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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.

Keywords

Mast cells; Sphingosine-1-Phosphate; inflammation; cancer; plasticity; microRNA

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,

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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 [1]. Certain stimuli prompt tissue-resident MC to re-acquire the ability to proliferate, suggesting the possibility for these cells to de-differentiate [2–6]. Circulating agranular MC progenitors (MCp) are recruited in inflamed tissues, an effect associated with CCL2 [7] and other chemotactic factors, where microenvironmental milieu influences their maturation and phenotype [2].

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 [8]. 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 [9]. These phenotypic differences could later affect MC migratory patterns and inflammatory features in disease states. 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 [10]. 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 nonallergic 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 [11].

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 [12, 13]. 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 [14]. Recently, Qi *et al.* identified a population of granulocyte-macrophage progenitors that could differentiate into basophils or MC, depending on selective and mutually exclusive transcription factor expression [15]. 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 [16], the latter repressing CCAAT/enhancer binding protein α (C/EBP α , required for basophil differentiation and a MC repressor) [15, 17]. However, this MC derivation pathway may be more relevant to pathological rather than steady-state conditions [16]. 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 [18] and MC [19]. MC transcription factors Pu.1 [20] and Gata2 [21] are direct targets of the Notch pathway in mice, which induces MHC class II expression [22] and therefore antigen presenting abilities in MC, a critical function we first reported as well [23]. Moreover, Notch2 signaling in MC is required for proper localization of intestinal MC during murine parasitic infection [24]. 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 [25]. 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* [25]. 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 [26]. In contrast, *gata2* deficiency resulted in a significant loss of Kit and Fc ϵ RI α expression on MC. Using the human MC leukemia cell line LAD2 and human primary MC generated from peripheral blood, Inage *et al.* reported critical roles for PU.1, GATA1 and GATA2 in the expression of human Fc ϵ RI on MC, where PU.1 and GATA1 are involved in Fc ϵ RI α transcription through recruitment to its promoter and GATA2 positively regulates Fc ϵ RI β transcription [27]. 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 [28], in peripheral blood [29] and in umbilical cord blood [30]. The presence of MCp in human tissues, although likely, has yet to be conclusively demonstrated [31].

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) [32]. 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 [33]. We reported that addition of sphingosine-1-phosphate (S1P), a potentially bioactive sphingolipid metabolite, to SCF accelerates the development of CBMC and promotes chymase-expressing human MC

with functional features similar to skin MC [34]. S1P-triggered chymase expression was mediated by macrophage-derived IL-6, a cytokine we had demonstrated as pivotal in regulating chymase expression [33, 34]. In agreement with our studies, Olivera *et al.* recently reported hyperresponsive MC generated from S1P lyase-null bone marrow cells, which may not degrade S1P therefore chronically exposing MC to S1P [35]. 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 [36]. 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 [2]. 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.* recently established these circulating cells have the potential to express all granule proteases, strongly suggesting the existence of a common human MC progenitor cell [37]. We also have observed that addition of IL-6 to SCF on *in vitro* cultured human cord blood mononuclear cells triggered chymase expression without altering chymase mRNA expression in these cells, suggesting a common MC progenitor cell (Oskeritzian, Min and Schwartz, unpublished results). Similarly, post-transcriptional regulation of chymase expression has been demonstrated in mouse bone marrow-derived MC [38]. This concept strongly supports MC phenotypic plasticity, particularly in inflammatory settings and in protective immunity where the local microenvironment is altered [2].

2. MC plasticity in activation

Functional plasticity is illustrated by MC's unique ability to secrete an armamentarium of preformed or de novo synthesized mediators exerting pro-inflammatory, anti-inflammatory or immunosuppressive actions released upon activation by a composite range of stimuli [3, 32, 39–40]. Moreover, the magnitude, duration and nature of the stimulation conditions MC responses and secretory patterns [41, 42]. In addition to the canonical IgE/Ag activation pathway, skin MC express receptors for FcγRI and FcγRIIα activated IgG-dependently [43]. MC expression of pattern recognition receptors, including Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns, promotes the development of innate and adaptive immune responses to acute or persistent bacterial infections. Interestingly, whereas MC functions are largely antimicrobial in acute infections, leading to resolution, MC may promote chronic infections, especially when inflammatory conditions, including asthma and atopic dermatitis, pre-exist [44].

