Review

Mast cells and ocular surface: An update review

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ABSTRACT

Mast cells (MCs), traditionally viewed as key players in IgE-mediated allergic responses, are increasingly recognized for their versatile roles. Situated at critical barrier sites such as the ocular surface, these sentinel cells participate in a broad array of physiological and pathological processes. This review presents a comprehensive update on the immune pathophysiology of MCs, with a particular focus on the mechanisms underlying innate immunity. It highlights their roles at the ocular surface, emphasizing their participation in allergic reactions, maintenance of corneal homeostasis, neovascularization, wound healing, and immune responses in corneal grafts. The review also explores the potential of MCs as therapeutic targets, given their significant contributions to disease pathogenesis and their capacity to modulate immunity. Through a thorough examination of current literature, we aim to elucidate the immune pathophysiology and multifaceted roles of MCs in ocular surface health and disease, suggesting directions for future research and therapeutic innovation.

1. Introduction

Mast cells (MCs) are tissue-resident immune cells mainly distributed throughout the connective tissues of the body, particularly close to blood and lymphatic vessels (Krystel-Whittemore et al., 2016; Micera et al., 2020; Norrby, 2002). Situated at key interfaces with the external environment, including the skin, respiratory, gastrointestinal systems, and ocular surface, they play a pivotal role in immunological response as gatekeepers (Galli and Tsai, 2012; Janssens et al., 2005; Krystel-Whittemore et al., 2016; Kumar and Sharma, 2010; Metcalfe et al., 1997; Rodewald and Feyerabend, 2012; Royer et al., 2015).

At the ocular surface, MCs are distributed in the peripheral cornea, limbus, and conjunctiva and have been typically associated with the pathogenesis of allergic keratoconjunctivitis (Leonardi et al., 2008; Liu et al., 2015; Micera et al., 2020). Nevertheless, in line with the recent findings and progress, they also contribute to non-allergic ocular conditions, including corneal neoangiogenesis, lymphangiogenesis, tissue remodeling and graft rejection (Cho et al., 2021; Li et al., 2019; Sahu et al., 2018).

Herein, this review underscores the pivotal role of MCs in immune responses and ocular surface, extending beyond their traditional involvement in allergic responses. Recognizing the versatile functions of MCs highlights their potential as therapeutic targets in immune disorders.

2. Pathophysiology of MCs: a focus on the innate response

MCs originate from CD34$^+$ myeloid precursors in the bone marrow; these progenitor cells enter the bloodstream as mononuclear leukocytes devoid of the typical secretory granules, expressing surface markers such as CD13, CD33, CD38, CD34, and Kit (Kirshenbaum et al., 1999; M O Muench et al., 1994).

Under the influence of Stem Cell Factor (SCF) and tissue-specific chemokines and cytokines, MCs progenitors migrate into peripheral tissues where they develop and differentiate into mature MCs (Dahlin and Hallgren, 2015; Grootens et al., 2018). SCF, the ligand for the c-kit receptor (CD117), is the main survival and developmental factor for MCs and is produced by several cell types, including fibroblasts and stromal cells (Flanagan and Leder, 1990; Galli et al., 1993; Hu et al., 2007). In peripheral tissues, the phenotypic characteristics of MCs are further

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regulated by distinct factors provided by the microenvironment where they ultimately reside, such as IL-3, IL-4, and IL-9 (Galli et al., 2005a, 2005b; Hamaguchi et al., 1987; Marone et al., 2005).

Fully developed MCs are strategically located throughout the body near blood vessels, lymphatics, and mucosal surfaces such as the skin, the ocular surface, and the gastrointestinal tract, where they interact and react with the external environment; however, their distribution can vary with age and sex (Fuda et al., 2023; Galli et al., 2005b, 2005a; Metcalfe et al., 1997; Y K., 1989). This strategic localization enables the facilitation of systemic reactions to different local triggers, playing a pivotal role in coordinating crucial elements of both innate and adaptive immunity, alongside various physiological functions. Within the mast cell cytoplasm lie 50–200 pre-formed secretory granules, which are reservoirs for pro-inflammatory agents such as histamine, heparin, TNFα, chymase, tryptase, carboxypeptidase A, bradykinin, nitric oxide, cathelicidin, neuropeptide Y (NPY), and more (da Silva et al., 2014; Galli et al., 2005a, 2005b; Molderings and Afrin, 2023; Wang et al., 2024). Additionally, MCs have the capability to generate and secrete lipid-derived mediators like leukotrienes and prostaglandins, as well as an array of cytokines, chemokines, and growth factors, including IL-13, IL-33, and CXCL8, through de novo synthesis (Boyce, 2003; Galli et al., 2005b; Gurish and Austen, 2001; Marshall, 2004; Rivera and Gilfillan, 2006). Remarkably, the number of postulated MCs mediators, which is at least 390, is significantly greater than the number of signaling molecules identified as being synthesized and secreted by other immune cells (Molderings and Afrin, 2023).

MCs in rodents are divided into two primary subtypes based on their specific staining characteristics, localization, and granules: mucosal-type MCs (MMC) and connective tissue-type MCs (CTMC) (Befus et al., 1982; Enerbäck, 1966). MMCs are major effector cells in allergic responses mediated by IgE (Bischoff, 2009; Reber et al., 2017). In contrast, CTMCs play an essential role in degrading proteins and peptides, significantly contributing to wound healing and tissue remodeling (Harvima and Nilsson, 2011).

Human MCs also exhibit significant heterogeneity and are classified based on their serine protease content into three categories: tryptase-only MCs (MCT), chymase-only MCs (MCC), and MCs containing both tryptase and chymase (MCTC) (Irani and Schwartz, 1994; Welle, 1997). MCT cells share similarities with rodent MMCs, while MCTC cells resemble rodent CTMCs. However, the distribution of these subtypes in human tissues is less distinct compared to rodents, with most human tissues containing a mixed population of MC types (Moon et al., 2010; Welle, 1997). Moreover, MC phenotypes are not static and can undergo trans-differentiation depending on microenvironmental conditions. (Y K., 1989) This plasticity underscores the significant role of the surrounding microenvironment, including cytokine exposure and the developmental stage of the MCs, in shaping their characteristics (Friend et al., 1996; Kanakura et al., 1988; Levi-Schaffer et al., 1986; Otsu et al., 1987; S S et al., 1986). As a result, the traditional classifications of MCs are evolving to reflect their dynamic and versatile nature (Shea-Donohue et al., 2010).

The adaptability of MCs allows them to form distinct subsets with varying functions and mediator profiles, enabling them to serve diverse roles (Bienenstock et al., 1983; Galli, 1990; Y K., 1989).

The most well-known pathway for mast cell degranulation involves the interaction between allergen-specific IgE and the FcεRI receptor on the mast cell surface (Sibilano et al., 2014; Turner and Kinet, 1999). This process is initiated when IgE, produced by mature B cells under the influence of CD4$^+$ Th2 cells, binds to antigens, resulting in the cross-linking of FcεRI receptors. This interaction triggers the release of stored inflammatory mediators, driving the allergic response through mechanisms such as vascular dilation and increased expression of endothelial adhesion molecules (Amin, 2012; Galli and Tsai, 2012; Siraganian, 2003). The involvement of MCs in IgE-mediated allergic reactions is often attributed to an exaggerated immune response initially developed to combat parasites (Galli and Tsai, 2012).

