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Review

Mast cell plasticity and sphingosine-1-phosphate in immunity, inflammation and cancer☆

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ABSTRACT

Mast cells (MC) are found in all vascularized tissues at homeostasis and, until recently, were viewed only as effector cells of allergic reactions via degranulation, the canonical process through which MC release mediators, including histamine and pre-formed proteases and cytokines such as TNF. Cross-linking of IgE bound to surface high affinity receptors for IgE (FcεRI) by a specific antigen (Ag) triggers signaling events leading to degranulation. We and others have reported the concomitant production and export of an influential multifaceted sphingolipid mediator, sphingosine-1-phosphate (S1P) transported outside of MC by ATP-binding cassettes (ABC) transporters, i.e., independently of degranulation. Indeed, the MC horizon expanded by the discovery of their unique ability to selectively release mediators depending upon the stimulus and receptors involved. Aside from degranulation and transporter usage, MC are also endowed with piecemeal degranulation, a slower process during which mediator release occurs with minor morphological changes. The broad spectrum of pro- and anti-inflammatory bioactive substances MC produce and release, their amounts and delivery pace render these cells bona fide fine-tuners of the immune response. In this viewpoint article, MC developmental, phenotypic and functional plasticity, its modulation by microRNAs and its relevance to immunity, inflammation and cancer will be discussed.

1. MC plasticity in development and maturation

1.1. Mastopoiesis: General principles

MC rise from bone marrow-derived hematopoietic stem cells and circulate as progenitors in steady-state conditions. MC precursors transmigrate into tissues where they locally undergo differentiation and maturation, including the acquisition of granules in their cytoplasm, where many preformed mediators are harbored. MC anatomical distribution close to blood vessels at the interface of host and environmental antigens, allergens and pathogens underlines their premier sensor functions, further supported by their ability to release an array of preformed mediators upon activation via antigen and FcεRI or IgG-dependent mechanisms, Toll-like receptors as well as receptors to many endogenous peptides and proteins (Gilfillan and Tkaczyk, 2006). Certain stimuli prompt tissue-resident MC to re-acquire the ability to proliferate, suggesting the possibility for these cells to de-differentiate (Galli et al., 2011; Ryan et al., 2007; Kanakura et al., 1988; Dvorak et al., 1988; Levi-Schaffer and Shalit, 1993). Circulating agranular MC progenitors (MCp) are recruited in inflamed tissues, an effect associated with CCL2 (Collington et al., 2010) and other chemotactic factors, where microenvironmental milieu influences their maturation and phenotype (Galli et al., 2011).

1.2. Influence of genetic variation on MC phenotype

Upon stimulation, mechanisms driving MCp recruitment are complex and strain- and tissue-dependent. Thus, BALB/c-derived MCp are recruited to the lungs upon challenge by IL-9 and NKT cells, independently of the Th2 cytokines involved in MC maturation in the small intestine. However, Ag-triggered MCp influx to the lungs of C57BL/6 mice is promoted by T regulatory (Treg) cells, TGFβ1 and IL-10 (Jones et al., 2010). A rare population of circulating MC cell-committed progenitors has been recently identified in adult mice of both strains with similar frequency but displaying a major difference in maturity based on FcεRI expression where 66% of BALB/c-derived MCp were FcεRI$^+$, compared to only 25% in C57BL/6-MCp (Dahlin et al., 2013). These phenotypic differences could later affect MC migratory patterns and inflammatory features in disease states.

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Indeed, bronchial responsiveness, pulmonary inflammation and bronchoalveolar lavage fluid (BALF) cellular composition following antigen (Ag) exposure varied significantly between Th2-prone BALB/c and Th1-prone C57BL/6 mice (Gueders et al., 2009). While both strains presented similar circulating levels of Ag-specific IgE, airway reactivity to methacholine was enhanced in sensitized BALB/c mice, whereas sensitized C57BL/6 mice displayed more pronounced BALF and airway eosinophilia compared to BALB/c mice. BALB/c-derived lung tissues presented higher MC numbers accompanied with higher levels of IL-4, IL-13 and CCL11, whereas BALF contents of CCL11 and CCL5 was higher in C57BL/6 mice. Whether similar differential MCp maturity exists in allergic versus non-allergic subjects and could condition the development of atopic respiratory disorders in adulthood warrants further investigation. In IgE-challenged skin, functional phosphoinositide 3-kinase (PI3K) γ but not δ is critical to MCp accumulation, TNF release and transendothelial migration and anaphylaxis (Collmann et al., 2013).

1.3. MC and basophils: Shared or distinct progenitors?

MC ontogeny is still a matter of debate, in particular regarding their affiliation to basophils. Using colony formation assays, two teams reported a common precursor cell to both basophils and eosinophils but not MC (Denburg et al., 1985; Leary and Ogawa, 1984). Galli and collaborators characterized a rare but MC lineage-restricted bone marrow progenitor (independent from the granulocyte and macrophage lineages), supported by in vitro cultures, in vivo transplantation and single-cell gene expression approaches (Franco et al., 2010). Recently, Qi et al. (2013) identified a population of granulocyte-macrophage progenitors that could differentiate into basophils or MC, depending on selective and mutually exclusive transcription factor expression. More intriguing findings suggest that Notch signaling, a key regulator of T and B lymphocytes, is also involved in MC development via coordinated transcriptional regulation of GATA3 and Hes-1 (Sakata-Yanagimoto et al., 2008), the latter repressing CCAAT/enhancer binding protein α (C/EBPα, required for basophil differentiation and a MC repressor) (Qi et al., 2013; Iwasaki et al., 2006). However, this MC derivation pathway may be more relevant to pathological rather than steady-state conditions (Sakata-Yanagimoto et al., 2008). The contrasted conclusions of these elegant studies stem from the likely usage of different starting progenitor populations.