2.1 Activated MC as immune-modulators of innate immunity in infections

Even though IgE is classically specific to Ag, it may also be targeted against bacteria, including *Helicobacter pylori* and *S. aureus* [45, 46] and cross-communication between IgE and TLRs amplifies pro-inflammatory cytokine production [47], contributing to effector cells recruitment, including neutrophils, and promote bacterial clearance. In addition to effector cells, MC mediators can attract Ag-presenting cells (APC) to sites of infection, to mount an Ag-specific cytotoxic response. Pre-stored MC-derived proteases, including tryptase and chymase, contribute to APC recruitment. Intratracheal administration of human tryptase β 1 decreased susceptibility to *Klebsiella pneumonia* airway bacterial infection [48] likely via Protease-Activated Receptor-2 signaling (PAR-2) shown to stimulate DC development [49]. Human chymase, another preformed MC protease, potently and selectively attracts monocytes *in vitro* [50]. TNF is a pre-stored and MC granule-associated pleiotropic cytokine endowed with the ability to enhance maturation and chemotaxis of DC in mice [51] and in human [52]. Dengue-virus infection of human MC triggers a significant release of CCL5 [53] whereas CCL20, another DC chemottractant, will preferentially be released upon infection of human MC with *P. aeruginosa* [54]. A number of reports demonstrate that both viral and bacterial infections could lead to rapid DC chemokine secretion from human MC, including CCL2, CCL3, CCL4, CCL5 and CCL20 (reviewed in [55]). MC themselves can serve as Ag presenting cells [23, 56]. Whereas in certain chronic infections, including *Mycobacterium tuberculosis*, MC will contribute to confine infection in granulomas, in most inflamed sites, sustained MC hyperresponsiveness will exacerbate chronic infections, underlining both spatial and temporal contributions of MC phenotypic flexibility to either benefit or harm the host. Some exciting new insights shed lights on using MC activation by small molecules such as compound 48/80 as vaccine adjuvants to boost host immunity [57, 58] or conversely, preventing MC activation to better control chronic infections. Similarly, under acute MC activation, Kit activation by binding of its ligand SCF, critical for human MC development and supplementary to IL-3 for mouse MC generation, potentiates IgE/Ag-driven MC activation [59, 60]. However, chronic exposure to SCF renders MC hyporesponsive, regarding both degranulation and cytokine production [61].

2.2 Proteases determine MC functional responses

In humans, the differential content in tryptase and chymase governs MC functional abilities. There is some evidence that MC β tryptases contribute to extracellular matrix proteolysis, by activating metalloproteinases (MMP) and promote leukocyte influx. Human Tryptase- β has been reported to possess potent gelatin degrading properties, similar to that seen by the gelatinases MMP-2 and MMP-9 [62]. MCs themselves are known to express MMPs [63] as well as other proteinases (e.g., chymases [64]) that can potentially activate MMPs. Contributing to MC functional plasticity, tryptase may also convey inhibitory actions by degrading chemokines and neuropeptides [65, 66]. Similarly, chymase may contribute to the recruitment of inflammatory cells [67] but can also degrade proinflammatory cytokines, including IL-6, IL-13, IL-5 and TNF [68] and neuropeptides [69]. New insights have recently unveiled MC involvement in the pathogenesis of connective tissue disorders including wound healing and fibrosis (reviewed in [70]). Wound repair is conceptually divided into three phases-inflammation, proliferation and remodeling- initiated by tissue

