Signaling Pathways Of Tissue Factor Expression In

This book is a printed edition of the Special Issue "Antiphospholipid Antibodies and Syndrome" that was published in Antibodies

Disease Pathways: An Atlas of Human Disease Signaling Pathways is designed to fill a void of illustrated reviews about the cellular mechanisms of human diseases. It covers 42 of the most common non-oncologic diseases and illustrates the connections between the molecular causes of the disease and its symptoms. This resource provides readers with detailed information about the disease molecular pathways, while keeping the presentation simple. Pathway models that aggregate the knowledge about protein–protein interactions have become indispensable tools in many areas of molecular biology, pharmacology, and medicine. In addition to disease pathways, the book includes a comprehensive overview of molecular signaling biology and application of pathway models in the analysis of big data for drug discovery and personalized medicine. This is a must-have reference for general biologists, biochemists, students, medical workers, and everyone interested in the cellular and molecular mechanisms of human disease. Over 145 full-color illustrations of the molecular and cellular cascades underlying the disease pathology. Disease pathways are based on computational models from Elsevier’s Disease Pathway Collection, published for the first time outside of Pathway Studio® commercial software. Each relationship on the pathway models is supported by references to scientific articles and can be examined at freely available online resources.

Covering one of the most important research topics in cancer biology, this is an ideal ready reference for oncologists, cell biologists, pharmaceutists, pathologists, molecular biologists, internists, and researchers working in the pharmaceutical industry. Following an introduction that provides an overview of tumor angiogenesis, the book goes on to look at mechanisms of angiogenesis and lymphangiogenesis, signal transduction, therapeutic approaches in combination with established treatments, and concludes with a section on imaging and biomarkers in angiogenesis.

Now in its Third Edition, this authoritative text continues to provide a comprehensive and systematic review of the biology, pathobiology, and clinical disorders of the hemostatic system. Its unique organization of the basic sciences coupled with clinical sections yields a user-friendly integrated text, and a reference tool that meets the needs of diverse investigators and clinicians of contemporary medicine for understanding the hemostatic system. New chapter topics covered in this edition include angiogenesis and vasculogenesis; hemorrhagic complications of antithrombotic therapy; interactions of coagulation and fibrinolytic proteins with the vessel wall; and less common thrombotic disorders.

Using a multidisciplinary approach, this book describes the biochemical mechanisms associated with dysregulation of proteases and the resulting

pathophysiological consequences. It highlights the role and regulation of different types of proteases as well as their synthetic and endogenous inhibitors. The role of proteases was initially thought to be limited to general metabolic digestion. However, we now know that the role of protein breakdown is much more complex, and proteases have multiple functions: they are coupled to turnover and can affect protein composition, function and synthesis. In addition to eliminating abnormal proteins, breakdown has many modulatory functions, including activating and inactivating enzymes, modulating membrane function, altering receptor channel properties, affecting transcription and cell cycles and forming active peptides. The ubiquity of proteases in nature makes them an important target for drug development. This in-depth, comprehensive is a valuable resource for researchers involved in identifying new targets for drug development. With its multidisciplinary scope, it bridges the gap between fundamental and translational research in the biomedical and pharmaceutical industries, making it thought-provoking reading for scientists in the field.

Signal transduction comprises the intracellular biochemical signals which induce the appropriate cell response to an external stimulus. The players in signal transduction are diverse, from small molecules as first messengers, to proteins, receptors, transcription factors, among many others. The different signaling pathways and the crosstalk between them originates the unique signaling profile of every cell type in the human body. The cell signaling specificity depends on several aspects including protein composition, subcellular localization and complexes and gene promoters. This textbook provides a comprehensive overview of the specific signaling pathways on a variety of human tissues. This information can be of great value for health science researchers, professionals and students to understand key pathways for tissue-specific functions in the plethora of signals, signals receptors, transducers and effectors. Chapter 3 and 15 are available open access under a Creative Commons Attribution 4.0 International License via link.springer.com.

