, demonstrating the necessity of active CDK1 for MK-1775 induced mitotic catastrophe. To assess the extensibility of targeting Wee1 and the G2/M checkpoint in GBM, we treated patientderived xenograft (PDX) cell lines with MK-1775. The response was more heterogeneous, but we measured decreased CDK1 phosphorylation, increased DNA damage, and death by apoptosis. These results were validated in a flank GBM PDX model where treatment with MK-1775 increased mouse survival by 1.74-fold. We also quantified the signaling differences in our murine GBM model after treatment with sunitinib, an inhibitor of its driver receptor tyrosine kinase, PDGFRA. Treatment increased survival but lead to a morphological change causing a more invasive phenotype. Pro-migratory signaling was characterized by mass spectrometry, such as increased phosphorylation of Eno1, ELMO2, and tubulins. Invasion was further characterized in a lung cancer model where we identified signaling specific to different ligands that result in similar

levels of invasion. We have demonstrated that unbiased, quantitative phosphotyrosine proteomics has the ability to reveal therapeutic targets in tumor models and signaling differences between treatments.

Quantitative Analysis of Signaling Networks in Proneural Glioblastoma - Rebecca Susan Lescarbeau - 2015
Glioblastoma (GBM) is the most common malignant form of brain cancer. Even with treatment including surgery, radiation, and temozolomide chemotherapy, the 1 year survival rate is only 35%. To identify specific mediators of GBM progression in a genetically engineered murine model of proneural GBM, we quantified signaling networks using mass spectrometry. We identified oncogenic signaling associated with the GBM model, such as increased phosphorylation of ERK1/2, P13K, and PDGFRA, relative to murine brain. Phosphorylation of CDK1 Y15, which causes G2 /M cell cycle arrest, was measured to be the most differentially phosphorylated site, with a 14-fold increase in the tumors. We used syngeneic cell lines to investigate this checkpoint further and treated these cells with MK-1775, an inhibitor of Wee1, the kinase responsible for phosphorylation of CDK1 Y15. MK-1775 treatment resulted in mitotic catastrophe of these cells, as measured by increased DNA damage, abnormal percentages of cells in cell cycle phases, and death by apoptosis. This response was abrogated by inhibiting CDK1 with roscovitine, a CDK inhibitor, demonstrating the necessity of active CDK1 for MK-1775 induced mitotic catastrophe. To assess the extensibility of targeting Wee1 and the G2/M checkpoint in GBM, we treated patientderived xenograft (PDX) cell lines with MK-1775. The response was more heterogeneous, but we measured decreased CDK1 phosphorylation, increased DNA damage, and death by apoptosis. These results were validated in a flank GBM PDX model where treatment with MK-1775 increased mouse survival by 1.74-fold. We also quantified the signaling differences in our murine GBM model after treatment with sunitinib, an inhibitor of its driver receptor tyrosine kinase, PDGFRA. Treatment increased survival but lead to a morphological change causing a more invasive phenotype. Pro-migratory signaling was characterized by mass spectrometry, such as increased phosphorylation of Eno1, ELMO2, and tubulins. Invasion was further characterized in a lung cancer model where we identified signaling specific to different ligands that result in similar levels of invasion. We have demonstrated that unbiased, quantitative phosphotyrosine proteomics has the ability to reveal therapeutic targets in tumor models and signaling differences between treatments.

Chemical Genetic Analysis of Signaling by the Saccharomyces Cerevisiae Mitotic Kinases Cdc15, Dbf2, and Cdc5 - Jennifer L. Paulson - 2006
Protein phosphorylation is a ubiquitous regulatory mechanism for cellular signal propagation, and the complexity of signaling networks presents a challenge to protein kinase substrate identification. Chemical genetic control of kinase function provides a handle for kinase pathway analysis. Here, we apply this approach to three kinases that function in a signaling network that regulates exit from mitosis in the budding yeast, Saccharomyces cerevisiae. These include the mitogen-activating protein kinase, Cdc15, the nuclear Dbf2-related kinase, Dbf2, and the Polo-like kinase, Cdc5. Each kinase was successfully engineered for selective chemical inhibition in vivo. We found that monospecific pharmacological inhibition of Cdc5 delays anaphase nucleus migration into the bud, revealing a novel Cdc5 function. Additionally, chemical genetic, bioinformatic, and yeast proteomic tools were combined for Cdc5 substrate identification. Systematically chosen candidate Cdc5 substrates were examined for loss of phosphorylation upon cellular Cdc5 inhibition. The identified Cdc5 targets include Spc72, a spindle pole body (SPB) component and microtubule anchor required for nuclear positioning. Spc72 binds Cdc5 in a cell cycle specific manner, and in vivo Cdc5 inhibition prevents mitotic Spc72 phosphorylation. Studies in vitro demonstrate direct Spc72 phosphorylation by Cdc5. Finally, we expanded our knowledge of Cdc5 function at the SPB by examining SPB-localized proteins for presence in a Cdc5 complex. In summary, a chemical genetic approach was used to inhibit three protein kinases from diverse families, which led to a greater understanding of Cdc5 cellular function.