trauma. Chymase is mitogenic for fibroblasts but exerts minimal effects on keratinocytes, suggesting a primary function in normal connective repair. Abnormal continuation of wound healing process can be observed consequently to burns and trauma, leading to pathologic aberrant scars named keloids. High MC numbers are found in keloids and correlate with elevated levels of TGF- β . Overexpressed TGF- β stimulates collagen transcription while decreasing its degradation resulting in excess deposition. MC-restricted chymase is primarily an angiotensin II-forming enzyme, which acts on vasoconstriction and vascular proliferation. Angiotensin II can also promote vascular endothelial cell growth factor (VEGF) expression to stimulate MMP-9 expression. Chymase also converts precursors of TGF- β and MMP-9 to their active form both leading to ECM degradation and tissue remodeling. S1P, a potent bioactive sphingolipid metabolite, is secreted from activated MC [71] and can act either extracellularly on G-protein coupled S1P receptors of mast and other cells, or intracellularly, a concept also valid in the context of fibrotic processes [72]. Opposing effects of S1P have been reported on the progression of fibrosis, with pro-fibrotic functions of S1PR-ligand S1P and its anti-fibrotic effects when acting as an intracellular signaling molecule [72]. During fibrosis, MC proteoglycan composition could be modulated as they interact with fibroblasts [73] by the presence of membrane-anchored or soluble SCF. Whether phenotypic conversion is reversible upon resolution of inflammation is still a matter of debate.

2.3 Activated MC and immunosuppression

One key element dictating MC activation resides in the receptors displayed at their cell surface. Unlike classic receptor-ligand relationship, higher IgE concentrations lead to higher surface expression of Fc ϵ RI, feeding forward MC activation. In contrast, the IgG-dependent immune response observed for example in contact dermatitis might favor the secretion of MC-derived immunosuppressive IL-10 [74], though this concept has been recently challenged using MC-conditional knockout mice for IL-10 [75]. Exposure of mouse skin to UVB irradiation induces increased vitamin D3 production, which, in turn, interacts with MC-expressed vitamin D3 receptor to induce IL-10 secretion from MC [76], UV radiation triggering the presence of IL-10⁺ MC in the draining lymph nodes [77]. A MC-dependent IL-10-mediated immunosuppression has also been observed in a mouse skin model of delayed-type hypersensitivity [78]. In preclinical models using MC-deficient mice based on Kit-deficiencies, it has been suggested that MC could promote tolerance to skin grafts [79] and suppress murine graft versus host disease in hematopoietic cell transplantation independently of regulatory T cells in a mechanism also involving IL-10 [80]. Moreover, IL-10 down-regulates MC development and functions [81]. Of note, MC-deficient mice due to Kit mutations, though widely used to investigate MC functions, are characterized with splenomegaly displaying aberrant myelopoiesis and myeloid-derived suppressor cell accumulation [82], necessitating a re-evaluation of MC functions in many experimental models with newly-developed MC-deficient mice, independently of Kit mutations [83]. Interestingly, T regs could produce IL-9, a MC growth factor, chemoattractor and activator. Recruited MC then aid Treg immunosuppressive functions [84]. In some instances, peripheral tolerance could be reversed by systemic MC degranulation [85] and MC can also down-regulate Treg immunosuppressive functions via histamine H1 receptor signaling [86].

2.4 Interaction with other cells influence MC phenotype

We described how MC plasticity arises from MC-harbored bioactive compounds and their mechanism of release. But MC plasticity may also be governed by their interaction with other cells or influence neighboring cell phenotype. As previously indicated, MC-fibroblast (via SCF) or MC-macrophage (via S1P and IL-6) interaction could influence MC phenotype. MC-derived TNF stimulates T cells, a phenomenon particularly relevant to psoriatic and atopic dermatitis lesions since skin MC are a unique source of pre-formed TNF and increased in number in inflamed skin [87]. MC pro-inflammatory functions are further documented *in vivo* by their ability, with the aid of IL-6, to convert Tregs into Th17 cells and promote airway inflammation [88]. In addition, MC express co-stimulatory molecules essential to T cell activation [89] and stimulate dendritic cell maturation leading to improve Ag presentation [90].

