Signal Transduction In Mast Cells And Basophils

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Regulation of Fc[epsilon]RI Signal Transduction by the Mast Cell Function-associated Antigen (MAFA) Springer Science & Business Media
The editors of Mast Cell Biology, Drs. Gilfillan

and Metcalfe, have enlisted an outstanding group of investigators to discuss the emerging concepts in mast cell biology with respect to development of these cells, their homeostasis, their activation, as well as their roles in maintaining health on the one hand and on the other, their participation in disease.

Functional Programs, Signal Transduction, and Regulation by Cytokines Springer Science & Business Media

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.

Mast Cells and Basophils Springer Science & Business Media

Signal Transduction in Mast Cells and BasophilsSpringer Science & Business Media

Using Mast Cells to Probe Regulation of Plasma Membrane Heterogeneity, Membrane Trafficking and Host-pathogen Interactions Academic Press

Focussing on the molecular mechanisms that govern mast cell and basophil cell biology and function, this book also provides a comprehensive summary of the field of signal transduction, giving insights into areas that have therapeutic potential. It gives detailed insights into mast cell and basophil growth and development, their activation by allergens, including details of receptor activation and downstream events,

and the regulators of morphology and degranulation. The metabolic pathways involved in prostaglandin and leukotriene production are discussed as is the role of transcription factors in mast cell growth and cytokine production. Written by leaders in the field, this volume will provide readers with an up-to-date account of a topic whose rapid progress makes conventional information gathering difficult.

IgE Receptor (FcεRI) Function in Mast Cells and Basophils

Academic Press

The IgE-mediated allergic response is initiated by antigen-induced aggregation of IgE-Fc & egr;RI receptor complexes on the surface of mast cells and basophils. Evidence exists that conformational constraints of crosslinked receptors modulate the efficacy of signal transduction. To investigate how receptor-receptor distances of crosslinked receptors affect the competency of signal transduction, we have synthesized and extensively characterized dinitrophenyl(DNP)-modified, rigid, double stranded DNA oligomers of 13, 15, 20, and 30 base pairs. All of these bivalent ligands effectively bind and crosslink IgE in solution and cell-bound IgE with similar affinities in the nanomolar range. The 13mer (DNA length of 44 A) and 15mer (51 A) effectively induce cellular degranulation, whereas the 20mer (68

A) is less effective, and the 30mer (102 A) is ineffective. Although the magnitude of the degranulation responses for optimal doses of these ligands is twenty-five percent or less of that induced by multivalent antigen, all ligands stimulate Fc & egr;RI beta, LAT, and Syk phosphorylation similar to multivalent antigen. The magnitude of the calcium responses induced by these ligands is small. These results are consistent with the hypothesis that structural or orientational constraints on IgE-Fc & egr;RI aggregates by these DNP-DNA ligands prevent robust activation of signaling immediately downstream of tyrosine phosphorylation, and limits, to a lesser extent, signaling events more proximal to receptor aggregation. Interestingly, the concentration of ligand that induces maximum cellular activation for the DNP-DNA ligands (50--100 nM) is significantly higher than that which corresponds to maximum receptor crosslinking (5--10 nM). We present evidence to suggest that these ligands form cyclic aggregates, preferentially cyclic dimers, at concentrations where crosslinking is maximal and, although these types of aggregates do not cause any downstream activation, they stimulate early tyrosine phosphorylation events in a length-dependent manner.