Beyond their established role in mediating allergic responses, MCs have been recognized for their broader involvement in a variety of critical biological processes. Their capacity to produce and discharge an array of potent mediators places them at the center of complex immunological activities and physiological processes (Chan et al., 2012; Coussens et al., 1999; Galli and Tsai, 2010; Gilfillan and Beaven, 2011; Leveson-Gower et al., 2013; Lu et al., 2006). Moreover, MCs have been implicated in the development of various pathological conditions, such as disorders of the gastrointestinal system, cancer progression, and the pathogenesis of metabolic syndromes like diabetes and obesity (Liu et al., 2009; Tlsty and Coussens, 2006).

Their pivotal role includes orchestrating the early phases of inflammation upon infection, alerting nearby innate immune cells such as macrophages, neutrophils, dendritic cells, and NK cells to the presence of pathogens and producing antimicrobial agents including cathelicidins and defensins (Abraham and St. John, 2010; Arifuzzaman et al., 2019; Rönnberg et al., 2010; Supajatura et al., 2001).

The ability to directly recognize and bind to pathogens, including bacteria, viruses, and parasites, or their soluble components like lipopolysaccharide and peptidoglycan, occurs through direct interaction with pathogens via Toll-like receptors (TLRs) or indirectly through the complement system (Cook et al., 2004; Malaviya and Abraham, 2001; Marshall, 2004). MCs express various TLRs, which enable them to recognize pathogen-associated molecular patterns (PAMPs) and respond accordingly by releasing cytokines, chemokines, and lipid mediators. TLR ligands can enhance the mast cell's response to antigens, affecting cytokine secretion without necessarily inducing degranulation. Activating MCs simultaneously via IgE and TLR ligands significantly boosts cytokine production, although it doesn't affect IgE-induced degranulation (Suurmond et al., 2015). Furthermore, MCs can amplify the complement system's effects by generating and activating complement proteins such as C3a and C5a through mast cell-derived proteases like tryptase and chymase. This interaction enhances inflammatory responses, positioning MCs as key players in complement-mediated activation (Fukuoka et al., 2013; Rahkola et al., 2019). Additionally, MCs express receptors for complement components like C3a and C5a, which facilitates their activation in both paracrine and autocrine manners, leading to further mediator release and perpetuation of the immune response (Ali, 2010; Kashem et al., 2011; Lohman et al., 2017). The expression of complement receptors varies among MCs from different tissues, influencing their response to complement proteins and their susceptibility to complement-mediated attacks through surface proteins such as CD46, CD55, and CD59 (Lubbers et al., 2017).

The immunomodulatory function of the innate immune cells may be mediated through the release of cytokines like TNF-α and IL-1; these cytokines aid in the migration and maturation of dendritic cells towards local lymph nodes to activate cytotoxic T cells and promote neutrophil migration to infection and inflammation sites (Cumberbatch et al., 2000; Nakae et al., 2006; Steinman and Inaba, 1999; Zhang et al., 1992).

MCs regulate T cells function both directly, acting as antigen presenting cells (APC) through the expression of MHC molecules, and indirectly, secreting chemotactic factors and regulating the expression of adhesion molecules on endothelial cells; MC's also affect B cells function by supporting their proliferation and the immunoglobulin synthesis (Gauchat et al., 1993; Mekori and Metcalfe, 1999, 1999, 1999; Merluzzi et al., 2010; Nakae et al., 2005; Ott et al., 2003; Shelburne et al., 2009).

The interaction and regulation of MCs with other immune cells represent a sophisticated mechanism in which sialic acid-binding immunoglobulin-like lectins (Siglecs) are increasingly recognized for their significance. Siglecs facilitate a tailored cellular response through their ability to detect distinct sialylation patterns, thanks to the variety of Siglecs expressed by each cell (Gonzalez-Gil and Schnaar, 2021; O'Sullivan et al., 2020). Specifically, MCs are known to express a range of Siglecs, including CD22/Siglec-2, CD33/Siglec-3, Siglec- 5, Siglec-6, Siglec-7, Siglec-8, Siglec-9, and Siglec-10 (Miralda et al., 2023; Yokoi

et al., 2006). Siglecs functions include decreasing the release of mast cell mediators, reducing the production of arachidonic acid metabolites, diminishing the severity of mast cell-dependent anaphylaxis, curbing the proliferation of human mast cell lines in mastocytosis models, alleviating mast cell activation and inflammation in experimental models of nonallergic airway inflammation, and decreasing mast cell populations in models of eosinophilic gastrointestinal disorders (Duan et al., 2019; Landolina et al., 2020; Miralda et al., 2023; Mizrahi et al., 2014; Robida et al., 2022; Schanin et al., 2021; Yokoi et al., 2008; Youngblood et al., 2019).

3. MCs and ocular surface diseases: the forgotten side of the innate response

The ocular surface is a complex and dynamic environment, rich in cellular diversity, among which MCs, localized at the peripheral cornea, limbus, and conjunctiva, play a significant role (McMenamin et al., 1996; Micera et al., 2020).

Investigations into corneal development have delineated two distinct phases of mast cell migration that are critical for ocular development. Initially, MCs are found to populate both the central and peripheral regions of the corneal stroma, spreading throughout the corneal surface. In a subsequent phase of migration MCs relocate to the corneal limbus, where they form a perivascular network around limbal blood vessels. These limbus-resident MCs are characterized by their longevity and proliferative capabilities, playing a pivotal role in the promotion of neurovascular crosstalk (Liu et al., 2015; Liu and Li, 2021).

Beyond their involvement in corneal development, MCs situated on the ocular surface are increasingly recognized for their critical contributions to ocular health and disease. Notably, they are integral in the

pathogenesis of allergic keratoconjunctivitis, but their role extends beyond this to encompass the maintenance of ocular surface homeostasis, neoangiogenesis, lymphangiogenesis, tissue remodeling, and alloimmunity, highlighting their importance in the intricate network of ocular immunity and physiology (see Fig. 1) (Chauhan et al., 2011; Church and McGill, 2002; Li et al., 2019; Sahu et al., 2018; Xie et al., 2018).

3.1. Allergic keratoconjunctivitis

The eye frequently encounters allergic inflammation due to its direct exposure to the external environment and airborne allergens. The underlying mechanism of allergic inflammation primarily involves an IgE-mediated hypersensitivity reaction, with conjunctival MCs playing a crucial role in the allergic response's effector phase (Elieh Ali Komi et al., 2018; P. Mishra et al., 2011; Villegas and Benitez-Del-castillo, 2021).