The immune system mediates tissue responses under both physiological and pathological conditions, impacting the inflammatory, fibrogenic and regenerative components. In addition to various leukocyte subsets, it is now recognized that epithelial, endothelial and other non-hematopoietic tissue cell types actively contribute to the interplay shaping tissue responses. Further understanding the molecular pathways and mechanisms mediating these tissue responses is of great interest. In the past decade, TNF-like weak inducer of apoptosis (TWEAK) and its receptor, FGF-inducible molecule-14 (Fn14), members of the TNF/TNFR superfamily, have emerged as a prominent molecular axis regulating tissue responses. Generally leukocyte-derived, TWEAK signals through Fn14 which is highly induced in injured and diseased tissues on the surface of parenchymal, stromal and progenitor cells, thereby orchestrating a host of tissue-shaping responses, including inflammation, angiogenesis, cell proliferation or death, and the regulation of progenitor cells. Compelling preclinical results indicate that

whereas transient TWEAK/Fn14 activation promotes productive tissue responses after acute injury, excessive or persistent TWEAK/Fn14 activation drives pathological tissue responses, leading to progressive damage and degeneration in target organs of injury, autoimmune and inflammatory diseases and cancer. Given that the highly inducible pattern of Fn14 expression is well conserved between mouse and man, the role of TWEAK/Fn14 in human disease is an area of intense investigation. Recent findings have also begun to shed light on how the TWEAK/Fn14 pathway fits into the immune network, interplaying with other well-established pathways, including TNFa, IL-17, IL-13 and TGFb, in regulating tissue responses. The noncanonical nuclear factor kB (NF?B) pathway plays a role in immunity and disease pathologies and appears to be activated by only a subset of TNF/ TNFR superfamily members. Of the various signaling pathways downstream of TWEAK/Fn14, particular attention has been placed on the noncanonical NF?B pathway given that given that TWEAK induces acute activation of canonical NF?B but prolonged activation of noncanonical pathway. Thus dovetailing of the TWEAK/Fn14 axis with noncanonical NF?B pathway activation may be a key mechanism underlying tissue responses. Also of great interest is a deeper understanding of where, when and how tissue responses are regulated by other TNF/ TNFR superfamily members that can signal through noncanonical NF?B. This Research Topic issue will cover: 1. TWEAK/Fn14 pathway biology, role in tissue responses, injury, and disease pathogenesis 2. Role of noncanonical NFkB signaling cascade in tissue responses 3. Translational studies of relevance of TWEAK/Fn14 and noncanonical NFkB in human disease 4. Other TNF superfamily members' signaling through noncanonical NFkB in the regulation of tissue responses 5. Reviews and Perspectives on the above

Targeting the Tissue Factor-Factor VIIa Signaling Pathway to Enhance Activity of MTOR Inhibitors in the Treatment of Breast Cancer

LPA is a component of oxidized low density lipoproteins (oxLDL) which has been shown to accumulate in human atherosclerotic plaques. Tissue factor (TF) is the principal initiator of blood coagulation. Tissue factor upregulation in atherosclerotic plaque can lead to undesirable vascular thrombosis. The generation of reactive oxygen species (ROS), which act as signaling molecules in the vascular system, is enhanced in response to injury and has been associated with a procoagulant state and the progression of atherosclerotic disease. Oxidative stress might contribute to the increased expression of pro atherosclerotic genes at sites of vascular injury, including TF. Little is known about the regulation of TF by LPA in smooth muscle cells (SMC) which is a major player in the process of atherosclerosis. Data generated by this study demonstrate that LPA markedly induces TF expression in rat aorta smooth muscle cells (RASMCs) and human aorta smooth muscle cells (HASMCs). The signaling pathways involved are multiple.

Signal transduction pathways are at the core of most biological processes and are critical regulators of heart physiology and pathophysiology. The heart is both a transmitter and dynamic receptor of a variety of intracellular and extracellular stimuli,

playing a critical role of an integrator of diverse signaling mechanisms. Alterations in signaling pathways are contributing factors in the development and progression of a broad spectrum of diseases, ranging from dysrhythmias and atherosclerosis to hypertension and the metabolic syndrome. Targeting specific components of these signaling pathways has been shown to be effective in preclinical studies with significant therapeutic impact. This book brings together current knowledge in cardiovascular cell signal transduction mechanisms, advances in novel therapeutic approaches to improve cardiac function, and discussion of future directions. Presented from a post-genomic perspective, this exciting book introduces important new ideas in cardiovascular systems biology. It is an invaluable reference for cardiology researchers and practitioners.