3. MC plasticity in cancer

MC hyperplasia is a hallmark of many cancers, further emphasizing their intervention in innate and acquired immunity. Tumor-infiltrating MC have been observed in many instances but their precise contribution pertaining to tumor-promoting chronic inflammation, though suspected, remains elusive. The tumor microenvironment encompasses many mediators, including cytokines, chemokines, angiogenic factors, ECM-degrading proteinases and S1P, all of which could be produced by MC. The role of S1P is of particular interest in the context of tumor microenvironment and inflammation [91]. S1P exerts many pro-inflammatory and tumorigenic functions including cancer cell transformation, growth, survival and motility, chemoresistance and metastasis by promoting neovascularization (Reviewed in [92]). However, S1P has also been shown, in the nucleus and independently of extracellular S1P receptors, to act as an endogenous histone deacetylase (HDAC) inhibitor, therefore endowed with the ability to regulate gene expression and could serve as another cancer-targeting strategy, as HDAC inhibitors are often used in combinational therapy to fight cancer [93]. Elevated intratumoral levels of S1P pairing with increased sphingosine kinase (the enzymes that produce S1P) activity is observed in inflammation and cancer but its cellular source(s) remain to be elucidated. We are tempted to speculate that MC could represent the local source of tumor S1P and be the nexus between innate immunity, inflammation and cancer.

3.1 MC as tumor promoters

Recent studies have pointed out an essential role for SCF in mediating MC recruitment, tumor-associated inflammation, remodeling and immunosuppression [94]. SCF-stimulated MC produce MMP-9 that facilitates recruitment of MC and other cells to the tumor and augments tumor-derived SCF production in an amplification feedback loop. MC tumor-promoting potential is augmented through co-stimulation with tumor-derived SCF and Toll-like receptor 4 (TLR4) ligand, inhibiting MC degranulation but triggering their production and secretion of VEGF and IL-10, whereas MC stimulation by TLR4 ligand alone induces IL-12, an important regulator of T and NK cell responses [95]. MC can also produce large amounts of IL-1 β after its precursor form processing by MC chymase or by caspase-1 in an Nlrp3 inflammasome-dependent manner. Inflammasomes are microbial sensing complexes

part of the innate immune system. The Nlrp3 inflammasome may be activated by many pathogen-derived stimuli, including lipopolysaccharide (LPS), as well as by endogenous stimuli and particulates, such as cholesterol, fatty acids or silica and asbestos [96] but requires two signals: for example, TLR ligands or TNF and bacterial toxins (recently reviewed in [97]). Activated Nlrp3 induces self-cleavage of caspase-1, which, in turn, converts inactive precursors of IL-1 β and IL-18 into bioactive forms. IL-1 β plays a central role in chronic inflammation recognized as a pro-tumorigenic event [98]. Therefore, activated MC Nlrp3 inflammasome and MC-derived IL-1 β might be promoting silica and asbestos carcinogenesis [99, 100]. Interestingly, dermal MC have been reported as main source of IL-1 β in antihistamine-resistant forms of urticaria called “urticaria-like rash”, an Nlrp3-mediated auto-inflammatory syndrome [101]. In the same study, the authors showed that bone marrow-derived MC from wild type mice displayed *in vitro* caspase-1 activation and subsequent IL-1 β secretion upon LPS and adenosine tri-phosphate stimulation through Nlrp3 inflammasome triggering [101]. Moreover, it was demonstrated that preformed-TNF secreted by MC constitutes the first signal necessary to activate the Nlrp3 inflammasome in IL-1 β -driven skin inflammation associated with a pathogenic mutation of the nlrp3 protein [102]. The link between MC and tumor-associated angiogenesis has been well established, most likely leading to tumor progression. Indeed, MC can secrete VEGF and promote tumor angiogenesis [103–106].

3.2 MC as tumor suppressors

It is noteworthy that tumor-infiltrating MC secrete mediators through piecemeal degranulation rather than classic degranulation seen in IgE/Ag-mediated MC activation. This mechanism of mediator release, also observed in chronic inflammation, consists in the generation of micro-vesicles from original cytoplasmic granules which transport small aliquots of the granular content to the extracellular milieu [107].