The sensitization phase in genetically predisposed individuals begins with the initial contact with a new allergen. Dendritic cells and other antigen-presenting cells (APCs), such as macrophages in the conjunctiva and limbus, process and present these allergens. The engagement of these APCs with naïve CD4$^+$ T cells in the eye-draining lymph nodes prompts the maturation and differentiation of these T cells into Th1 or Th2 effector lymphocytes. Th2 cells play a key role in the IgE-mediated allergic response by releasing cytokines that stimulate IgE production by B cells and promote mast cell proliferation (Irkec and Bozkurt, 2012; Schlereth et al., 2012). Upon re-exposure to the allergen, allergen-specific IgE binds to the high-affinity IgE receptor (FcεRI) on MCs, triggering their degranulation and the release of pro-inflammatory mediators, lipid-derived mediators, and cytokines. This results in
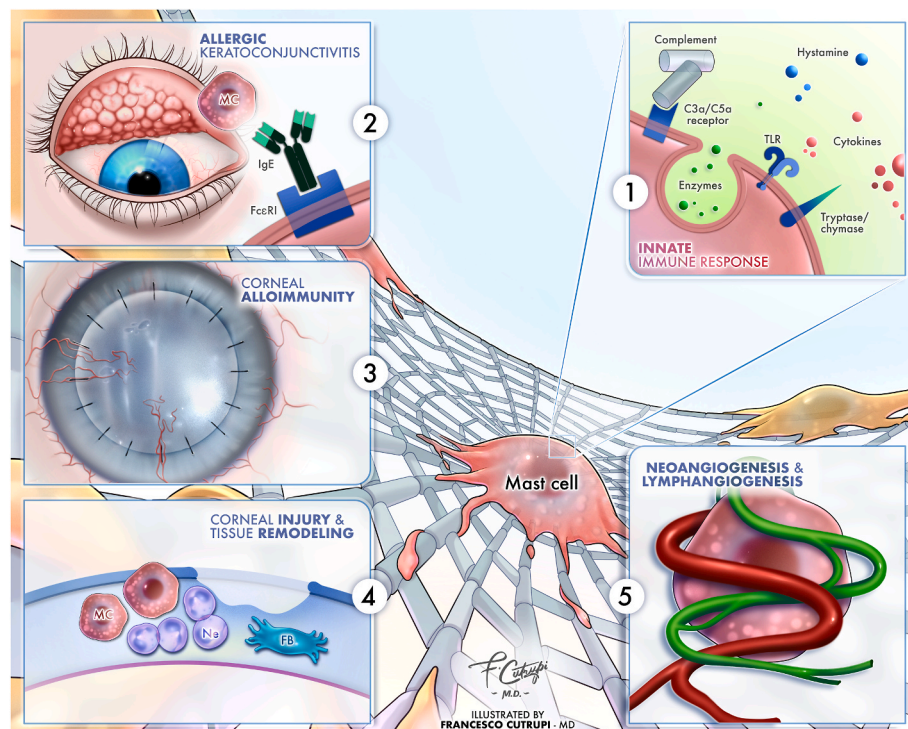

Fig. 1. Illustration of Mast Cell Functions in Ocular Immunity
1. Innate immune response: essential mechanisms through which mast cells contribute to the innate immune defense, underscoring the role of Toll-Like Receptors, chymase and tryptase, in conjunction with the activation of the complement system. The scaffold-like depiction of the complement system illustrates its supportive role in bolstering mast cells during the innate inflammatory response. 2. Allergic keratoconjunctivitis: mast cells have a pivotal function in adaptive immunity, particularly in the context of allergic reactions. 3. Corneal alloimmunity: mast cells have a pivotal role in corneal transplant graft rejection. 4. Corneal injury and tissue remodeling: mast cells have a key role in the process of tissue remodeling post-corneal injury. The process is facilitated by the cooperative action of neutrophils and fibroblasts. 5. Neoangiogenesis and lymphangiogenesis: mast cells are essential in the processes of neovascularization and lymphangiogenesis. FB - Fibroblasts, FcεRI - High Affinity IgE Receptor, MC - Mast Cell, Ne – Neutrophils, TLR - Toll-Like Receptor.

increased tear levels of histamine and tryptase, leading to vasodilation and enhanced vascular permeability, marking the acute phase of the ocular surface reaction (Ackerman et al., 2016; Dupuis et al., 2020). The subsequent late-phase reaction, lasting from 6 to 72 h post-exposure, features the release of lipid mediators, pro-inflammatory cytokines, chemokines, and macrophage inflammatory protein 1α (MIP-1α, CCL3), contributing to the inflammatory process (Cook et al., 2002; Draber et al., 2012; Ellmeier et al., 2011).

Pro-inflammatory cytokines and chemokines further contribute to the recruitment and activation of eosinophils, basophils, T cells, neutrophils, and macrophages, intensifying the inflammatory response within the conjunctival mucosa (Leonardi, 2002; Miyazaki et al., 2008). These recruited cells can cause tissue damage through the release of cytotoxic substances, including eosinophil cationic protein, eosinophil peroxidase, and neutrophil-derived toxic radicals, establishing a perpetuating cycle of damage (Leonardi, 2002).

3.2. Corneal neoangiogenesis and lymphangiogenesis

Normal human corneas lack both blood and lymphatic vessels; indeed, corneal avascularity is fundamental to guaranteeing optimal visual acuity (Cursiefen et al., 2003; Foulsham et al., 2018). The unique quality of being a completely avascular tissue is called "angiogenic privilege" and distinguishes the cornea from most other tissues, which rely on blood and lymphatic vessels for sustenance. In the cornea, nutrient and oxygen supply is met through glucose diffusion from the aqueous humor and oxygen diffusion from the tear film, allowing the tissue to remain avascular under normal conditions (Ellenberg et al., 2010).

The maintenance of corneal avascularity is the result of a balance between pro-angiogenic and anti-angiogenic factors. Disruption of this equilibrium, due to pathological conditions, can lead to an excess of angiogenic stimulators like VEGF, bFGF, and matrix metalloproteinases, coupled with a decrease in angiogenesis inhibitors such as pigment epithelium-derived factor, angiostatin, and endostatin, leading to vascular proliferation from existing limbal vessels (Abdelfattah et al., 2016; Ambati et al., 2006; Dawson et al., 1999; Ellenberg et al., 2010; Jin et al., 2011). This process undermines corneal clarity through chronic inflammation, swelling, scarring, and deposition of intrastromal protein and lipid, potentially leading to significant vision reduction or blindness (Abdelfattah et al., 2015; Clements and Dana, 2011; Maddula et al., 2011).

As neighboring sentinel cells to blood vessels, MCs play a crucial role in various angiogenesis processes: they produce pro-angiogenic agents including VEGF, bFGF, TGF-β, TNF-α, and IL-8; facilitate the liberation of pro-angiogenic elements that interact with heparin through the secretion of proteases; and increase the permeability of microvascular structures through histamine, further promoting angiogenesis (Norrby, 2002).

Recently, Cho et al. used a well-characterized murine model of inflammatory corneal neovascularization to determine how non-IgE mediated activation of MCs promotes neovascularization. They found that mast cell-deficient mice developed significantly fewer new blood vessels compared to controls, suggesting a direct role of MCs in promoting neovascularization by secreting high levels of VEGF-A and promoting vascular endothelial cell proliferation and tube formation. In line with this, pharmacological inhibition of mast cell activation with cromolyn significantly reduced corneal neovascularization, underscoring their critical involvement in corneal neoangiogenesis, and highlighting them as a potential therapeutic target to inhibit the pathological growth of blood vessels in the cornea (Cho et al., 2020).