"During this thesis project we uncovered a new and reciprocal link between genetic progression of glioblastoma multiforme (GBM) and activation of coagulation system effectors, notably the tissue factor (TF) pathway. GBM is a highly aggressive (grade IV) astrocytic primary brain tumor affecting both adults and children. Florid angiogenesis, intravascular and systemic thrombosis, pseudopalisading necrosis surrounding occluded vessels and cellular invasion are cellular hallmarks of this disease, in which epidermal growth factor receptor (EGFR) and its mutant (EGFRvIII) play a prominent oncogenic role. We have observed a close parallel between the expression levels of EGFR (Classical subtype of GBM) and TF, the procoagulant receptor for clotting factor VIIa, while analyzing gene expression data of 202 patients represented in The Cancer Genome Atlas (TCGA). This link was further substantiated through our analyses of EGFRvIII expressing human GBM cell lines that revealed that oncogenic EGFRvIII upregulates the expression of TF, coagulation factor VII (FVII) and protease activated receptors 1 and 2 (PAR-1/2). Moreover, we observed that signals generated by the TF/VIIa complex cooperated with EGFRvIII to regulate angiogenic factors (VEGF, IL8). Interestingly, experiments performed in vivo suggest that GBM xenograft aggressiveness can be diminished with the use of either an anticoagulant or anti-signaling antibodies, targeting the corresponding TF functions which suggests that both components of TF activity (coagulation and signaling) are important in tumor progression. Moreover, selective targeting of the host (mouse) TF reveals its independent, albeit modest, role in glioma tumorigenesis. Lastly, we observed that amidst TF-induced procoagulant, inflammatory and angiogenic responses in vivo, dormant glioma cells acquire mutational and epigenetic changes that propel their tumorigenic conversion. Thus, coagulation system represents a functionally important element in the GBM microenvironment, a property that could potentially be targeted using traditional and new anticoagulants." --

Showcasing the expertise of top-tier specialists who contributed to the newly released guidelines for the care of thrombosis in cancer patients, this exciting guide was written and edited by members of the American Society of Clinical Oncology panel, (ASCO), on the prevention and treatment of cancer-associated thrombosis, among others, and provides

Systemic lupus erythematosus (SLE), commonly called lupus, is a chronic autoimmune disorder that can affect virtually any organ of the body. In lupus, the body's immune system, which normally functions to protect against foreign invaders, becomes hyperactive, forming antibodies that attack normal tissues and organs, including the

skin, joints, kidneys, brain, heart, lungs, and blood. Lupus is characterized by periods of illness, called flares, and periods of wellness or remission. Because its symptoms come and go and mimic those of other diseases, lupus is difficult to diagnose. There is no single laboratory test that can definitively prove that a person has the complex illness. To date, lupus has no known cause or cure. Early detection and treatment are the key to a better health outcome and can usually lessen the progression and severity of the disease. Anti-inflammatory drugs, antimalarials, and steroids (such as cortisone and others) are often used to treat lupus. Cytotoxic chemotherapies, like those used in the treatment of cancer, are also used to suppress the immune system in lupus patients. A new edition of this established and well-regarded reference combines basic science with clinical science to provide a translational medicine model. Systemic Lupus Erythematosus, Sixth Edition, is a useful reference for specialists in the diagnosis and management of patients with SLE, a tool for measurement of clinical activity for pharmaceutical development and basic research of the disease, and a reference work for hospital libraries. Completely updated, revised, and expanded with the most comprehensive and accessible reference on SLE for clinicians and scientists Full-color presentation throughout the book Provides the latest information available on diagnosis and treatment Incorporates an international panel of authors who are experts in their fields, with an emphasis on young, cutting-edge scientists and physicians
Atherosclerosis is the most significant cause of cardiovascular disease worldwide. Vascular biology is the key to understanding how atherosclerosis arises and operates. The ESC Textbook of Vascular Biology is a rich and clearly laid-out guide by leading European scientists providing comprehensive information on vascular physiology, disease, and research. The textbook covers molecular findings and novel targets within the speciality while also providing the basics of vascular biology and disease pathophysiology. It also covers the major changes in the diagnosis, prevention and treatment of atherosclerosis that have occurred in recent years, developments and recent breakthroughs in the field are specifically highlighted. The official publication of the ESC Working Group on Arthrosclerosis and Vascular Biology, this print edition comes with access to the online version on Oxford Medicine Online, for as long as the edition is published by Oxford University Press. By activating your unique access code, you can read and annotate the full text online, follow links from the references to primary research materials, and view, enlarge and download all the figures and tables. The textbook is also linked to the ESC's online learning platform (ESCel) and their core specialist training curriculum (ESC Core Curriculum). The textbook particularly appeals to vascular biologists, cardiologists, and other practising clinicians.
Chronic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, inflammatory bowel diseases, and others typically stimulate a systemic response of the entire body. This response has a uniform character in many diseases because common pathways are switched on. The uniform response regulates systemic energy and water provision. However, long-term application of this program leads to typical disease sequelae such as fatigue / depressive symptoms, sleep disturbances, anorexia, malnutrition, muscle wasting – cachexia, cachectic obesity, insulin resistance, dyslipidemia, alterations of steroid hormone axes, disturbances of the hypothalamic-pituitary-gonadal axis,