Chemical Genetic Analysis of Signaling by the Saccharomyces Cerevisiae Mitotic Kinases Cdc15, Dbf2, and Cdc5 - Jennifer L. Paulson - 2006
Protein phosphorylation is a ubiquitous regulatory mechanism for cellular signal propagation, and the complexity of signaling networks presents a challenge to protein kinase substrate identification. Chemical genetic control of kinase function provides a handle for kinase pathway analysis. Here, we apply this approach to three kinases that function in a signaling

network that regulates exit from mitosis in the budding yeast, Saccharomyces cerevisiae. These include the mitogen-activating protein kinase, Cdc15, the nuclear Dbf2-related kinase, Dbf2, and the Polo-like kinase, Cdc5. Each kinase was successfully engineered for selective chemical inhibition in vivo. We found that monospecific pharmacological inhibition of Cdc5 delays anaphase nucleus migration into the bud, revealing a novel Cdc5 function. Additionally, chemical genetic, bioinformatic, and yeast proteomic tools were combined for Cdc5 substrate identification. Systematically chosen candidate Cdc5 substrates were examined for loss of phosphorylation upon cellular Cdc5 inhibition. The identified Cdc5 targets include Spc72, a spindle pole body (SPB) component and microtubule anchor required for nuclear positioning. Spc72 binds Cdc5 in a cell cycle specific manner, and in vivo Cdc5 inhibition prevents mitotic Spc72 phosphorylation. Studies in vitro demonstrate direct Spc72 phosphorylation by Cdc5. Finally, we expanded our knowledge of Cdc5 function at the SPB by examining SPB-localized proteins for presence in a Cdc5 complex. In summary, a chemical genetic approach was used to inhibit three protein kinases from diverse families, which led to a greater understanding of Cdc5 cellular function.

Regulation and Functions of Cdc14 in Mitotic Exit in Saccharomyces Cerevisiae - Brett N. Tomson - 2008

In order to ensure the accurate formation of two daughter cells from one parental cell, the series of events that comprise the mitotic cell division cycle must be carefully regulated. Much of this regulation affects the transitions between the stages of the cell cycle, which are controlled by proteins known as cyclin dependent kinases (CDKs). High levels of CDKs promote mitotic entry, whereas the inactivation of CDKs drives exit from mitosis and entry into the next cell cycle at the G stage. In the budding yeast Saccharomyces cerevisiae, the evolutionarily conserved phosphatase Cdcl4 regulates many events in anaphase, including the inactivation of CDKs. The activity of Cdcl4 is thought to be restricted to anaphase due to two signaling networks, the Cdc fourteen early anaphase release (FEAR) network and the mitotic exit network (MEN). Although the major components of these two pathways have been identified, their regulation is not fully understood. Here we examine how the members of the FEAR network function together to regulate Cdc 14 and its targets in anaphase. One function of Cdc 14 in early anaphase is to promote proper segregation of ribosomal DNA (rDNA). We have determined that Cdcl4 is required to resolve a novel type of linkage between chromosomes, which occurs at the rDNA locus due to transcription-dependent processes. We also characterize the regulation of Cdc 14 activity by the FEAR network component Spo 12. Specifically, we found that Spo 2 must be phosphorylated in a conserved domain during anaphase in order for Cdc 14 to function in early anaphase. Spol2 phosphorylation is dependent on the CDK, Cdc28, whereas Cdcl4 contributes to the dephosphorylation of Spol2. Lastly, we show that Spol2 phosphorylation is regulated by the FEAR network components Espl and Slk19, but not by the MEN. Overall, this thesis describes research that establishes a new model for both the regulation and significance of the FEAR network in controlling Cdc 14 during anaphase in Saccharomyces cerevisiae.

Regulation and Functions of Cdc14 in Mitotic Exit in Saccharomyces Cerevisiae - Brett N. Tomson - 2008

In order to ensure the accurate formation of two daughter cells from one parental cell, the series of events that comprise the mitotic cell division cycle must be carefully regulated. Much of this regulation affects the transitions between the stages of the cell cycle, which are controlled by proteins known as cyclin dependent kinases (CDKs). High levels of CDKs promote mitotic entry, whereas the inactivation of CDKs drives exit from mitosis and entry into the next cell cycle at the G stage. In the budding yeast Saccharomyces cerevisiae, the evolutionarily conserved phosphatase Cdcl4 regulates many events in anaphase, including the inactivation of CDKs. The activity of Cdcl4 is thought to be restricted to anaphase due to two signaling networks, the Cdc fourteen early anaphase release (FEAR) network and the mitotic exit network (MEN). Although the major components of these two pathways have been identified, their regulation is not fully understood. Here we examine how the members of the FEAR network function together to regulate Cdc 14 and its targets in anaphase. One function of Cdc 14 in early anaphase is to promote proper segregation of ribosomal DNA (rDNA). We have determined that Cdcl4 is required to resolve a novel type of linkage between chromosomes, which occurs at the rDNA locus due to transcription-dependent processes. We also characterize the regulation of Cdc 14 activity by the FEAR network component Spo 12. Specifically, we found that Spo 2 must be phosphorylated in a conserved domain during anaphase in order for Cdc 14 to function in early anaphase.