Further investigation highlighted that MCs are unevenly distributed across the corneal surface, with a higher concentration along the nasal limbus compared to the temporal side, and that this distribution pattern correlates with more extensive angiogenesis following injury on the nasal side than the temporal side. In mast cell-deficient mice, this asymmetry in blood vessel growth following nasal or temporal corneal injury was not observed, indicating that the presence of MCs is crucial for this differential angiogenic response. Moreover, pharmacological inhibition of MCs with cromolyn attenuated the asymmetrical neovascularization (Cho et al., 2021).

Additionally, the interplay between MCs and lymphangiogenesis has been established; Cho et al. found that MCs migrate adjacent to newly forming lymph vessels, suggesting that they are actively involved in the process of lymphangiogenesis; moreover, in vitro co-culture assays demonstrated that MCs, expressing high levels of the lymphangiogenic factor VEGF-D, directly enhance the tube formation and proliferation of lymphatic endothelial cells. Furthermore, mast cell knockout mice and cromolyn-mediated mast cell inhibition showed that mast cell deficiency suppresses the induction of pathological lymphangiogenesis (Cho et al., 2022).

3.3. Corneal injury and tissue remodeling

The cornea, being a barrier directly exposed to the environment, is susceptible to harm from physical scrapes, chemicals, pathogens, and exposure to UV light. Damage to the cornea manifests through the breakdown of its epithelial layer and the recruitment and activation of immune cells from the surrounding limbus area as well as the cornea's own immune cells. This leads to an inflammatory response and disrupts the cornea's natural homeostasis (Liu and Li, 2021).

Healing from such corneal injuries involves a complex, multi-phase process that includes stages of inflammation, cell proliferation, re-epithelialization, and tissue remodeling (Li et al., 2006, 2011a, 2011b; Liu et al., 2012). To facilitate effective healing, intricate interactions among various cell types, soluble mediators, and extracellular matrix elements are necessary to reconstruct the tissue (Schultz et al., 2011). The inflammatory process is pivotal during wound healing. In its initial phase, inflammation serves a protective role, combating pathogens and removing dead cells to pave the way for tissue repair. Subsequently, it stimulates the generation of growth factors that promote the phases of proliferation and tissue remodeling (Bukowiecki et al., 2017; Eming et al., 2014). Nonetheless, if this inflammatory response becomes excessive or prolonged, it can impede proper re-epithelialization. The overactive immune cells may produce myeloperoxidase (MPO) and TNFα, leading to additional tissue harm that can slow the healing of corneal wounds, potentially causing the cornea to become thinner, develop perforations, or scar (Ljubimov and Saghizadeh, 2015; Wilson, 2020). MCs are among the cellular players involved in various stages of the healing process, contributing significantly to different facets of wound repair (Noli and Miolo, 2001). MCs become notably active shortly after an injury, triggering acute inflammation by releasing a variety of mediators. These mediators, some of which are pre-stored in granules and others synthesized on-demand, play a crucial role in initiating the inflammatory response (Galli et al., 2005b). A significant number of these substances promote inflammation, leading to increased blood flow, enhanced vascular permeability, and the mobilization and attraction of immune cells, particularly neutrophils, to the site of injury (Dvorak, 2005; Egozi et al., 2003; Weller et al., 2006).

During the subsequent phases of healing, activated MCs contribute by secreting cytokines and growth factors. These substances are vital for the proliferation and movement of various cell types, thus facilitating the repair process. They stimulate the reformation of the epithelial layer, new blood vessel formation, and scar formation (Egozi et al., 2003; Iba et al., 2004; Ng, 2010; Younan et al., 2011). Furthermore, MCs influence fibroblasts, which are pivotal for collagen deposition and tissue remodeling, during the later stages of wound repair. They release several pro-fibrotic agents including TGF-β and PDGF, among others, to aid in this process (Gailit et al., 2001; Gruber, 2003; Kupietzky and Levi-Schaffer, 1996). However, MCs are also known for producing anti-inflammatory and immunosuppressive cytokines such as interleukin IL-4 and IL-10 (Grimbaldeston et al., 2007; Hügle et al., 2011;

Trautmann et al., 2000). This dual role underscores their ability to initiate inflammation at the early stages of tissue repair and subsequently help dampen the inflammatory response as healing progresses (Galli et al., 2008; Serhan et al., 2008; Tsai et al., 2011).

Using a mouse model of corneal injury, Sahu et al. observed that neutrophils quickly gather in the cornea shortly after the injury. This gathering is closely linked to the activation of MCs and a surge in CXCL2 expression, a chemoattractant molecule naturally produced by MCs that is further over-expressed in response to corneal harm, thereby facilitating the early arrival of neutrophils. The study also examined the effects of suppressing MCs using cromolyn sodium. The results showed a decrease in CXCL2 levels, a reduction in the early entry of neutrophils, and a consequent reduction in corneal inflammation (Sahu et al., 2018).

Elbasiony et al. highlighted the dual role of MCs in the inflammatory response: initially drawing neutrophils to the injury site and subsequently enhancing their activation. This increased activation leads to a higher discharge of myeloperoxidase (MPO), thus promoting its tissue-destructive properties (Elbasiony et al., 2022).

Additionally, MCs, when activated by corneal injury, may also engage with corneal nerves, fostering neuroinflammation and nerve damage, thereby hindering the wound healing process (Guan et al., 2022).

Furthermore, Guan et al. revealed that cells of the injured corneal epithelium produce high amounts of IL-33. This cytokine, known for its broad influence on various types of immune responses, prompts MCs to release elevated levels of CXCL2. Moreover, the application of agents that neutralize IL-33 directly on the ocular surface was found to hinder the activation of MCs, lessen the invasion of neutrophils, and diminish inflammatory clouding of the cornea, thereby maintaining the integrity of the tissue structure (Guan et al., 2022).

3.4. Corneal alloimmunity

Corneal transplantation has become one of the most common forms of solid tissue grafting, often being the only possible intervention for vision restoration. However, the success of transplantation is often compromised by the inherent reactivity of the immune system toward allogeneic tissues (Dana et al., 2000; Niederkorn, 2002; Singh et al., 2019). The process of graft rejection involves a complex series of interactions between the innate and adaptive branches of the immune system (Murphy et al., 2011; Singh et al., 2019). Surgical trauma and the associated tissue damage trigger an initial response from the innate immune system, marked by an influx of inflammatory cells such as DCs and macrophages, alongside a surge in pro-inflammatory cytokines. APCs then travel from the transplant site to the recipient's nearby lymphoid tissues, initiating an adaptive immune response by presenting the donor's antigens to the recipient's naïve T cells. This process leads to the creation of T-helper type 1 (Th1) cells that target the graft. (Alegre et al., 2016; Amouzegar et al., 2016; Zhu et al., 2021).

Additionally, Treg dysfunction plays an important role in corneal graft rejection (Inomata et al., 2016). In acute rejection, mast cells (MCs) support graft survival by promoting the immunosuppressive properties of Treg cells and inhibiting effector T cells. Conversely, in chronic rejection, MCs contribute to graft damage, particularly through the release of profibrotic mediators (Elieh Ali Komi and Ribatti, 2019; Kritas et al., 2013). This highlights the importance of studying the interplay between these cells to better understand and potentially mitigate the mechanisms underlying graft rejection.