elevated sympathetic tone, hypertension, volume expansion, decreased parasympathetic tone, inflammation–related anemia, bone loss, hypercoagulability, circadian rhythms of symptoms, and disease exacerbation by stress . The Origin of Chronic Inflammatory Systemic Diseases and Their Sequelae demonstrates concepts of neuroendocrine immunology, energy and water regulation, and evolutionary medicine in order to show that the uniform response that regulates systemic energy and water provision, has been positively selected for acute physiological responses and short-lived disease states, but is a misguided program in chronic inflammatory diseases and aging. Offers a broad conceptual framework with a strong clinical link, written in an easy to grasp style and demonstrating the link to aging research Describes the important principles derived from basic immunology that are used to explain pathogenesis of chronic inflammatory systemic diseases with a focus on autoimmunity Defines the bioenergetics and energy regulation of the body explaining common response pathways typical for systemic inflammation Makes use of evolutionary medicine theory to demonstrate the uniformity of the systemic response Explains the appearance of typical disease sequelae on the basis of the three pillars: neuroendocrine immunology, energy regulation, and evolutionary medicine theory Contains color figures and tables that explain the field to newcomers Tissue factor (TF) is a 47 kDa transmembrane glycoprotein that complexes with activated factor VII (FVIIa) to initiate blood coagulation. Breast cancer tumors and cell lines that have high expression of TF appear to be aggressive and have high metastatic potentia. Formation of the TF-FVIIa complex induces signaling that leads to activation of p44/42 mitogen-activated protein kinase and protein kinase B (Akt) pathways and inhibition of apoptosis in breast cancer cells. The Akt-mammalian target of rapamycin (mTOR) pathway regulates cell growth and survival and plays a major role in the pathogenesis of breast cancer. Inhibition of mTOR has been shown to increase TF expression in some cell types which might increase tumor TF expression leading to enhanced TF-mediated signaling as well as an increased hypercoagulable state. Inhibition of mTOR, downstream of Akt, is a recent, emerging strategy in the treatment of breast cancer. In this proposal we test the hypothesis that the TF-VIIa signaling pathway interacts with the mTOR pathway to play a critical role in promoting dysregulated proliferation of breast cancer cells. In the present study, we show that formation of TF-FVIIa-FXa complex induces phosphorylation of mammalian target of rapamycin (mTOR) and p70 S6 kinase in a human breast cancer cell line, Adr-MCF-7. Activation of the mTOR pathway, which is probably mediated by PAR1 and/or PAR2, was associated with enhanced cell migration, a key step in the metastatic cascade. Inhibition of this pathway with the specific mTOR inhibitor, rapamycin, markedly decreased cell migration induced by formation of TF-FVIIa-FXa complex and modestly increased tumor cell TF expression. Targeting the TF-mediated cell signaling pathway along with mTOR inhibition might represent a novel strategy for the treatment of breast cancer.