Spol2 phosphorylation is dependent on the CDK, Cdc28, whereas Cdcl4 contributes to the dephosphorylation of Spol2. Lastly, we show that Spol2 phosphorylation is regulated by the FEAR network components Espl and Slk19, but not by the MEN. Overall, this thesis describes research that establishes a new model for both the regulation and significance of the FEAR network in controlling Cdc 14 during anaphase in Saccharomyces cerevisiae.

Inferring Stress-activated Signaling Networks in Saccharomyces Cerevisiae Reveals Complex Pathway Integration - Matthew Edward MacGilvray - 2017

Cells respond to stressful conditions by coordinating a complex, multi-faceted response that spans many levels of physiology. Much of the response is coordinated by changes in protein phosphorylation. Although the regulators of transcriptome changes during stress are well characterized in Saccharomyces cerevisiae, the upstream regulatory network controlling protein phosphorylation is less well dissected. In this thesis, we developed a computational approach to infer the stress-activated signaling network that regulates phosphorylation changes in response to salt stress and the ER stressor dithiothreitol (DTT). The method uses integer linear programming (ILP) to integrate stress-responsive phospho-proteome responses in wild-type and mutant strains, predicted phosphorylation motifs on groups of coregulated peptides, and published protein interaction data. The inferred salt-network predicted new regulatory connections between stress-activated and growth-regulating pathways and suggested mechanisms coordinating metabolism, cell-cycle progression, and growth during stress. Further, kinase inference during DTT suggested new functions for the HOG and PKA pathways in augmenting the unfolded protein response (UPR). Together, our work shows how a high-quality computational network model can facilitate discovery of new pathway interactions during diverse stress responses.

Inferring Stress-activated Signaling Networks in Saccharomyces Cerevisiae Reveals Complex Pathway Integration - Matthew Edward MacGilvray - 2017

Cells respond to stressful conditions by coordinating a complex, multi-faceted response that spans many levels of physiology. Much of the response is coordinated by changes in protein phosphorylation. Although the regulators of transcriptome changes during stress are well characterized in Saccharomyces cerevisiae, the upstream regulatory network controlling protein phosphorylation is less well dissected. In this thesis, we developed a computational approach to infer the stress-activated signaling network that regulates phosphorylation changes in response to salt stress and the ER stressor dithiothreitol (DTT). The method uses integer linear programming (ILP) to integrate stress-responsive phospho-proteome responses in wild-type and mutant strains, predicted phosphorylation motifs on groups of coregulated peptides, and published protein interaction data. The inferred salt-network predicted new regulatory connections between stress-activated and growth-regulating pathways and suggested mechanisms coordinating metabolism, cell-cycle progression, and growth during stress. Further, kinase inference during DTT suggested new functions for the HOG and PKA pathways in augmenting the unfolded protein response (UPR). Together, our work shows how a high-quality computational network model can facilitate discovery of new pathway interactions during diverse stress responses.

Regulation of G1 Phase Progression - Johannes Boonstra - 2003-09-30

In this contribution, several specialists describe the current knowledge on the molecular networks that regulate cell cycle progression, with an emphasis on the G1 phase of the cell cycle. The first part of Regulation of G1 Phase Progression is concerned with the individual molecules that form the network, including cyclins, cyclin-dependent kinases, inhibitors of these kinases and retinoblastoma and p53. The second section describes the signaling cascades by which external factors influence the cell cycle network, including mitogens, the extracellular matrix, nutrients and oxygen radicals. The last section describes the effects of specific external conditions on cell cycle progression and are presented such as serum starvation and subsequent re-addition and stress conditions (heat, osmolarity). The final two chapters describe the relation between cell cycle progression with cell differentiation and with apoptosis.

Regulation of G1 Phase Progression - Johannes Boonstra - 2003-09-30

In this contribution, several specialists describe the current knowledge on the molecular networks that regulate cell cycle progression, with an emphasis on the G1 phase of the cell cycle. The first part of Regulation of G1 Phase Progression is concerned with the individual molecules that form

the network, including cyclins, cyclin-dependent kinases, inhibitors of these kinases and retinoblastoma and p53. The second section describes the signaling cascades by which external factors influence the cell cycle network, including mitogens, the extracellular matrix, nutrients and oxygen radicals. The last section describes the effects of specific external conditions on cell cycle progression and are presented such as serum starvation and subsequent re-addition and stress conditions (heat, osmolarity). The final two chapters describe the relation between cell cycle progression with cell differentiation and with apoptosis.