MCs, key players in both innate and adaptive immune responses, have been demonstrated to participate in the process of allosensitization on the ocular surface, contributing to the challenges of corneal transplantation. Li et al. identified that MCs are instrumental in promoting allosensitization post-transplantation, as evidenced by the increased presence and activation of MCs at the site of the graft. They highlight a significant rise in TNF-α secretion by MCs after transplantation. This increase in TNF-α is known to encourage the maturation of APCs and

enhance interactions between APCs and CD4$^+$ Th1 cells in the draining lymph nodes. Furthermore, the inhibition of MCs achieved with the topical application of 2% cromolyn sodium was found to reduce the inflammatory cell invasion and APC maturation, decrease Th1 cell formation within draining lymphoid organs, and diminish the infiltration of alloimmune-inflammatory cells into the graft (Li et al., 2019).

Elbasiony et al. observed that MCs not only possess high levels of MHC II but also exhibit an increased expression of MHC II upon stimulation by IFNγ. When CD4$^+$ T cells, previously primed to recognize alloantigens, were cultured together with MCs, there was a marked elevation in IFNγ production compared to when T cells were cultured independently. This effect mirrors the response seen with traditional allogeneic APCs (Elsayed Elbasiony et al., 2021).

4. Conclusion

This extensive review of MCs physiology, their roles in the immune response, and specific contributions to ocular surface homeostasis, underscores the complexity and significance of these cells beyond their traditional perception as mere facilitators of allergic reactions. The capacity of MCs to interact with a wide array of immune cells through their diverse mediators, as well as their strategic positioning across barrier sites, highlights their essential role in coordinating immune responses.

Given the breadth of functions attributed to MCs, coupled with their involvement in a range of ocular conditions, targeting these cells and their mediators presents a promising avenue for therapeutic intervention. Therefore, the administration of mast cell stabilizers may play a promising role in modulating corneal immune homeostasis and influencing the course of chronic inflammatory ocular surface diseases.

CRediT authorship contribution statement

Vincenzo Barone: Writing – review & editing, Writing – original draft, Project administration, Investigation. **Laura Scirocco:** Writing – review & editing, Visualization, Resources. **Pier Luigi Surico:** Writing – review & editing, Validation, Supervision. **Alessandra Micera:** Validation, Supervision, Data curation. **Francesco Cutrupi:** Visualization. **Marco Coassin:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Antonio Di Zazzo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Data availability

Data will be made available on request.

References

Abdelfattah, N.S., Amgad, M., Zayed, A.A., Salem, H., Elkhanany, A.E., Hussein, H., El-Baky, N.A., 2015. Clinical correlates of common corneal neovascular diseases: a literature review. Int. J. Ophthalmol. 8, 182–193. https://doi.org/10.3980/J.ISSN.2222-3959.2015.01.32.

Abdelfattah, N.S., Amgad, M., Zayed, A.A., Hussein, H., El-Baky, N.A., 2016. Molecular underpinnings of corneal angiogenesis: advances over the past decade. Int. J. Ophthalmol. 9, 768–779. https://doi.org/10.18240/IJO.2016.05.24.

Abraham, S.N., St John, A.L., 2010. Mast cell-orchestrated immunity to pathogens. Nat. Rev. Immunol. 10, 440–452. https://doi.org/10.1038/NRI2782.

Ackerman, S., Smith, L.M., Gomes, P.J., 2016. Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. Ther Adv Chronic Dis 7, 52–67. https://doi.org/10.1177/2040622315612745.

Alegre, M.L., Lakkis, F.G., Morelli, A.E., 2016. Antigen presentation in transplantation. Trends Immunol. 37, 831–843. https://doi.org/10.1016/J.IT.2016.09.003.

Ali, H., 2010. Regulation of human mast cell and basophil function by anaphylatoxins C3a and C5a. Immunol. Lett. 128, 36–45. https://doi.org/10.1016/J.IMLET.2009.10.007.

Ambati, B.K., Nozaki, M., Singh, N., Takeda, A., Jani, P.D., Suthar, T., Albuquerque, R.J. C., Richter, E., Sakurai, E., Newcomb, M.T., Kleinman, M.E., Caldwell, R.B., Lin, Q., Ogura, Y., Orecchia, A., Samuelson, D.A., Agnew, D.W., St Leger, J., Green, W.R., Mahasreshti, P.J., Curiel, D.T., Kwan, D., Marsh, H., Ikeda, S., Leiper, L.J., Collinson, J.M., Bogdanovich, S., Khurana, T.S., Shibuya, M., Baldwin, M.E., Ferrara, N., Gerber, H.P., De Falco, S., Witta, J., Baffi, J.Z., Raisler, B.J., Ambati, J., 2006. Corneal avascularity is due to soluble VEGF receptor-1. Nature 443, 993–997. https://doi.org/10.1038/NATURE05249.

Amin, K., 2012. The role of mast cells in allergic inflammation. Respir. Med. 106, 9–14. https://doi.org/10.1016/J.RMED.2011.09.007.

Amouzegar, A., Chauhan, S.K., Dana, R., 2016. Alloimmunity and tolerance in corneal transplantation. J. Immunol. 196, 3983–3991. https://doi.org/10.4049/JIMMUNOL.1600251.

Arifuzzaman, M., Mobley, Y.R., Choi, H.W., Bist, P., Salinas, C.A., Brown, Z.D., Chen, S. L., Staats, H.F., Abraham, S.N., 2019. MRGPR-mediated activation of local mast cells clears cutaneous bacterial infection and protects against reinfection. Sci. Adv. 5 https://doi.org/10.1126/SCIADV.AAV0216.

Befus, A.D., Pearce, F.L., Gauldie, J., Horsewood, P., Bienenstock, J., 1982. Mucosal mast cells. I. Isolation and functional characteristics of rat intestinal mast cells. J. Immunol. 128, 2475–2480. https://doi.org/10.4049/jimmunol.128.6.2475.

Bienenstock, J., Befus, A.D., Denburg, J., Goodacre, R., Pearce, F., Shanahan, F., 1983. Mast cell heterogeneity. Monogr. Allergy 18, 124–128.

Bischoff, S.C., 2009. Physiological and pathophysiological functions of intestinal mast cells. Semin. Immunopathol. 31, 185–205. https://doi.org/10.1007/S00281-009-0165-4.

Boyce, J.A., 2003. Mast cells: beyond IgE. J. Allergy Clin. Immunol. 111, 24–32. https://doi.org/10.1067/mai.2003.60.

Bukowiecki, A., Hos, D., Cursiefen, C., Eming, S.A., 2017. Wound-healing studies in cornea and skin: parallels, differences and opportunities. Int. J. Mol. Sci. 18 https://doi.org/10.3390/IJMS18061257.

Chan, C.Y., St John, A.L., Abraham, S.N., 2012. Plasticity in mast cell responses during bacterial infections. Curr. Opin. Microbiol. 15, 78–84. https://doi.org/10.1016/J.MIB.2011.10.007.

