CHAPTER 1

MAST CELL BIOLOGY: Introduction and Overview

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Abstract: In recent years, the field of mast cell biology has expanded well beyond the boundaries of atopic disorders and anaphylaxis, on which it has been historically focused. The biochemical and signaling events responsible for the development and regulation of mast cells has been increasingly studied, aided in large part by novel breakthroughs in laboratory techniques used to study these cells. The result of these studies has been a more comprehensive definition of mast cells that includes added insights to their overall biology as well as the various disease states that can now be traced to defects in mast cells. This introductory chapter outlines and highlights the various topics of mast cell biology that will be discussed in further detail in subsequent chapters.

INTRODUCTION

Mast cells are cells of hematopoietic origin which have gained notoriety over the years for their role as central players in atopic disorders and anaphylaxis. Indeed, it has been in this context that much of the research in this field has been conducted. It is only recently that their role in other aspects of health and disease has been fully appreciated. The manifestations of mast cell-driven disease are considered to be a consequence of an inappropriate activation of mast cell immune responses which have evolved to protect the body against a host of pathogens and perhaps toxins. The biochemical processes regulating mast cell development and mast cell activation have been extensively investigated and comprehensively reviewed in recent years. Hence, rather than reviewing these topics at length, in this work we have opted to focus on the emerging concepts in mast cell biology

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with regards not only to mast cell development and activation, but also on the newly defined roles of mast cells in health and disease. To accomplish this goal, we have solicited contributions from recognized experts in the field of mast cell biology who are focusing on these topics. The scope of this effort cannot be all encompassing and accordingly, not all recent contributions to the field of mast cell biology can be covered. The lack of citation of specific studies thus does not imply that they are of lesser merit or impact.

To set the stage for the more in depth discussions that follow, we begin by presenting a brief overview of mast cell biology in general, in which we indicate those topics that will be elaborated upon in subsequent chapters.

MAST CELL GROWTH, DEVELOPMENT AND SURVIVAL

Mast cells, at least in the human, develop from $CD34^+/CD117^+$ pluripotent progenitor cells originating in the bone marrow.[1] The progression of these cells to fully mature mast cells is dependent on KIT activation which occurs as a consequence of stem cell factor (SCF)-induced KIT dimerization and auto-phosphorylation. Hence, $Kit^{W/W\text{-}v}$ and $Kit^{W\text{-}sh/W\text{-}sh}$ mice in which surface expression of KIT, or KIT catalytic activity, is defective, have substantially reduced mast cell numbers.[2] Nevertheless, whereas human mast cells in culture require SCF for growth, mouse mast cell growth and expansion from bone marrow progenitors can be maintained by IL-3 in the absence of SCF.[1]

In both the mouse and human, committed bone marrow mast cell progenitors are released into the bloodstream from where they subsequently migrate into the peripheral tissues, during which time they mature and become terminally differentiated under the influence of cytokines within the surrounding milieu.[3] As discussed by Jenny Hallgren and Michael F Gurish in Chapter 2,[4] the migration of mast cell progenitors appears to be controlled in a tissue specific manner. They describe, for example, that basal trafficking of mast cell progenitors into the intestine, a process regulated by dendritic cells expressing the transcriptional regulatory protein, T-bet, requires that $\alpha4\beta7$ integrin and the chemokine receptor, CXCR2, be expressed on the surface of the mast cell progenitors and that MAdCAM-1 and VCAM-1 be expressed on the intestinal endothelium. In contrast, the marked recruitment of committed mast cell progenitors to the lung, observed with the onset of pulmonary allergic inflammation, requires the expression of the $\alpha4\beta7$ and $\alpha4\beta1$ integrins on the mast cell progenitors and associated expression of VCAM-1 on the endothelium, as regulated by CXCR2. Full recruitment however requires activation of CCR2 pathways following binding of CCL2. Such migration of mast cell progenitors from the vasculature into the peripheral tissues is increased under inflammatory conditions, thus providing an explanation for the increased mast cell burden observed at sites of inflammation.[4]

Terminally differentiated, tissue-resident mast cells are long lived, a feature, at least in the human, that is dependent upon the continued presence of SCF. Accordingly, inhibition of KIT catalytic activity by tyrosine kinase inhibitors induces human mast cell apoptosis.[5] As discussed by Maria Ekoff and Gunnar Nilsson in Chapter 4,[6] the Bcl-2 family of proteins are key regulators of such mast cell homeostasis through balancing mast cell survival and apoptosis. They further explain that apoptosis is regulated by both extrinsic pathways and intrinsic pathways which respond to stress from SCF deprivation, DNA damage and other intracellular stimuli and that these pathways involve caspase activation. Extrinsic apoptotic signals are transmitted through death receptors belonging