What molecular switch(es) drives the conversion from proinflammatory to immunosuppressive (and vice versa) in MC remains to be elucidated. In line with MC pleiotropism, MC can produce tumor suppressive mediators, including IL-4 and TNF. Huang *et al.* also suggested MC and Treg cells may partner to suppress immune responses in tumor tissues [94]. MC-derived IL-10 and TGF- β can aid to induced Treg (iTreg), which positively correlate with MC density in cancer. Reciprocally, Tregs modulate MC progenitor frequency in polyps of the small intestine [108]. However, polyposis-prone Min mice crossed with MC-deficient mice (Kit^{Wsh/Wsh}) develop more polyps, suggesting a protective role for MC in this model [109], not seen in all models. These contrasting data are most likely due to the fact that MC deficiency in Kit^{Wsh/Wsh} mice stems from chromosomal rearrangements affecting the Kit locus therefore perturbing other elements of the immune and oncogenic responses. A better prognosis is associated with MC in certain human cancers, including colorectal and colon cancers, mesothelioma and large B cell lymphoma [110]. This apparent dichotomy in MC functions could be explained by 1) the phenotype of tumor-infiltration MC (tryptase⁺, chymase⁺ MC are seen in benign breast lesions, tryptase⁺ MC in malignant ones [111] 2) their location (stromal MC favor the host [112], whereas intratumoral MC promote the tumor [113] 3) the type of cancer and 4) the different stages of the same cancer. Therefore, it is essential to evaluate the role of MC in cancer progression

for they are indispensable orchestrators of innate and adaptive immune responses. Moreover and conversely to mice, there is no documented occurrence of MC-deficient humans.

We suggest MC phenotypic plasticity might partly explain how the presence of tumor-infiltrating MC could govern cancer prognosis.

4. MC plasticity: a role for microRNAs?

In resting MC, it is conceivable that phenotype stability is ensured by transcriptional regulation of gene expression, whereas genes governing the acquisition of alternate phenotypes are repressed. Epigenetic modifications and microRNA (miRNA) [114] expression might contribute to this stability. In T cells, O'Shea and Paul have elegantly reported that both the *Il4* and *Ifng* genes display remarkable CpG demethylation, an epigenetic modification associated with gene expression, in their promoters and in enhancers regions during Th1 and Th2 cell differentiation, respectively [115]. It is tempting to speculate that similar events accompany MC differentiation and maturation in diseased tissues as they are exposed to changing microenvironment.

4.1 MC acquired responsiveness to stimuli

The ability for MC to become responsive to C5a, an anaphylatoxin resulting from complement activation, is depending upon their expression for C5a receptor, CD88. We showed that not only IL-6 but also S1P enabled MC to express intragranular chymase protein and surface CD88, rendering them functionally responsive to C5a by degranulation [33, 34]. In another report, we showed that mature *ex vivo*-derived human lung MC, where tryptase is the predominant granule-associated protease, can display enhanced chymase expression upon exposure to IL-6 [116]. These studies strongly support the notion that MC phenotype skewing and immune-regulation could occur in changing local micro-environmental conditions encountered in inflamed tissues. To date, the molecular mechanisms driving expression of CD88 and chymase remain unknown. The central role of both molecules in regulating MC functions of relevance to many inflammatory disorders is pressing for defining their own transcriptional regulation mechanisms. Future studies should address whether miRNA-mediated post-transcriptional regulation intervenes in controlling chymase expression and also whether surface CD88 and intragranular chymase expression regulation are linked.

4.2 MiRNA and MC function

Our current understanding of miRNA functions in regulating MC development and activation remains limited. Because it has been estimated that one third of the human genome may be subject to post-transcriptional regulation by miRNAs [117–119], miRNA intervention in MC function is highly conceivable. Indeed, miRNA-221/-222 family is transcriptionally up-regulated upon MC activation correlating with reduced MC proliferation and actin dysregulation [120, 121] but may also have a role in regulating MC Kit expression, cell cycle and homeostasis. MiRNA-146a expression could lead to MC activation-induced apoptosis [122]. Interestingly, miRNA-146a expression is also increased in splenic CD4⁺ T lymphocytes in ovalbumin (OVA)-induced mouse asthma models [123] but dampens NF-