Chauhan, S.K., Jin, Y., Goyal, S., Lee, H.S., Fuchsluger, T.A., Lee, H.K., Dana, R., 2011. A novel pro-lymphangiogenic function for Th17/IL-17. Blood 118, 4630–4634. https://doi.org/10.1182/BLOOD-2011-01-332049.

Cho, W.K., Mittal, S.K., Elbasiony, E., Chauhan, S.K., 2020. Activation of ocular surface mast cells promotes corneal neovascularization. Ocul. Surf. 18, 857–864. https://doi.org/10.1016/J.JTOS.2020.09.002.

Cho, W.K., Mittal, S.K., Elbasiony, E., Chauhan, S.K., 2021. Spatial distribution of mast cells regulates asymmetrical angiogenesis at the ocular surface. Am. J. Pathol. 191, 1108–1117. https://doi.org/10.1016/J.AJPATH.2021.02.016.

Cho, W.K., Mittal, S.K., Elbasiony, E., Chauhan, S.K., 2022. Ocular surface mast cells promote inflammatory lymphangiogenesis. Microvasc. Res. 141 https://doi.org/10.1016/J.MVR.2022.104320.

Church, M.K., McGill, J.I., 2002. Human ocular mast cells. Curr. Opin. Allergy Clin. Immunol. 2, 419–422. https://doi.org/10.1097/00130832-200210000-00009.

Clements, J.L., Dana, R., 2011. Inflammatory corneal neovascularization: etiopathogenesis. Semin. Ophthalmol. 26, 235–245. https://doi.org/10.3109/08820538.2011.588652.

Cook, E.B., Stahl, J.L., Barney, N.P., Graziano, F.M., 2002. Mechanisms of antihistamines and mast cell stabilizers in ocular allergic inflammation. Curr. Drug Targets - Inflamm. Allergy 1, 167–180. https://doi.org/10.2174/1568010023344733.

Cook, D.N., Pisetsky, D.S., Schwartz, D.A., 2004. Toll-like receptors in the pathogenesis of human disease. Nat. Immunol. 5, 975–979. https://doi.org/10.1038/NI1116.

Coussens, L.M., Raymond, W.W., Bergers, G., Laig-Webster, M., Behrendtsen, O., Werb, Z., Caughey, G.H., Hanahan, D., 1999. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev. 13, 1382–1397. https://doi.org/10.1101/GAD.13.11.1382.

Cumberbatch, M., Dearman, R.J., Griffiths, C.E.M., Kimber, I., 2000. Langerhans cell migration. Clin. Exp. Dermatol. 25, 413–418. https://doi.org/10.1046/J.1365-2230.2000.00678.X.

Cursiefen, C., Chen, L., Dana, M.R., Streilein, J.W., 2003. Corneal lymphangiogenesis: evidence, mechanisms, and implications for corneal transplant immunology. Cornea 22, 273–281. https://doi.org/10.1097/00003226-200304000-00021.

da Silva, E.Z.M., Jamur, M.C., Oliver, C., 2014. Mast cell function: a new vision of an old cell. J. Histochem. Cytochem. 62, 698–738. https://doi.org/10.1369/0022155414545334.

Dahlin, J.S., Hallgren, J., 2015. Mast cell progenitors: origin, development and migration to tissues. Mol. Immunol. 63, 9–17. https://doi.org/10.1016/J.MOLIMM.2014.01.018.

Dana, M.R., Qian, Y., Hamrah, P., 2000. Twenty-five-year panorama of corneal immunology: emerging concepts in the immunopathogenesis of microbial keratitis, peripheral ulcerative keratitis, and corneal transplant rejection. Cornea 19, 625–643. https://doi.org/10.1097/00003226-200009000-00008.

Dawson, D.W., Volpert, O.V., Gillis, P., Crawford, S.E., Xu, H.J., Benedict, W., Bouck, N. P., 1999. Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. Science 285, 245–248. https://doi.org/10.1126/SCIENCE.285.5425.245.

Draber, P., Halova, I., Levi-Schaffer, F., Draberova, L., 2012. Transmembrane adaptor proteins in the high-affinity IgE receptor signaling. Front. Immunol. 2 https://doi.org/10.3389/FIMMU.2011.00095.

Duan, S., Koziol-White, C.J., Jester, W.F., Nycholat, C.M., Macauley, M.S., Panettieri, R. A., Paulson, J.C., 2019. CD33 recruitment inhibits IgE-mediated anaphylaxis and desensitizes mast cells to allergen. J. Clin. Invest. 129, 1387–1401. https://doi.org/10.1172/JCI125456.

Dupuis, P., Prokopich, C.L., Hynes, A., Kim, H., 2020. A contemporary look at allergic conjunctivitis. Allergy Asthma Clin. Immunol. 16 https://doi.org/10.1186/S13223-020-0403-9.

Dvorak, A.M., 2005. Mast cell-derived mediators of enhanced microvascular permeability, vascular permeability factor/vascular endothelial growth factor, histamine, and serotonin, cause leakage of macromolecules through a new endothelial cell permeability organelle, the vesiculo-vacuolar organelle. Chem. Immunol. Allergy 85, 185–204. https://doi.org/10.1159/000086517.

Egozi, E.I., Ferreira, A.M., Burns, A.L., Gamelli, R.L., DiPietro, L.A., 2003. Mast cells modulate the inflammatory but not the proliferative response in healing wounds. Wound Repair Regen. 11, 46–54. https://doi.org/10.1046/J.1524-475X.2003.11108.X.

Elbasiony, Elsayed, Mittal, Sharad, Cho, WonKyung, Chauhan, Sunil, 2021. Mast cells directly activate corneal allograft-primed T cells. Invest. Ophthalmol. Vis. Sci. 62, 890.

Elbasiony, Elsayed, Cho, WonKyung, Guan, Yilin, Singh, Aastha, Mittal, Sharad, Chauhan, Sunil, 2022. Mast cells augment neutrophil activation and their secretion of tissue-damaging factor. Invest. Ophthalmol. Vis. Sci. 63, 1123, 1123.

Elieh Ali Komi, D., Ribatti, D., 2019. Mast cell-mediated mechanistic pathways in organ transplantation. Eur. J. Pharmacol. 857 https://doi.org/10.1016/J.EJPHAR.2019.172458.

Elieh Ali Komi, D., Rambasek, T., Bielory, L., 2018. Clinical implications of mast cell involvement in allergic conjunctivitis. Allergy 73, 528–539. https://doi.org/10.1111/ALL.13334.

Ellenberg, D., Azar, D.T., Hallak, J.A., Tobaigy, F., Han, K.Y., Jain, S., Zhou, Z., Chang, J. H., 2010. Novel aspects of corneal angiogenic and lymphangiogenic privilege. Prog. Retin. Eye Res. 29, 208–248. https://doi.org/10.1016/J.PRETEYERES.2010.01.002.

Ellmeier, W., Abramova, A., Schebesta, A., 2011. Tec family kinases: regulation of FcεRI-mediated mast-cell activation. FEBS J. 278, 1990–2000. https://doi.org/10.1111/J.1742-4658.2011.08073.X.

Eming, S.A., Martin, P., Tomic-Canic, M., 2014. Wound repair and regeneration: mechanisms, signaling, and translation. Sci. Transl. Med. 6 https://doi.org/10.1126/SCITRANSLMED.3009337.