Proceedings of the Fourth International Workshop on Signal Transduction in the Activation and Development of Mast Cells and Basophils CRC Press Signaling through antigen receptor initiates a complex series of events resulting in the activation of genes that regulate the development, proliferation and differentiation of lymphocytes. During the past few years, rapid progress has been made in understanding the molecular basis of signaling pathways mediated by antigen and cytokine receptors. These pathways involve protein tyrosine kinases which are coupled to downstream regulatory molecules, including small guanine nucleotide binding proteins (e. g. p21'OS), serine threonine kinases (e. g. , members of the ERK family), and a large group of transcription factors. More recently, there have been breakthroughs in elucidating the genetic defects underlying three X-linked primary immunodeficiency diseases in humans. This volume surveys aspects of these rapidly developing areas of research. The book is divided into 5 different sections. Section I deals with signaling pathways in B lymphocytes. It includes a contemporary assessment of B cell antigen receptor structures, and discussion of the role of Ig-a/Ig-B

polypeptides in linking the antigen receptor to intracellular signal transduction pathways. The role of accessory molecules in the regulation of signaling by the B cell antigen receptor is also considered. Section II adopts a similar approach to the analysis of the antigen receptor on T lymphocytes. The importance of specialized signaling motifs in the CD3 polypeptides, mechanisms whereby these motifs may interact with the lymphocyte-specific protein tyrosine kinases, and the downstream consequences of these interactions are reviewed. In addition, the role of antigen-induced apoptosis in the generation of immunological tolerance is discussed.

P21-activated Kinase 2 Springer Science & Business Media

Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various

systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.
Studies on the Regulation of Mast Cell Signal Transduction and Effector Functions with Focus on the Role of the PI3K Pathway and the Function of PKC Isoforms Uppsala Universitet
Upon immune cell activation with antigen, growth factors, or other stimuli, the cytoskeleton undergoes extensive reorganization to elicit a cellular response. The cytoskeleton, consisting of microtubules and actin, is a highly organized network regulated by various signal transduction pathways. Specifically, Rho GTPases (RhoA, Rac1 and Cdc42) regulate the cytoskeleton, albeit through different pathways. p21-activated kinases (Pak) are serine/threonine kinases directly bound and activated by Rac1 and Cdc42. There are 6 Pak isoforms separated into 2 groups (groups I&II) in this family of kinases, and only recently have isoform specificities been identified by the use of genetically-engineered mouse models deleted for individual isoforms. In this dissertation we sought to identify if differences exist between Pak1 and Pak2 in immune function, in particular how they differ in regulation of the cytoskeleton reorganization required for immune cell function. Using primary bone marrow derived

mast cells, an immune cell type responsible for anaphylaxis and allergic responses, we identified that Pak1 and Pak2 function in opposing manners with regard to antigen-induced degranulation. We identified key mechanisms involved in Pak2's negative regulation of mast cell degranulation. These findings identify potential therapeutic side effects with the use of recently developed pan-Pak inhibitors in the clinic. Pak2 deletion was additionally investigated in an in vivo mouse model. We discovered that Pak2 is critical for homeostasis and survival in an adult animal. We identified macrothrombocytopenia, cause by an increase in circulating platelet half-life and clearance, as well as other defects in Pak2 -deleted adult mice. Therefore, we evaluated the maturation process of the platelet-producing megakaryocyte and found that Pak2 -null megakaryocytes have altered microtubules, proplatelet extensions and polyploidization. Various signaling pathways that regulate these functions were also suppressed with Pak2 deletion. Together, our findings identify Pak2 as the predominant isoform in hematopoietic compartment and immune cells, and suggest further analysis of critical immune cell side effects, which could occur in the patient with the use of pan-Pak inhibitors in the treatment of various cancers.

Molecular Basis of Signal Transduction Karger Medical and Scientific Publishers
Protein Kinases in Blood Cell Function provides an up-to-date, comprehensive review of protein kinases in various types of blood cell function. Blood cells discussed include T lymphocytes, B lymphocytes, platelets, mast cells, neutrophils, and macrophages. The book will interest pathologists, physiologists, oncologists, hematologists, leukocyte biologists, and immunologists. It will also benefit anyone interested in signal transduction and blood cell functions such as host defense, hemostasis, and immune response.
Functional role of Bcl10 and Malt1 in signal transduction from the FceRI [Fc-epsilon-RI] in mast cells and the LPA receptor in murine embryonic fibroblasts Frontiers Media SA
This book provides a comprehensive overview on current histamine and histamine receptor research in context of human health and disease and reflect the multidisciplinary nature of the field. While the editors realize that it is almost impossible to cover the field completely within the constraints of a single HEP volume, nonetheless, all important aspects will be covered in one way or the other. An overarching introductory chapter will link the individual chapters and provide an overview on the field. This chapter will