Based on the most current evidence and best practices, Perioperative Medicine: Managing for Outcome, 2nd Edition, is an easy-to-follow, authoritative guide to achieving optimal outcomes in perioperative care. Written and edited by recognized authorities in anesthesiology and surgical critical care, this fully updated edition helps you think critically about complex, long-term issues surrounding the care of the surgical patient, providing decision trees that define strategies to enhance the medical outcome of care. Focuses on what anesthesiologists, surgeons, and intensivists need to know in order to improve outcomes through evidence- and outcome-based approaches. Provides practical guidance on potential risks to all major organ systems, the etiology of particular organ dysfunctions, preoperative and intraoperative risk factors, and perioperative protection strategies to minimize potential complications. Features a consistent chapter format - with even more color-coded algorithms, summary tables, and boxes – that enables you to quickly explore and determine the best management approaches. Includes six all-new chapters: Perioperative Fluid Management; Delirium and POCD; Role of Palliative Care/ICU; Value-Based Care: The UK Model; CFO Perspective on Value; Hospital to Home (Perioperative Transitions of Care) Discusses timely topics such as quality improvement, pay-for-performance, preexisting disease and comorbid conditions in anesthesiology, and the team-based model of care. Features two new editors, surgeon Clifford Ko, MD, and Perioperative Summit leader, Michael (Monty) Mythen, MD.

This book surveys healthy and diseased vascular systems in a multitude of model organisms and systems. It explores a plethora of functions, characteristics, and pathologies of the vascular system such as angiogenesis, fibroblast growth factor signaling, lymphangiogenesis, junctional signaling, the extracellular matrix, vascular permeability, leukocyte extravasation, axon guidance factors, the angiopoietin system, and chronic obstructive lung disease. Following a preface from leading researcher Dr. Holger Gerhardt, the text is divided into three sections- the first examining the development of the vascular system in a variety of contexts, the second delving into its homeostatic characteristics, and the third discussing its pathophysiologies. The sixteen chapters, which represent international clinical and research perspectives, highlight the importance of molecular and signaling pathways for translational basic science and clinical medicine. Additionally, the text explores new and exciting fields in vascular biology research. Comprehensive in both content and approach, Vascular Signaling in Health and Disease is ideal for graduate students, researchers, and clinicians interested in vascular biology, pneumology, and molecular biology.

This leading text reflects both the new direction and explosive growth of the field of hematology. Edited and written by practitioners who are the leaders in the field, the book covers basic scientific foundations of hematology while focusing on its clinical aspects. This edition has been thoroughly updated and includes ten new chapters on cellular biology, haploidentical transplantation, hematologic

manifestations of parasitic diseases, and more. The table of contents itself has been thoroughly revised to reflect the rapidly changing nature of the molecular and cellular areas of the specialty. Over 1,000 vivid images, now all presented in full color for the first time, include a collection of detailed photomicrographs in every chapter, selected by a hematopathology image consultant. What's more, this Expert Consult Premium Edition includes access to the complete contents of the book online, fully searchable and updated quarterly by Dr. Hoffman himself. - Publisher.

Introduction to Bioorganic Chemistry and Chemical Biology is the first textbook to blend modern tools of organic chemistry with concepts of biology, physiology, and medicine. With a focus on human cell biology and a problems-driven approach, the text explains the combinatorial architecture of biooligomers (genes, DNA, RNA, proteins, glycans, lipids, and terpenes) as the molecular engine for life. Accentuated by rich illustrations and mechanistic arrow pushing, organic chemistry is used to illuminate the central dogma of molecular biology. Introduction to Bioorganic Chemistry and Chemical Biology is appropriate for advanced undergraduate and graduate students in chemistry and molecular biology, as well as those going into medicine and pharmaceutical science.

Cancers of the central nervous system are among the most lethal of human neoplasms. They are recalcitrant to even intensive multimodality therapies that include surgery, radiotherapy, and chemotherapy. Moreover, especially in children, the consequences of these therapies can itself be devastating and involve serious cognitive and developmental disorders. It is small wonder that such cancers have come under the intense scrutiny of each of the subspecialties of clinical care and investigation as well as attracting some of the best basic research scientists. Their joint efforts are gradually peeling away the mysteries surrounding the genesis and progression of these tumors and inroads are being steadily made into understanding why they resist therapies. This makes it an especially opportune time to assemble some of the best investigators in the field to review the ‘‘state of the art’’ in the various arenas that comprise the assault on CNS tumors. The breadth of this effort by the clinical and basic neuro-oncology community is quite simply amazing. To a large extent, it evolves from the knowledge of the human genome and its regulation that has been hard won over the past two decades.