Molecular Oncology: Underlying Mechanisms and Translational Advancements - Ammad Ahmad Farooqi - 2017-03-29
Cancer is a multifaceted and genomically complex disease and data obtained through high throughput technologies has provided near complete resolution of the landscape of how genomic, genetic and epigenetic mutations in cancerous cells effectively influence homeostasis of signaling networks within these cells, between cancerous cells, tumor microenvironment and at the organ level. Increasingly sophisticated information has helped us in developing a better understanding of the underlying mechanisms of cancer, and it is now known that intra-tumor genetic heterogeneity, cellular plasticity, dysregulation of spatio-temporally controlled signaling cascades, and loss of apoptosis are contributory in cancer development, progression and the development of resistance against different therapeutics. It is becoming progressively more understandable that earlier detection of pre-existing or emerging resistance against different therapeutics may prove to be helpful in personalizing the use of targeted cancer therapy. Despite the fact that there is a continuously increasing list of books, being guest edited by researchers, books on the subject are often composed of invited reviews without proper sequence and continuity and designed for a particular readership. This book progressively shifts and guides the readers from basic underlying mechanisms to translational approaches to treat cancer.

Molecular Oncology: Underlying Mechanisms and Translational Advancements - Ammad Ahmad Farooqi - 2017-03-29
Cancer is a multifaceted and genomically complex disease and data obtained through high throughput technologies has provided near complete resolution of the landscape of how genomic, genetic and epigenetic mutations in cancerous cells effectively influence homeostasis of signaling networks within these cells, between cancerous cells, tumor microenvironment and at the organ level. Increasingly sophisticated information has helped us in developing a better understanding of the underlying mechanisms of cancer, and it is now known that intra-tumor genetic heterogeneity, cellular plasticity, dysregulation of spatio-temporally controlled signaling cascades, and loss of apoptosis are contributory in cancer development, progression and the development of resistance against different therapeutics. It is becoming progressively more understandable that earlier detection of pre-existing or emerging resistance against different therapeutics may prove to be helpful in personalizing the use of targeted cancer therapy. Despite the fact that there is a continuously increasing list of books, being guest edited by researchers, books on the subject are often composed of invited reviews without proper sequence and continuity and designed for a particular readership. This book progressively shifts and guides the readers from basic underlying mechanisms to translational approaches to treat cancer.

Handbook of Systems Biology - Marian Walhout - 2012-12-31
This book provides an entry point into Systems Biology for researchers in genetics, molecular biology, cell biology, microbiology and biomedical science to understand the key concepts to expanding their work. Chapters organized around broader themes of Organelles and Organisms, Systems Properties of Biological Processes, Cellular Networks, and Systems Biology and Disease discuss the development of concepts, the current applications, and the future prospects. Emphasis is placed on concepts and insights into the multi-disciplinary nature of the field as well as the importance of systems biology in human biological research. Technology, being an extremely important aspect of scientific progress overall, and in the creation of new fields in particular, is discussed in 'boxes' within each chapter to relate to appropriate topics. 2013 Honorable Mention for Single Volume Reference in Science from the Association of American Publishers' PROSE Awards Emphasizes the interdisciplinary nature of systems biology with contributions from leaders in a variety of disciplines Includes the latest research developments in human and animal models to assist with translational research Presents biological and computational aspects of the science side-by-side to facilitate collaboration between computational and biological researchers

Handbook of Systems Biology - Marian Walhout - 2012-12-31
This book provides an entry point into Systems Biology for researchers in genetics, molecular biology, cell biology, microbiology and biomedical science to understand the key concepts to expanding their work. Chapters organized around broader themes of Organelles and Organisms, Systems Properties of Biological Processes, Cellular Networks, and Systems Biology and Disease discuss the development of concepts, the current applications, and the future prospects. Emphasis is placed on concepts and insights into the multi-disciplinary nature of the field as well as the importance of systems biology in human biological research. Technology, being an extremely important aspect of scientific progress overall, and in the creation of new fields in particular, is discussed in 'boxes' within each chapter to relate to appropriate topics. 2013 Honorable Mention for Single Volume Reference in Science from the Association of American Publishers' PROSE Awards Emphasizes the interdisciplinary nature of systems biology with contributions from leaders in a variety of disciplines Includes the latest research developments in human and animal models to assist with translational research Presents biological and computational aspects of the science side-by-side to facilitate collaboration between computational and biological researchers