also link the book to the previous HEP volume on histamine receptors and the recent HEP volume on the pharmacology of itch. Great attention will be paid to complementation of existing literature while avoiding undue duplication. The book will cover new methods for analysis of histamine and histamine metabolites, development of methods for histamine receptor analysis, signal transduction, histamine release, regulation of immune cells by histamine, histamine metabolism and associated diseases, regulation of major organ systems by histamine and development of new drugs and experimental tools for the study of histamine receptors.

Mechanisms of Lymphocyte Activation and Immune Regulation V BoD – Books on Demand

Mast cell activation is a central eventÂ in development ofÂ allergic disorders and contribute to pathogenesis of many other inflammatory and neoplastic conditions.Â Improved understanding of normal and pathologic mechanisms regulatingÂ mast cellÂ differentiation, survival and activationÂ mayÂ thereforeÂ lead toÂ development ofÂ new therapies forÂ theseÂ disorders.Â A number ofÂ important breakthroughs have recently been realizedÂ inÂ our understanding of mastocytosis,Â a disorder characterized

byÂ pathologic mast cell growth and activation.Â Significant advancesÂ were made in such key areas asÂ uncovering geneticÂ basis of disease,Â establishment of objective diagnostic criteria, and emergence of novel treatment concepts based onÂ its molecular pathogenesis.Â This issue of the Clinics brings together many of the experts who made these breakthroughs in mast cell biology and mastocytosis possible.

Functional role of Bcl10 and Malt1 in signal transduction from the FcεRI [Fc-epsilon-RI] in mast cells and the LPA receptor in murine embryonic fibroblasts Springer

This book uniquely relates the broad impact of signal transduction research on the understanding and treatment of human disease. There have been significant advances in the area of signaling in disease processes, yet no resource presently connects these advances with understanding of disease processes and applications for novel therapeutics. Given the emphasis on translational research and biological relevance in biotechnology, and, conversely, the importance of molecular approaches for clinical research, it is evident that a single resource bridging signaling research and human disease will be invaluable.

Signal Transduction

in Lung Cells CRC Press
This issue of Immunology and Allergy Clinics, edited by Dr. Cem Akin, is devoted to Mastocytosis. Articles in this issue include Human Mast Cell Signal Transduction; Mast cell tryptase role in homeostasis and coagulation; Mastocytosis: Current Classification and Diagnostic criteria; Epidemiology, risk factors and prognosis of mastocytosis; Mast cell sarcoma: Clinical management; Molecular defects in mastocytosis: c-kit mutations and beyond; Flow cytometry in mastocytosis: Utility as a diagnostic and prognostic tool; Morphology of mastocytosis with special reference to immunophenotypical aberrancies; CD30 expression in mastocytosis; Extramedullary mastocytosis: Pathologic aspects; Bone involvement and osteoporosis in mastocytosis; Drug allergy in mastocytosis; Eosinophilia in mastocytosis; Venom allergy and mastocytosis; Skin disease in mastocytosis; Treatment of advanced mastocytosis; Treatment strategies of mediator related symptoms in mastocytosis; and Neuro and psychological involvement in Mastocytosis.