First published in 1943, Vitamins and Hormones is the longest-running serial published by Academic Press. In the early days of the Serial, the subjects of vitamins and hormones were quite distinct. The Editorial Board now reflects expertise in the field of hormone action, vitamin action, X-ray crystal structure, physiology, and enzyme mechanisms. Under the capable and qualified editorial leadership of Dr. Gerald Litwack, Vitamins and Hormones continues to publish cutting-edge reviews of interest to endocrinologists, biochemists, nutritionists, pharmacologists, cell biologists, and molecular biologists. Others interested in the structure and function of biologically active molecules like hormones and vitamins

will, as always, turn to this series for comprehensive reviews by leading contributors to this and related disciplines. Vitamins are organic substances not naturally produced by the body that are necessary in trace amounts for normal physiologic and metabolic functioning. Hormones are biochemical substances produced in cells and tissues that cause a specific biological change or activity to occur elsewhere in the body Study of both vitamins and hormones is essential to our understanding of physiology

Rationale: Tissue Factor (TF) is a transmembrane glycoprotein that canonically functions as the initiator of the coagulation cascade. Increased levels of TF have been associated with inflammatory airway diseases. Since lipopolysaccharide (LPS) is known to elicit and inflammatory response in airway epithelium, we hypothesized that airway epithelial cells release TF when exposed to LPS. Since TF aids in local wound healing, we also hypothesized that inhibition of TF would decrease NHBE growth. The specific aim of this work was to evaluate the effects of LPS exposure on TF production and release from airway epithelia and determine the signaling pathways involved. A secondary aim was to evaluate the effects of TF inhibition on NHBE growth. Methods: Normal human bronchial epithelial cells were grown in submerged cell culture and exposed to LPS as well as several intracellular signaling pathway agonist and inhibitors. Measurements: Tissue Factor mRNA and protein were measured in culture media and cell lysate by reverse-transcriptase polymerize chain reaction and enzyme-linked immunosorbent assay, respectively. Signaling pathways were evaluated using selective agonists and inhibitors. Main results: TF protein levels increased nearly two-fold in cell media after exposure to LPS (p

Now more than ever, thrombotic and thromboembolic disorders as well as related diseases such as malignancies, arteriosclerosis, diabetes mellitus, hypertension, and obesity are the leading causes of morbidity and mortality. They have become urgent medical problems with serious economic consequences in industrialized and devel- ing countries alike. At the same time, the impact of molecular biology and genetics on our understanding of thrombosis and hemostasis is rapidly growing stronger as well as our knowledge of regeneration and development of specific tissues, organs, and embryos. Researchers are also constantly learning more about cardiovascular diseases as well as regulatory mechanisms for various intrinsic and extrinsic stimuli in viable tissues. In this volume, our intention has been to present the latest relevant information in molecular biology and genetics as well as the clinical implications of a better understanding of pathophysiology, novel diagnostic methodologies, and therapeutic applications for new methods of prevention in thrombosis/hemostasis and related disorders, including atherosclerosis. The dramatic advances in knowledge of thrombosis/hemostasis and vascular biology since the first publication of Recent Advances in Thrombosis and Fibrinolysis, edited with Japanese colleagues, in 1991, have required extensive revision in order to highlight and review recent progress in the field. The editors also gratefully welcome the seven distinguished

non Japanese authors, who, with their valuable contributions on subjects beyond the coverage by Japanese authors, have made this new edition truly international.