Molecular Biology of the Cell - Bruce Alberts - 2004

Molecular Biology of the Cell - Bruce Alberts - 2004

The DNA Damage Response: Implications on Cancer Formation and Treatment - Kum Kum Khanna - 2009-09-18
The ?eld of cellular responses to DNA damage has attained widespread recognition and interest in recent years commensurate with its fundamental role in the ma- tenance of genomic stability. These responses, which are essential to preventing cellular death or malignant transformation, are organized into a sophisticated s- tem designated the “DNA damage response”. This system operates in all living organisms to maintain genomic stability in the face of constant attacks on the DNA from a variety of endogenous by-products of normal metabolism, as well as exogenous agents such as radiation and toxic chemicals in the environment. The response repairs DNA damage via an intricate cellular signal transduction network that coordinates with various processes such as regulation of DNA replication, tr- scriptional responses, and temporary cell cycle arrest to allow the repair to take place. Defects in this system result in severe genetic disorders involving tissue degeneration, sensitivity to speci?c damaging agents, immunode?ciency, genomic instability, cancer predisposition and premature aging. The ?nding that many of the crucial players involved in DNA damage response are structurally and functionally conserved in different species spurred discoveries of new players through similar analyses in yeast and mammals. We now understand the chain of events that leads to instantaneous activation of the massive cellular responses to DNA lesions. This book summarizes several new concepts in this rapidly evolving ?eld, and the advances in our understanding of the complex network of processes that respond to DNA damage.

The DNA Damage Response: Implications on Cancer Formation and Treatment - Kum Kum Khanna - 2009-09-18
The ?eld of cellular responses to DNA damage has attained widespread recognition and interest in recent years commensurate with its fundamental role in the ma- tenance of genomic stability. These responses, which are essential to preventing cellular death or malignant transformation, are organized into a sophisticated s- tem designated the “DNA damage response”. This system operates in all living organisms to maintain genomic stability in the face of constant attacks on the DNA from a variety of endogenous by-products of normal metabolism, as well as exogenous agents such as radiation and toxic chemicals in the environment. The response repairs DNA damage via an intricate cellular signal transduction network that coordinates with various processes such as regulation of DNA replication, tr- scriptional responses, and temporary cell cycle arrest to allow the repair to take place. Defects in this system result in severe genetic disorders involving tissue degeneration, sensitivity to speci?c damaging agents, immunode?ciency, genomic instability, cancer predisposition and premature aging. The ?nding that many of the crucial players involved in DNA damage response are structurally and functionally conserved in different species spurred discoveries of new players through similar analyses in yeast and mammals. We now understand the chain of events that leads to instantaneous activation of the massive cellular responses to DNA lesions. This book summarizes several new concepts in this rapidly evolving ?eld, and the advances in our understanding of the complex network of processes that respond to DNA damage.

Oxidative Stress Mechanisms and their Modulation - Mohinder Bansal - 2014-10-17

Research over the years has demonstrated that free radicals mediated oxidative stress lies at the helm of almost all patho-physiological phenomena. These findings emphasize on the need to understand the underlying molecular mechanism(s) and their critical role in the pathogenesis. This book aims to focus on these areas to provide readers a comprehensive outlook about the major redox sensitive pathways and networks involved in various disease conditions. In the first chapter of the book, basic information about the oxidative stress, its generation, its biomarkers and its role in body are discussed. In the next three chapters, the role of oxidative stress in various pathologies ranging from neurological disorders, to cardiovascular diseases, cancers, metabolic diseases and ageing have been described. Chapter 5 cumulatively describes the most important molecular signaling pathways that are affected by reactive oxygen species (ROS). These are the mechanisms which are common denominators in various pathological states. In the next part of the book, various antioxidant strategies to target and mitigate ROS have been discussed with details on the mechanisms. Selenium, being the research focus and interest of the authors for years, the role of selenium as an antioxidant as part of selenoproteins has been included in the book. Finally, the book culminates with authors' perspective on the future of the redox biology field. Throughout the book, efforts have been made to use simplified language and suitable figures for ease to understand the contents. Although the authors have tried to touch on all the different aspects of oxidative stress in detail, the fact that it is a continuously growing field with updates coming every day, there might be some areas which might not be described in depth. This book is designed for students, young scientists to get acquainted with the redox biology. Overall, this book is a reference to understand the redox regulation of cellular signaling pathways involved in pathogenesis.