kB-mediated inflammatory responses [124]. Upregulated miRNA-132 was also reported in activated mouse and human MC [125], whereas miRNA-126 is down-regulated during MC differentiation to positively regulate MC proliferation [126]. MiRNA-126 silencing abolished house dust mite-induced airway hyperresponsiveness, dampened Th2 cytokines and reduced allergic inflammation in a mouse model [127]. Of note, miRNA-126 effects and functions are likely to be temporally composite with an initial up-regulation after 2 weeks of antigen challenge, followed by a decrease to near baseline levels after 6 weeks of allergen challenge, in a chronic experimental model of asthma [128]. Because a particular miRNA can target hundreds of genes, it is tempting to speculate that several miRNAs could coordinately target a common pathway and control mast (and other) cells polarization. However, information pertaining to miRNA profiling in patients with allergic diseases though very limited should be further investigated for they could serve as potential biomarkers (found in peripheral blood or other body fluids) and local tissue-specific targets of anti-inflammatory gene therapy [129]. Altering miRNA expression could be achieved using several strategies: *in vitro*, cells could be transfected with miRNA mimics (for overexpression [130]) or complementary inhibitors (RNA-based oligonucleotides with a complementary sequence to the targeted miRNA [131]). Antagomirs constitute one class of long-lasting miRNA inhibitors with attached cholesterol to facilitate cellular uptake [132]. Alternatively, miRNA sponges are engineered RNA molecules with multiple repeats of a miRNA target site that compete with the endogenous mRNA target. However, miRNAs may regulate specific, e.g., acute versus chronic aspects of allergic diseases and/or may be expressed by different cells at different stages of disease process, rendering temporal and cell-type specific intervention a key to successful therapy [132]. *In silico* analyses aid identifying mRNA targets, signaling pathways and disease processes, differentially regulated by miRNAs of dynamic expression in various disease phases [133].

4.3 MiRNA influence on S1P: consequences on MC

The emergence of data pertaining to miRNA-mediated regulation of sphingosine kinases (SphK), enzymes making S1P, a sphingolipid metabolite potentially implicated in MC development and functions underpins miRNA intervention in molecular processes controlling S1P production [134]. Interestingly, it has been shown that S1P formed in the nucleus by SphK can bind and inhibit histone deacetylase (HDAC) 1 and HDAC2 leading to epigenetic alterations in histone acetylations and gene expression [93]. Previous studies reported 1) beneficial effects of S1P in dystrophic muscle and 2) special contribution of HDAC2 in the pathogenesis of Duchenne muscular dystrophy. These findings suggest S1P could exert its beneficial effects by inhibiting HDAC2 activity which de-represses HDAC2 target gene expression, including miRNA-29, leading to disease amelioration [135]. Indeed, elevated miRNA-29 suppresses fibrosis and dystrophy pathology [136, 137]. The molecular mechanisms governing S1P-mediated MC developmental and phenotypic alterations are not well understood and we are speculating they may involve S1P-regulated miRNA expression.

Moreover, since miRNAs have been shown to regulate macrophage functional polarization [138], we propose miRNA could also modulate MC plasticity and effector functions. Finally, the accessibility of lungs and skin, two important sites of allergic inflammation involving MC, for local drug delivery makes asthma and atopic dermatitis good disease

candidates for miRNA-directed therapies. The relevance to human allergic disease could be evaluated by using systems biology approaches, such as exome sequencing, to unveil mutations in patients which could correlate with altered miRNA expression and contribute to disease pathogenesis [139, 140].

5. Concluding remarks

In this viewpoint, we demonstrate how MC plasticity is becoming a well-established concept, likely to be driven by local microenvironment, neighboring stroma cells, MC homeostatic or inflammation-induced receptor expression, maturation and activation status, the disease type and stage. By analogy to T helper cell plasticity, we foresee future MC classification into “lineages” based on their immune functions, surface receptor expression, cytokine production and secretion patterns and transcription factor profiles. Their exquisite ambivalence (protective vs. pathogenic) also warrants caution when targeting MC in therapeutic interventions and favors modulating their functional phenotype rather than silencing MC. Manipulating MC plasticity requires its full understanding which remains to be accomplished.

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Highlights

- Mast cells (MC) can be pro or anti-inflammatory cells depending on local conditions.
- Substantial phenotypic and functional plasticity characterize mast cells.
- Lipids, including SIP and miRNAs are emerging regulators of mast cell subsets.
- How they alter MC functions in inflammation and cancer warrant further studies.