Hepatic fibrosis and cirrhosis are the common endpoint of a variety of liver diseases and represent a major global health burden. The current model for hepatic fibrosis development is that progressive injurious stimuli lead to dysregulation of extracellular matrix (ECM) turnover. Activation of the hepatic stellate cell (HSC) has been identified as the key cellular event resulting in the accumulation of extracellular matrix (Friedman 2008) and therefore there is considerable interest in factors that regulate HSC activation and collagen expression. There is a strong linkage between inflammation, coagulation and fibrosis (Tacke, Luedde et al. 2009). One proposed mechanism for this linkage is signalling by coagulation factors through their cellular receptors protease-activated receptors (PARs) to activate stellate cells (Anstee, Wright et al. 2009).This thesis has explored the role of PAR-1, PAR-2 and the cytoplasmic domain of tissue factor in the development of hepatic fibrosis. The close relationship between the coagulation cascade and the inflammatory response led to the hypothesis that coagulation factors and their receptors may play an important role in hepatic fibrogenesis. In order to mimic human liver disease processes, a mouse model was studied using carbon tetrachloride administration to generate liver fibrosis. Mice with deletion of the PAR-1 gene, PAR-2 gene, with deletion of the cytoplasmic domain of TF and with dual deletion of PAR-2 gene and TF cytoplasmic domain were individually studied and compared to wildtype. Common fibrosis endpoints were studied in vivo. In vitro experiments were performed with a line of human hepatic stellate cells. Initial experiments demonstrate PAR-1 deficiency protects against liver fibrosis with reduced histological fibrosis, hydroxyproline content, TGF [beta] gene and protein expression seen. This adds evidence to support the view that PAR-1 is involved in hepatic fibrogenesis. PAR-2 deficiency was also found to afford protection from hepatic fibrosis. PAR-1 and PAR-2 activation also induce a profibrogenic phenotype in human hepatic stellate cells in vitro adding weight to the evidence these receptors are important in fibrosis development. In addition to its important role in haemostasis, tissue factor is increasingly recognised as a signalling receptor in a number of non coagulant roles. Deletion of the cytoplasmic domain of tissue factor led to reduction in profibrogenic cytokines, HSC activation and reduced macrophage recruitment and activation which supports the reduced hepatic fibrosis observed. Macrophages play a pivotal role as regulators of fibrosis. They are profibrogenic in fibrosis development but also play a role and are necessary for fibrosis resolution. The reduced macrophage recruitment and activation observed in the PAR-2 and mice with deletion of the cytoplasmic domain of tissue factor may in part explain the amelioration of hepatic fibrosis seen in these mice. A single treatment to completely ameliorate fibrosis may be difficult to achieve given the complex and multiple pathways involved in ECM

remodelling. Understanding the mechanisms of fibrosis provide a platform to develop antifibrotic therapies. This thesis has provided further insight into the role of PAR-1 and PAR-2 and the cytoplasmic domain of tissue factor in hepatic fibrogenesis. Both PAR-1 and PAR-2 antagonists are being developed and may represent a novel therapeutic approach in preventing fibrosis in patients with liver disease. The cytoplasmic domain of tissue factor is an attractive therapeutic target as the coagulation is not affected in the host, particularly important in patients with cirrhosis.

G Protein-Coupled Receptors in Immune Response and Regulation, Volume 136 presents emerging concepts related to the role of GPCRs in immune response and regulation. Users will find updated chapters on a variety of topics, including Beta-adrenergic signaling in the onset and progression of asthma, the Emerging roles of Regulators of G protein signaling (RGS) proteins in the immune system, information on Kinin receptors in immune response and pathogenic infections, and sections on GPCR signaling in C. elegans and its implications in immune response, GPCR Kinases in Inflammatory response and signaling, and GRK2 in Inflammation: Regulation of T cell receptors and IgE signaling. Chapters in this book discuss not only the well-known aspects of GPCR signaling in immunology, but also presents many emerging paradigms that have not yet been reported in classical textbooks. Each chapter presents a forward-looking discussion, providing a glimpse of the tremendous potential associated with the specific receptor systems discussed. Brings together contributions from leading experts in the area of GPCR biology Discusses current paradigms and the future potential of understanding GPCR signaling in immune response and regulation Presents the first of its kind book to focus on specific GPCR systems in various aspects of immunology, all brought together in one volume

Issues in Blood and Circulatory Pathology / 2013 Edition is a ScholarlyEditions™ book that delivers timely, authoritative, and comprehensive information about Hemophilia. The editors have built Issues in Blood and Circulatory Pathology: 2013 Edition on the vast information databases of ScholarlyNews.™ You can expect the information about Hemophilia in this book to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Issues in Blood and Circulatory Pathology: 2013 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/.

This volume focuses on the relationship between the regulation of signal transduction and disease mechanisms, and discusses how the dysregulation of intracellular signals cause diseases, cell death, carcinogenesis, and other disorders. Growth, survival, transformation, and metabolic activities at the cellular

level are regulated by various intracellular signal transduction pathways. Sources that stimulate intracellular signals include intracellular stresses and signal regulators/modulators, as well as extracellular growth factors. Recent studies on signal transduction analysis using animal and human cell lines have revealed how the intracellular signals are regulated and why their dysregulation leads to pathological states such as tumorigenesis, metabolic diseases, cell death, and so on. This book highlights several important key molecules and intracellular signaling pathways such as microRNA, the TGF-beta signaling pathway, the Wnt signaling pathway and MET signaling pathway as topical and highly relevant issues in human cell research related to signal transduction. In addition to assessing the pathogenic role of these signaling pathways, it focuses on the molecular design of small molecule regulators/inhibitors of said pathways, one of the most important approaches in this area. This book offers a valuable guide, helping not only research scientists but also clinicians to understand how the dysregulation of intracellular signals leads to diseases.