Oxidative Stress Mechanisms and their Modulation - Mohinder Bansal - 2014-10-17

Research over the years has demonstrated that free radicals mediated oxidative stress lies at the helm of almost all patho-physiological phenomena. These findings emphasize on the need to understand the underlying molecular mechanism(s) and their critical role in the pathogenesis. This book aims to focus on these areas to provide readers a comprehensive outlook about the major redox sensitive pathways and networks involved in various disease conditions. In the first chapter of the book, basic information about the oxidative stress, its generation, its biomarkers and its role in body are discussed. In the next three chapters, the role of oxidative stress in various pathologies ranging from neurological disorders, to cardiovascular diseases, cancers, metabolic diseases and ageing have been described. Chapter 5 cumulatively describes the most important molecular signaling pathways that are affected by reactive oxygen species (ROS). These are the mechanisms which are common denominators in various pathological states. In the next part of the book, various antioxidant strategies to target and mitigate ROS have been discussed with details on the mechanisms. Selenium, being the research focus and interest of the authors for years, the role of selenium as an antioxidant as part of selenoproteins has been included in the book. Finally, the book culminates with authors' perspective on the future of the redox biology field. Throughout the book, efforts have been made to use simplified language and suitable figures for ease to understand the contents. Although the authors have tried to touch on all the different aspects of oxidative stress in detail, the fact that it is a continuously growing field with updates coming every day, there might be some areas which might not be described in depth. This book is designed for students, young scientists to get acquainted with the redox biology. Overall, this book is a reference to understand the redox regulation of cellular signaling pathways involved in pathogenesis.

Systems Biology of Cancer - Sam Thiagalingam - 2015-04-09

With over two hundred types of cancer diagnosed to date, researchers the world over have been forced to rapidly update their understanding of the biology of cancer. In fact, only the study of the basic cellular processes, and how these are altered in cancer cells, can ultimately provide a background for rational therapies. Bringing together the state-of-the-art contributions of international experts, Systems Biology of Cancer proposes an ultimate research goal for the whole scientific community: exploiting systems biology to generate in-depth knowledge based on blueprints that are unique to each type of cancer. Readers are provided with a realistic view of what is known and what is yet to be uncovered on the aberrations in the fundamental biological processes, deregulation of major signaling networks, alterations

in major cancers and the strategies for using the scientific knowledge for effective diagnosis, prognosis and drug discovery to improve public health.

Systems Biology of Cancer - Sam Thiagalingam - 2015-04-09
With over two hundred types of cancer diagnosed to date, researchers the world over have been forced to rapidly update their understanding of the biology of cancer. In fact, only the study of the basic cellular processes, and how these are altered in cancer cells, can ultimately provide a background for rational therapies. Bringing together the state-of-the-art contributions of international experts, Systems Biology of Cancer proposes an ultimate research goal for the whole scientific community: exploiting systems biology to generate in-depth knowledge based on blueprints that are unique to each type of cancer. Readers are provided with a realistic view of what is known and what is yet to be uncovered on the aberrations in the fundamental biological processes, deregulation of major signaling networks, alterations in major cancers and the strategies for using the scientific knowledge for effective diagnosis, prognosis and drug discovery to improve public health.

The Influence of Signaling Networks on the Pathogenesis of Cancers of the Lung - Tim Nico Beck - 2016
Lung cancer is the leading cause of cancer related mortality and head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally. Both cancers are still not fully understood on a molecular level and treatment efforts frequently fail to cure patients. Analysis of broad signaling networks can provide new insights and is particularly powerful in combination with annotated patient data. We took advantage of available ‘omics’ databases to augment the study of Anti-Müllerian Hormone (AMH) and its receptor (AMHR2) – two proteins we identified as expressed and active in lung cancer – and of retinoblastoma 1 (RB1) associated cell cycle regulation. To better understand the importance of RB1 activity in HPV-negative HNSCC, we investigated the prognostic value of inhibitory CDK4/6 phosphorylation of RB1 on threonine 356 (T356) in archival HPV-negative tumor specimens from patients who underwent surgical resection and received adjuvant radiation. pT356RB1 was identified as a potential prognostic biomarker and a potential response predictor for CDK4/6 inhibitors. Regarding AMH and AMHR2, we discovered that 6-8% of non-small cell lung cancers express high levels of AMH or AMHR2. Furthermore, we were able to show that AMH/AMHR2 participate in a TGF-b/BMP signaling network and regulates epithelial-mesenchymal transition (EMT) in lung cancer. EMT is related to cancer cell metastasis and resistant to therapy, two dominant drivers of cancer mortality. In summary, we used publically available databases to augment the study of RB1 and AMH/AMHR2, with the goal to better understand the pathogenesis of cancers of the lung, head and neck.

The Influence of Signaling Networks on the Pathogenesis of Cancers of the Lung - Tim Nico Beck - 2016
Lung cancer is the leading cause of cancer related mortality and head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally. Both cancers are still not fully understood on a molecular level and treatment efforts frequently fail to cure patients. Analysis of broad signaling networks can provide new insights and is particularly powerful in combination with annotated patient data. We took advantage of available ‘omics’ databases to augment the study of Anti-Müllerian Hormone (AMH) and its receptor (AMHR2) – two proteins we identified as expressed and active in lung cancer – and of retinoblastoma 1 (RB1) associated cell cycle regulation. To better understand the importance of RB1 activity in HPV-negative HNSCC, we investigated the prognostic value of inhibitory CDK4/6 phosphorylation of RB1 on threonine 356 (T356) in archival HPV-negative tumor specimens from patients who underwent surgical resection and received adjuvant radiation. pT356RB1 was identified as a potential prognostic biomarker and a potential response predictor for CDK4/6 inhibitors. Regarding AMH and AMHR2, we discovered that 6-8% of non-small cell lung cancers express high levels of AMH or AMHR2. Furthermore, we were able to show that AMH/AMHR2 participate in a TGF-b/BMP signaling network and regulates epithelial-mesenchymal transition (EMT) in lung cancer. EMT is related to cancer cell metastasis and resistant to therapy, two dominant drivers of cancer mortality. In summary, we used publically available databases to augment the study of RB1 and AMH/AMHR2, with the goal to better understand the pathogenesis of cancers of the lung, head and neck.