Proceedings of the Fourth International Workshop on Signal Transduction in the Activation and

Development of Mast Cells and Basophils Springer Science & Business Media
This book looks in detail at human mast cells. It includes a review of previous and current ultrastructural studies, whereby the latter are illustrated with numerous high-quality electron micrographs obtained from a large number of structural and functional experiments using highly purified isolated human lung mast cells. Specifically, the book provides criteria for the identification of human mast cells, discusses the unique role in mast cell function of granules and lipid bodies, describes the ultrastructural anatomy of two release reactions - i.e., anaphylactic degranulation and piecemeal degranulation - and defines the recovery, cyclical and maturational properties of human mast cells. All of these new morphological-biochemical and functional studies are correlated with the author's wide experience in the visual properties of human mast cells as seen in biopsy material obtained from a diagnostic ultrastructural pathology service.
The MRGPRX2-dependent Pseudo-allergic/neurogenic Route in Human Skin Mast Cells Springer Science & Business Media
In this book, the editors have focused on the roles of mast cells in allergic diseases and

discuss the future direction of discovering drugs. Another implication of this book is to understand mast cells at the system level. System biology is a research category to understand biology at the system level by examining the structure and dynamics of cellular and organismal functions, rather than the characteristics of isolated parts of a cell or organism.

Signal Transduction in Mast Cell Migration Elsevier Health Sciences

Mast Cells and Basophils will be essential reading for immunologists, biochemists and medical researchers. Detailed chapters cover all aspects of mast cell and basophil research, from cell development, proteases, histamine, cysteinyl leukotrienes, physiology and pathology to the role of these cells in health and disease. Chapters also discuss the clinical implications of histamine receptor antagonists.

The Signal Transduction of Neurotensin Stimulated Rat Mast Cell Histamine Release

Signal Transduction in Mast Cells and Basophils

Cells of the immune system have many unique functions, but underlying similarities in signaling mechanisms and pathways make a well-defined model system useful. We utilize RBL mast cells to probe a variety of questions pertinent to immune cell function and

infection. Mast cells serve as innate immune responders as well as the mediators of allergic disease. A major signaling cascade in mast cells is initiated by multivalent antigen crosslinking of immunoglobulin E (IgE)-Fc[epsilon]RI receptor complexes. Membrane reorganization and signal transduction involving multiple players leads to Ca2+ mobilization and protein kinase C activation that ultimately triggers the release of preformed mediators from secretory lysosomes and, additionally, to outward trafficking of recycling endosomes (RE). The first study investigates the dynamic lipid environment surrounding crosslinked IgE-Fc[epsilon]RI complexes. By isolating detergent-resistant membranes and performing detailed mass spectrometry analysis, cytoskeletal interactions are found to be important for regulating membrane lipid reorganization resulting from antigen stimulation. Next, we characterized the molecular basis of sphingosine inhibition of cell function. We find that sphingosine derivatives electrostatically interfere with phosphoinositide-dependent membrane processes, including both Ca2+ mobilization and exocytic processes such as degranulation and RE outward trafficking. The function and regulation of RE trafficking in

immune cells, especially as it pertains to cytokine secretion, is of great interest. We provide evidence, by immunofluorescence microscopy and cytokine secretion assays, that mast cells secrete both IL-4 and TNF[alpha] in a manner that is consistent with a role for RE in their secretion. The dynamic trafficking of RE in RBL mast cells makes them likely candidates in many processes, including interactions with pathogens. We provide strong evidence for a role for RE in the formation of the parasitophorous vacuole (PV) of the obligate intracellular parasite, Toxoplasma gondii. In addition, we find that Toxoplasma gondii infection of mast cells results in suppression of IgE-Fc[epsilon]RI signaling by interfering with the activation of phospholipase C[gamma]. Colllectively, these studies show RBL mast cells as a versatile model of cellular immune function in both health and disease.