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.

Signaling Pathways in Liver Diseases, Third Edition again provides hepatologists and hepatology researchers with an expert overview of the complex and novel cellular/extracellular signaling pathways in the liver, and their role in liver diseases. The last few years have seen a great number of developments in this field, which in turn have led to new opportunities for innovative treatments; however, the intricacy of these pathways and their interactions continue to provide a real challenge for clinicians. This outstanding book compiles the emerging knowledge into a single expert resource, cataloguing and organizing it into an accessible and understandable format. With increased focus on the comprehension of cellular mechanisms involved in steatohepatitis, cirrhosis, and liver tumors, which has led to changes in the management of these diseases, this new edition also sees the introduction of exciting new chapters on key emerging areas such as: Autophagy Notch Pathway P13K/PTEN

Signaling in Liver Diseases Sirtuins Hepcidin and Iron Epigenetic Regulation of Hepatic Stellate Cells and Liver Fibrosis Oxidative Stress and Signaling in the Liver. Professors Dufour and Clavien have assembled an all-star cast of chapter authors, each of whom has provided clear and appropriate illustrations to reinforce the text, with a key points box offering a concise and handy summary. Self-assessment questions and answers allow the reader to test their own knowledge. Signaling Pathways in Liver Disease, Third Edition is the perfect educational and reference tool to bridge the information exchange between the laboratory, the clinical ward, and the operating room, and an essential tool for the modern-day hepatologist.

Since publication of the First Edition in 1982, Hemostasis and Thrombosis has established itself as the pre-eminent book in the field of coagulation disorders. No other book is as inclusive in scope, with coverage of the field from the standpoint of both basic scientists and clinicians. This comprehensive resource details the essentials of bleeding and thrombotic disorders and the management of patients with these and related problems, and delivers the most up-to-date information on normal biochemistry and function of platelets or endothelial cells, as well as in-depth discussions of the pharmacology of anticoagulant, fibrinolytic, and hemostatic drugs. NEW to the Sixth Edition... • A new team of editors, each a leader in his field, assures you of fresh, authoritative perspectives. • Full color throughout • A companion website that offers full text online and an image bank. • A new introductory section of chapters on basic sciences as related to the field • Entirely new section on Hemostatic and Thrombotic Disorders Associated with Systemic Conditions includes material on pediatric patients, women's health issues, cancer, sickle cell disease, and other groups. • Overview chapters preceding each section address broad topics of general importance. This is the tablet version which does not include access to the supplemental content mentioned in the text.

The Update compiles the most recent developments in experimental and clinical research and practice in one comprehensive reference book. The chapters are written by well recognized experts in the field of intensive care and emergency medicine. It is addressed to everyone involved in internal medicine, anesthesia, surgery, pediatrics, intensive care and emergency medicine.

Tissue Factor (TF) is the cell surface receptor that activates coagulation by binding the serine protease coagulation factor Vila (Vila). The activation of the coagulation cascade leads to thrombin generation, fibrin formation and platelet activation which together aide tumor growth and metastasis. While the role of TF in metastasis through thrombin pathways is well established, evidence is increasing that TF may drive tumor development dependent on cell signaling pathways. A newly developed breast cancer model with a tetracycline regulated TF expression cassette shows TF enhances breast cancer tumor growth. This model will be useful to mechanisms by which TF enhances breast cancer progresssion. In this grant, we further evaluated the role of the TF cytoplasmic domain in breast cancer progresssion. We established tumor prone transgenic models in the C57B1/6 background and compared tumor development in TF cytoplasmic domain deleted mice with wild-type animals. Consistent with a recent report, we found that the C57B116 03-TAg model is unsuitable for studying breast cancer, because mice developed debilitating chondromatosis prior to the appearance of breast tumors. Experiments are ongoing to evaluate the role of the TF cytoplasmic

domain in breast cancer development and progression to metastatic disease in the PyMT model.

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