Computational Systems Biology - Ursula Klingmüller - 2013-11-26
Cellular communication is mediated by extracellular stimuli that bind cellular receptors and activate intracellular signaling pathways. Principal biochemical reactions used for signal transduction are protein or lipid

phosphorylation, proteolytic cleavage, protein degradation and complex formation mediated by protein-protein interactions. Within the nucleus, signaling pathways regulate transcription factor activity and gene expression. Cells differ in their competence to respond to extracellular stimuli. A deeper understanding of complex biological responses cannot be achieved by traditional approaches but requires the combination of experimental data with mathematical modeling. Following a systems biology approach, data-based mathematical models describing sub-modules of signaling pathways have been established. By combining computer simulations with experimental verification systems properties of signaling pathway including cycling behavior or threshold response could be identified. Yet, to analyze complex growth and maturation processes at a systems level and quantitatively predict the outcome of perturbations further advances in experimental and theoretical methodologies are required.

Computational Systems Biology - Ursula Klingmüller - 2013-11-26
Cellular communication is mediated by extracellular stimuli that bind cellular receptors and activate intracellular signaling pathways. Principal biochemical reactions used for signal transduction are protein or lipid phosphorylation, proteolytic cleavage, protein degradation and complex formation mediated by protein-protein interactions. Within the nucleus, signaling pathways regulate transcription factor activity and gene expression. Cells differ in their competence to respond to extracellular stimuli. A deeper understanding of complex biological responses cannot be achieved by traditional approaches but requires the combination of experimental data with mathematical modeling. Following a systems biology approach, data-based mathematical models describing sub-modules of signaling pathways have been established. By combining computer simulations with experimental verification systems properties of signaling pathway including cycling behavior or threshold response could be identified. Yet, to analyze complex growth and maturation processes at a systems level and quantitatively predict the outcome of perturbations further advances in experimental and theoretical methodologies are required.

Dietary Modulation of Cell Signaling Pathways - Zigang Dong - 2008-09-26
A consequence of rapid progress in the science of nutrigenomics and nutrigenetics is the substantial accumulation of data covering nutrienal modulation of gene expression at the cellular and subcellular levels. Current research is increasingly focused on the role of nutrition and diet in modifying oxidative damage in the progression of disease. Dietary Modulation of Cell Signaling Pathways reviews some of these findings, focusing on nutrient-gene interactions with particular emphasis on the intracellular signaling network. Explore a Pivotal Function for Maintaining Homeostasis The book addresses the dietary modulation of particular gene expression systems and highlights the underlying molecular and cellular mechanisms that involve upstream signaling molecules, such as kinases and transcription factors in the context of their therapeutic potential. It describes nutrients' actions on the activation of an antioxidant and inflammatory transcription factor and the induction of their target gene expression. Provides a Mechanistic Understanding of the Action of Dietary Components Comprehensively covering dietary modulation of cell signaling, leading experts provide information on state-of-the-art research in their own specialty. For those working in the fields of dietary components, molecular mechanisms, and health benefits, this book presents a useful tool for mechanistic understanding of the action of dietary components.

Dietary Modulation of Cell Signaling Pathways - Zigang Dong - 2008-09-26
A consequence of rapid progress in the science of nutrigenomics and nutrigenetics is the substantial accumulation of data covering nutrienal modulation of gene expression at the cellular and subcellular levels. Current research is increasingly focused on the role of nutrition and diet in modifying oxidative damage in the progression of disease. Dietary Modulation of Cell Signaling Pathways reviews some of these findings, focusing on nutrient-gene interactions with particular emphasis on the intracellular signaling network. Explore a Pivotal Function for Maintaining Homeostasis The book addresses the dietary modulation of particular gene expression systems and highlights the underlying molecular and cellular mechanisms that involve upstream signaling molecules, such as kinases and transcription factors in the context of their therapeutic potential. It describes nutrients' actions on the activation of an antioxidant and inflammatory transcription factor and the induction of their target gene expression. Provides a Mechanistic Understanding of the Action of Dietary

Components Comprehensively covering dietary modulation of cell signaling, leading experts provide information on state-of-the-art research in their own specialty. For those working in the fields of dietary components, molecular mechanisms, and health benefits, this book presents a useful tool for mechanistic understanding of the action of dietary components.