1.4. Notch and GATA signaling determine MC fate

The evolutionary conserved Notch signaling pathway regulates fate determination of many cells, including lymphocytes (Radtke et al., 2004) and MC (Taghon et al., 2007). MC transcription factors Pu.1 (Schroeder et al., 2003) and Gata2 (Kumano et al., 2001) are direct targets of the Notch pathway in mice, which induces MHC class II expression (Nakano et al., 2009) and therefore antigen presenting abilities in MC, a critical function we first reported as well (Frandji et al., 1993). Moreover, Notch2 signaling in MC is required for proper localization of intestinal MC during murine parasitic infection (Sakata-Yanagimoto et al., 2011). A transgenic zebrafish line overexpressing *notch1a* recapitulated the MC accumulation observed in human systemic mastocytosis and was abrogated upon Notch pathway inhibition, also suggesting the dependence of human MC lineage on Notch signaling (Da'as et al., 2012). Although both *gata2* and *pu.1* are critical to MC lineage commitment, *gata2* is controlled by the Notch signaling pathway, whereas *pu.1* appears to be more selectively regulated by *notch1a* (Da'as et al., 2012). A recent study demonstrated that complete *gata1* ablation had minimal effects on MC numbers and tissue distribution in adult mice but reduced MC tryptase expression levels (Ohneda et al., 2014). In contrast, *gata2* deficiency resulted in a significant loss of Kit and FcεRIα expression on MC. Using the human MC leukemia cell line LAD2 and human primary MC generated from peripheral blood, Inage et al. (2014) reported critical roles for PU.1, GATA1 and GATA2 in the expression of human FcεRI on MC, where PU.1 and GATA1 are involved in FcεRIα transcription through recruitment to its promoter and GATA2 positively regulates FcεRIβ transcription. These findings further evoke the participation of GATA1 and GATA2 to IgE-mediated MC activation, including in human MC.

1.5. Phenotypic plasticity in MC development

Regardless of the controversy, it is well accepted that MC progenitors give rise to two major subsets of mature MC defined by their differential composition in proteases and proteoglycans and tissue distribution: connective tissue or serosal MC (CTMC) distributed in the skin and mucosal MC found in the gut and respiratory mucosa. A committed human MCp population is yet to be identified. Human MC progenitors are present at low frequency among the CD34+ cells in adult bone marrow (Kirshenbaum et al., 1991), in peripheral blood (Kirshenbaum et al., 1999) and in umbilical cord blood (Kempuraj et al., 1999). The presence of MCp in human tissues, although likely, has yet to be conclusively demonstrated (Dahlin and Hallgren, 2014).

Maturation of MC is driven by exposure to a mixture of cytokines provided by structural cells in local tissue microenvironments, such as stem cell factor (SCF) (Galli et al., 2008). Recent studies have highlighted the importance of lipid-based regulation of MC maturation. Human cord blood-derived MC (CBMC) developed in SCF alone express tryptase (Oskeritzian et al., 1999). We reported that addition of sphingosine-1-phosphate (S1P), a potently bioactive sphingolipid metabolite, to SCF accelerates the development of CBMC and promotes chymase-expressing human MC with functional features similar to skin MC (Price et al., 2009). S1P-triggered chymase expression was mediated by macrophage-derived IL-6, a cytokine we had demonstrated as pivotal in regulating chymase expression (Oskeritzian et al., 1999; Price et al., 2009). In agreement with our studies, Olivera et al. (2013) recently reported hyperresponsive MC generated from S1P lyase-null bone marrow cells, which may not degrade S1P therefore chronically exposing MC to S1P. These findings raise the possibility of autocrine regulation of MC maturation since IgE/Ag-activated MC secrete S1P, which, in turn can influence their development and function. Similarly, the MC-derived group III phospholipase PLA2G3 can regulate MC granule histamine and protease contents and activate degranulation (Taketomi et al., 2013). Moreover, the authors identify a novel MC-fibroblast axis controlling MC maturation and function, depending on fibroblast prostaglandin synthase, local production of PGD2 and MC DP1 (a prostaglandin receptor) expression. Of note, these latter studies apply to mouse MC cell maturation and function. Our work demonstrated a potent influential effect of lipid mediator S1P on human cord blood-derived MC, suggesting key regulatory functions of lipids in both human and mouse MC. Similarly to mouse MC, human MC are also divided into dichotomic populations, based on granule protease expression: one harboring tryptase only (MC_T), main MC phenotype localized in the lungs and another containing both tryptase and chymase (MC_{TC}), featured in the skin (Galli et al., 2011). This perhaps oversimplified MC phenotypic classification raised similar developmental questions also pertaining to mouse MC: do all MC arise from a common or distinct progenitors? Using human peripheral blood-derived progenitor cells, Maaninka et al. (2013) recently established these circulating cells have the potential to express all granule proteases, strongly suggesting the existence of a common human MC progenitor cell. We also have observed that addition of IL-6 to SCF on in vitro cultured human cord blood mononuclear cells