Enerbäck, L., 1966. Mast cells in rat gastrointestinal mucosa. 2. Dye-binding and metachromatic properties. Acta Pathol. Microbiol. Scand. 66, 303–312. https://doi.org/10.1111/APM.1966.66.3.303.

Flanagan, J.G., Leder, P., 1990. The kit ligand: a cell surface molecule altered in steel mutant fibroblasts. Cell 63, 185–194. https://doi.org/10.1016/0092-8674(90)90299-T.

Foulsham, W., Coco, G., Amouzegar, A., Chauhan, S.K., Dana, R., 2018. When clarity is crucial: regulating ocular surface immunity. Trends Immunol. 39, 288–301. https://doi.org/10.1016/J.IT.2017.11.007.

Friend, D.S., Ghildyal, N., Austen, K.F., Gurish, M.F., Matsumoto, R., Stevens, R.L., 1996. Mast cells that reside at different locations in the jejunum of mice infected with Trichinella spiralis exhibit sequential changes in their granule ultrastructure and chymase phenotype. J. Cell Biol. 135, 279–290. https://doi.org/10.1083/JCB.135.1.279.

Fuda, S., Angelini, D.F., Colopi, A., Guida, E., Onorato, A., Grimaldi, P., Travaglini, S., Jannini, E.A., Dolci, S., 2023. A minimal promoter region of Kit gene recapitulates mast cell differentiation in development, aging and inflammation. Mech. Ageing Dev. 212 https://doi.org/10.1016/J.MAD.2023.111820.

Fukuoka, Y., Hite, M.R., Dellinger, A.L., Schwartz, L.B., 2013. Human skin mast cells express complement factors C3 and C5. J. Immunol. 191, 1827–1834. https://doi.org/10.4049/JIMMUNOL.1202889.

Gailit, J., Marchese, M.J., Kew, R.R., Gruber, B.L., 2001. The differentiation and function of myofibroblasts is regulated by mast cell mediators. J. Invest. Dermatol. 117, 1113–1119. https://doi.org/10.1046/J.1523-1747.2001.15211.X.

Galli, S.J., 1990. New insights into "the riddle of the mast cells": microenvironmental regulation of mast cell development and phenotypic heterogeneity. Lab. Invest. 62, 5–33. https://doi.org/10.1007/978-1-4612-0485-5_5.

Galli, S.J., Tsai, M., 2010. Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity. Eur. J. Immunol. 40, 1843–1851. https://doi.org/10.1002/EJI.201040559.

Galli, S.J., Tsai, M., 2012. IgE and mast cells in allergic disease. Nat. Med. 18, 693–704. https://doi.org/10.1038/NM.2755.

Galli, S.J., Tsai, M., Wershil, B.K., 1993. The c-kit receptor, stem cell factor, and mast cells. What each is teaching us about the others. Am. J. Pathol. 142, 965–974.

Galli, S.J., Kalesnikoff, J., Grimbaldeston, M.A., Piliponsky, A.M., Williams, C.M.M., Tsai, M., 2005a. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. Annu. Rev. Immunol. 23, 749–786. https://doi.org/10.1146/ANNUREV.IMMUNOL.21.120601.141025.

Galli, S.J., Nakae, S., Tsai, M., 2005b. Mast cells in the development of adaptive immune responses. Nat. Immunol. 6, 135–142. https://doi.org/10.1038/NI1158.

Galli, S.J., Grimbaldeston, M., Tsai, M., 2008. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nat. Rev. Immunol. 8, 478–486. https://doi.org/10.1038/NRI2327.

Gauchat, J.F., Henchoz, S., Mazzei, G., Aubry, J.P., Brunner, T., Blasey, H., Life, P., Talabot, D., Flores-Romo, L., Thompson, J., Kishi, K., Butterfield, J., Dahinden, C.,

Bonnefoy, J.Y., 1993. Induction of human IgE synthesis in B cells by mast cells and basophils. Nature 365, 340–343. https://doi.org/10.1038/365340A0.

Gilfillan, A.M., Beaven, M.A., 2011. Regulation of mast cell responses in health and disease. Crit. Rev. Immunol. 31, 475–530. https://doi.org/10.1615/CRITREVIMMUNOL.V31.I6.30.

Gonzalez-Gil, A., Schnaar, R.L., 2021. Siglec ligands. Cells 10. https://doi.org/10.3390/CELLS10051260.

Grimbaldeston, M.A., Nakae, S., Kalesnikoff, J., Tsai, M., Galli, S.J., 2007. Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B. Nat. Immunol. 8, 1095–1104. https://doi.org/10.1038/NI1503.

Grootens, J., Ungerstedt, J.S., Nilsson, G., Dahlin, J.S., 2018. Deciphering the differentiation trajectory from hematopoietic stem cells to mast cells. Blood Adv 2, 2273–2281. https://doi.org/10.1182/BLOODADVANCES.2018019539.

Gruber, B.L., 2003. Mast cells in the pathogenesis of fibrosis. Curr. Rheumatol. Rep. 5, 147–153. https://doi.org/10.1007/S11926-003-0043-3.

Guan, Y., Cho, W., Elbasiony, E., Singh, A., Mittal, S., Chauhan, S., 2022. Ocular surface mast cells promote nerve damage and trigeminal ganglion inflammation following corneal injury. Invest. Ophthalmol. Vis. Sci. 63, 901. A0265-901 – A0265.

Gurish, M.F., Austen, K.F., 2001. The diverse roles of mast cells. J. Exp. Med. 194 https://doi.org/10.1084/JEM.194.1.F1.

Hamaguchi, Y., Kanakura, Y., Fujita, J., Takeda, S.I., Nakano, T., Tarui, S., Honjo, T., Kitamura, Y., 1987. Interleukin 4 as an essential factor for in vitro clonal growth of murine connective tissue-type mast cells. J. Exp. Med. 165, 268–273. https://doi.org/10.1084/JEM.165.1.268.

Harvima, I.T., Nilsson, G., 2011. Mast cells as regulators of skin inflammation and immunity. Acta Derm. Venereol. 91, 644–650. https://doi.org/10.2340/00015555-1197.

Hu, Z.-Q., Zhao, W.-H., Shimamura, T., 2007. Regulation of mast cell development by inflammatory factors. Curr. Med. Chem. 14, 3044–3050. https://doi.org/10.2174/092986707782793998.

Hügle, T., Hogan, V., White, K.E., Van Laar, J.M., 2011. Mast cells are a source of transforming growth factor β in systemic sclerosis. Arthritis Rheum. 63, 795–799. https://doi.org/10.1002/ART.30190.

Iba, Y., Shibata, A., Kato, M., Masukawa, T., 2004. Possible involvement of mast cells in collagen remodeling in the late phase of cutaneous wound healing in mice. Int. Immunopharm. 4, 1873–1880. https://doi.org/10.1016/J.INTIMP.2004.08.009.

Inomata, T., Hua, J., Di Zazzo, A., Dana, R., 2016. Impaired function of peripherally induced regulatory T cells in hosts at high risk of graft rejection. Sci. Rep. 6 https://doi.org/10.1038/SREP39924.