Proteomic Analysis Delineates the Signaling Networks of Plasmodium Falciparum - Brittany Nicole Pease - 2015
This study is the most comprehensive definition of the constitutive and regulated expression of the Plasmodium proteome during the intraerythrocytic developmental cycle, and offered an insight into the dynamics of phosphorylation during the asexual cycle progression (1). In summary, this study has 1) defined the constitutive and regulated expression of the Plasmodium proteome during its asexual life cycle, 2) demonstrated that fluctuation and reversible phosphorylation is important for the regulation of P. falciparum's unique cell cycle, 3) provided the foundation for quantitative phosphoproteomic analysis of kinase negative mutants to understand their function, 4) provided a major step towards defining kinase-substrate pairs operative within parasite's signaling networks, and 5) generated a preliminary interactome for PfPK6.

Proteomic Analysis Delineates the Signaling Networks of Plasmodium Falciparum - Brittany Nicole Pease - 2015
This study is the most comprehensive definition of the constitutive and regulated expression of the Plasmodium proteome during the intraerythrocytic developmental cycle, and offered an insight into the dynamics of phosphorylation during the asexual cycle progression (1). In summary, this study has 1) defined the constitutive and regulated expression of the Plasmodium proteome during its asexual life cycle, 2) demonstrated that fluctuation and reversible phosphorylation is important for the regulation of P. falciparum's unique cell cycle, 3) provided the foundation for quantitative phosphoproteomic analysis of kinase negative mutants to understand their function, 4) provided a major step towards defining kinase-substrate pairs operative within parasite's signaling networks, and 5) generated a preliminary interactome for PfPK6.

Guide to Signal Pathways in Immune Cells - E. Nigel Wardle - 2009-04-21
To read current biomedical science, one has to have a working knowledge of how important effector molecules cause transduction of their signal within cells, altering the control of genes. This work aims to provide that basic knowledge for medical readers. Students of immunology or cell biology will note its relevance. One will learn how platelets, macrophages, neutrophils, T and B lymphocytes and natural killer cells perform their functions and how skin, breast, prostate and colon cancers emerge. The associated diagrams and tables are used to obviate extensive text. Appropriate references to articles and reviews by workers in each field are given so that further consideration can easily be undertaken. We are all at differing stages of our appreciation of immunology and of pat- physiology. Some persons will have a profound background in biochemistry or molecular biology. Others will have a reminiscence of lectures received years ago. Since this work is principally for clinical doctors, the sections that can be avoided at first reading are marked with an asterisk (*). Always proceed line by line and think of associations that you know. Do you feel comfortable with the statement, “Interleukin 6 stimulates glucose uptake in renal proximal tubular cells, and that action is associated with Stat3, PI3K/Akt, MAPKs and NF-kB signal pathways”? If not, please read on.

Guide to Signal Pathways in Immune Cells - E. Nigel Wardle - 2009-04-21
To read current biomedical science, one has to have a working knowledge of how important effector molecules cause transduction of their signal within cells, altering the control of genes. This work aims to provide that basic knowledge for medical readers. Students of immunology or cell biology will note its relevance. One will learn how platelets, macrophages, neutrophils, T and B lymphocytes and natural killer cells perform their functions and how skin, breast, prostate and colon cancers emerge. The associated diagrams and tables are used to obviate extensive text. Appropriate references to articles and reviews by workers in each field are given so that further consideration can easily be undertaken. We are all at differing stages of our appreciation of immunology and of pat- physiology. Some persons will have a profound background in biochemistry or molecular biology. Others will have a reminiscence of lectures received years ago. Since this work is principally for clinical doctors, the sections that can be avoided at first reading are marked with an asterisk (*). Always proceed line by line and think of associations that you know. Do you feel comfortable

with the statement, “Interleukin 6 stimulates glucose uptake in renal proximal tubular cells, and that action is associated with Stat3, PI3K/Akt, MAPKs and NF-kB signal pathways”? If not, please read on.

Multi-Omics Approaches to Study Signaling Pathways - Jyoti Sharma - 2020-11-18

Multi-Omics Approaches to Study Signaling Pathways - Jyoti Sharma - 2020-11-18

Cell Signaling - Wendell Lim - 2014-06-16
Cell Signaling presents the principles and components that underlie all known signaling processes. It provides undergraduate and graduate students the conceptual tools needed to make sense of the dizzying array of pathways used by the cell to communicate. By emphasizing the common design principles, components, and logic that drives all signa

Cell Signaling - Wendell Lim - 2014-06-16
Cell Signaling presents the principles and components that underlie all known signaling processes. It provides undergraduate and graduate students the conceptual tools needed to make sense of the dizzying array of pathways used by the cell to communicate. By emphasizing the common design principles, components, and logic that drives all signa