Signal Transduction in Mast Cells and Basophils Birkhäuser The ability of pathogens, such as parasites, bacteria, fungi and viruses to invade, persist and adapt in both invertebrate and vertebrate hosts is multifactorial and depends on both pathogen and host fitness. Communication between a pathogen and its host relies on a wide and dynamic array of molecular interactions. Through

this constant communication most pathogens evolved to be relatively benign, whereas killing of its host by a pathogen represents a failure to adapt. Pathogens are lethal to their host when their interaction has not been long enough for adaptation. Evolution has selected conserved immune receptors that recognize signature patterns of pathogens as non-self elements and initiate host innate responses aimed at eradicating infection. Conversely, pathogens evolved mechanisms to evade immune recognition and subvert cytokine secretion in order to survive, replicate and cause disease. The cell signaling machinery is a critical component of the immune system that relays information from the receptors to the nucleus where transcription of key immune genes is activated. Host cells have developed signal transduction systems to maintain homeostasis with pathogens. Most cellular processes and cell signaling pathways are tightly regulated by protein phosphorylation in which protein kinases are key protagonists. Pathogens have developed multiple mechanisms to subvert important signal transduction pathways such as the mitogen activated protein kinase (MAPK) and the nuclear factor kB (NF-kB) pathways. Pathogens also secrete effectors that manipulate actin cytoskeleton and its

regulators, hijack cell cycle machinery and alter vesicular trafficking. This research topic focuses on the cellular signaling mechanisms that are essential for host immunity and their subversion by pathogens. Contemporary and Emerging Topics W B Saunders Company Plasma membrane compartmentalization and differential intracellular targeting have both been implicated as mechanisms underlying constitutive membrane heterogeneity and cell reorganization upon stimulation. We investigated the involvement of both mechanisms in mast cell signaling by using a novel antigen presenting strategy. Micrometer-size patterned lipid bilayers containing haptenated lipids are used to control the location of IgE-receptor clusters and enable direct visualization of structural reorganization of membrane bound cellular components as well as targeting of intracellular events. Subsequent to this concentration of the mast cell receptors for IgE (FcepsilonRI) and colocalized tyrosine phosphorylation activity, Lyn kinase and other lipidated GFP-markers anchored to the inner leaflet of the plasma membrane redistribute selectively with the receptor clusters in a process that depends on actin polymerization. These observations at physiological

conditions provide important evidence for dynamic lipid-mediated membrane compartmentalization. In addition, we found that release of individual secretory lysosomes occurs toward the cell-substrate interface but are spatially segregated from the patterned, hapten-clustered receptors and early signaling complexes, revealing polarized but not locally targeted secretion. Targeting of secretory lysosomes evolves with time and becomes more directional towards the clustered receptors, possibly reflecting functional roles of such organelles in immediate hypersensitive reaction distinct from late phase reactions. In contrast, stimulated outward trafficking of recycling endosomes is rapidly targeted towards the initial stimulus. Taken together, stimulating cells using patterned surfaces allows systematic examination of spatially regulated signal transduction and provides unique insights into cell membrane structural organization.

The Role of Tyrosine Kinases in Signal Transduction Mechanisms Utilised by Human Lung Mast Cells and Basophils John Wiley & Sons

Signal Transduction during Biomembrane Fusion begins with three review articles that put the problem of signal transduction and biomembrane fusion into a general

perspective. Each subsequent chapter begins with an introduction which reviews past work on a specific biological system. The authors' current research is then detailed. The chapters conclude with final comments wherein the contributors express viewpoints about the general significance and progression of their work. This book comprises 12 chapters, with the first focusing on signal transduction during biomembrane fusion. The succeeding chapters then discuss the ""focal membrane fusion"" model; osmotic phenomena in membrane fusion; cell signaling and regulation of exocytosis at fertilization of the egg; and signal transduction during exocytosis in mast cells. Other chapters cover protein kinase c and granule membrane fusion; GTP-binding proteins and formation of secretory vesicles; and signal transduction during phagocytosis. The remaining chapters discuss calcium signal transduction pathway and myoblast fusion; phospholipid metabolism during calcium-regulated myoblast fusion; protein kinase c, membrane protein phosphorylation, and calcium influx in chick embryo skeletal myoblast fusion; and signal transduction and cell fusion in dictyostelium. This book will be of interest to practitioners in the fields of neurobiology, zoology, and the biological sciences.

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