Irani, A.M., Schwartz, L.B., 1994. Human mast cell heterogeneity. Allergy Proc. 15, 303–308. https://doi.org/10.2500/108854194778816472.

Irkec, M.T., Bozkurt, B., 2012. Molecular immunology of allergic conjunctivitis. Curr. Opin. Allergy Clin. Immunol. 12, 534–539. https://doi.org/10.1097/ACI.0B013E328357A21B.

Janssens, A.S., Heide, R., Den Hollander, J.C., Mulder, P.G.M., Tank, B., Oranje, A.P., 2005. Mast cell distribution in normal adult skin. J. Clin. Pathol. 58, 285–289. https://doi.org/10.1136/JCP.2004.017210.

Jin, Y., Chauhan, S.K., Annan, J.E.I., Sage, P.T., Sharpe, A.H., Dana, R., 2011. A novel function for programmed death ligand-1 regulation of angiogenesis. Am. J. Pathol. 178, 1922–1929. https://doi.org/10.1016/J.AJPATH.2010.12.027.

Kanakura, Y., Thompson, H., Nakano, T., Yamamura, T., Asai, H., Kitamura, Y., Metcalfe, D.D., Galli, S.J., 1988. Multiple bidirectional alterations of phenotype and changes in proliferative potential during the in vitro and in vivo passage of clonal mast cell populations derived from mouse peritoneal mast cells. Blood 72, 877–885. https://doi.org/10.1182/blood.v72.3.877.bloodjournal723877.

Kashem, S.W., Subramanian, H., Collington, S.J., Magotti, P., Lambris, J.D., Ali, H., 2011. G protein coupled receptor specificity for C3a and compound 48/80-induced degranulation in human mast cells: roles of Mas-related genes MrgX1 and MrgX2. Eur. J. Pharmacol. 668, 299–304. https://doi.org/10.1016/J.EJPHAR.2011.06.027.

Kirshenbaum, A.S., Goff, J.P., Semere, T., Foster, B., Scott, L.M., Metcalfe, D.D., 1999. Demonstration that human mast cells arise from a progenitor cell population that is CD34(+), c-kit(+), and expresses aminopeptidase N (CD13). Blood 94, 2333–2342. https://doi.org/10.1182/blood.v94.7.2333.419k30_2333_2342.

Kritas, S.K., Saggini, A., Varvara, G., Murmura, G., Caraffa, A., Antinolfi, P., Toniato, E., Pantalone, A., Neri, G., Frydas, S., Rosati, M., Tei, M., Speziali, A., Saggini, R., Pandolfi, F., Cerulli, G., Theoharides, T.C., Conti, P., 2013. Impact of Mast Cells in Rejection of Allografts, pp. 609–614. https://doi.org/10.1177/1721727X130110030511 https://doi.org/10.1177/1721727X1301100305.

Krystel-Whittemore, M., Dileepan, K.N., Wood, J.G., 2016. Mast cell: a multi-functional master cell. Front. Immunol. 6 https://doi.org/10.3389/FIMMU.2015.00620.

Kumar, V., Sharma, A., 2010. Mast cells: emerging sentinel innate immune cells with diverse role in immunity. Mol. Immunol. 48, 14–25. https://doi.org/10.1016/J.MOLIMM.2010.07.009.

Kupietzky, A., Levi-Schaffer, F., 1996. The role of mast cell-derived histamine in the closure of an in vitro wound. Inflamm. Res. 45, 176–180. https://doi.org/10.1007/BF02285158.

Landolina, N., Zaffran, I., Smiljkovic, D., Serrano-Candelas, E., Schmiedel, D., Friedman, S., Arock, M., Hartmann, K., Pikarsky, E., Mandelboim, O., Martin, M., Valent, P., Levi-Schaffer, F., 2020. Activation of Siglec-7 results in inhibition of in vitro and in vivo growth of human mast cell leukemia cells. Pharmacol. Res. 158 https://doi.org/10.1016/J.PHRS.2020.104682.

Leonardi, A., 2002. The central role of conjunctival mast cells in the pathogenesis of ocular allergy. Curr. Allergy Asthma Rep. 2, 325–331. https://doi.org/10.1007/S11882-002-0061-7.

Leonardi, A., Motterle, L., Bortolotti, M., 2008. Allergy and the eye. Clin. Exp. Immunol. 153 (Suppl. 1), 17–21. https://doi.org/10.1111/J.1365-2249.2008.03716.X.

Leveson-Gower, D.B., Sega, E.I., Kalesnikoff, J., Florek, M., Pan, Y., Pierini, A., Galli, S.J., Negrin, R.S., 2013. Mast cells suppress murine GVHD in a mechanism independent of CD4+CD25+ regulatory T cells. Blood 122, 3659–3665. https://doi.org/10.1182/BLOOD-2013-08-519157.

Levi-Schaffer, F., Austen, K.F., Gravallese, P.M., Stevens, R.L., 1986. Coculture of interleukin 3-dependent mouse mast cells with fibroblasts results in a phenotypic change of the mast cells. Proc. Natl. Acad. Sci. U. S. A. 83, 6485–6488. https://doi.org/10.1073/PNAS.83.17.6485.

Li, Z., Burns, A.R., Smith, C.W., 2006. Lymphocyte function-associated antigen-1-dependent inhibition of corneal wound healing. Am. J. Pathol. 169, 1590–1600. https://doi.org/10.2353/AJPATH.2006.060415.

Li, Z., Burns, A.R., Han, L., Rumbaut, R.E., Smith, C.W., 2011a. IL-17 and VEGF are necessary for efficient corneal nerve regeneration. Am. J. Pathol. 178, 1106–1116. https://doi.org/10.1016/J.AJPATH.2010.12.001.

Li, Z., Burns, A.R., Miller, S.B., Smith, C.W., 2011b. CCL20, γδ T cells, and IL-22 in corneal epithelial healing. Faseb. J. 25, 2659–2668. https://doi.org/10.1096/FJ.11-184804.

Li, M., Mittal, S.K., Foulsham, W., Amouzegar, A., Sahu, S.K., Chauhan, S.K., 2019. Mast cells contribute to the induction of ocular mucosal alloimmunity. Am. J. Transplant. 19, 662–673. https://doi.org/10.1111/AJT.15084.

Liu, J., Li, Z., 2021. Resident innate immune cells in the cornea. Front. Immunol. 12 https://doi.org/10.3389/FIMMU.2021.620284.

Liu, J., Divoux, A., Sun, J., Zhang, J., Clément, K., Glickman, J.N., Sukhova, G.K., Wolters, P.J., Du, J., Gorgun, C.Z., Doria, A., Libby, P., Blumberg, R.S., Kahn, B.B., Hotamisligil, G.S., Shi, G.P., 2009. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat. Med. 15, 940–945. https://doi.org/10.1038/NM.1994.

Liu, Q., Smith, C.W., Zhang, W., Burns, A.R., Li, Z., 2012. NK cells modulate the inflammatory response to corneal epithelial abrasion and thereby support wound healing. Am. J. Pathol. 181, 452–462. https://doi.org/10.1016/J.AJPATH.2012.04.010.

Liu, J., Fu, T., Song, F., Xue, Y., Xia, C., Liu, P., Wang, H., Zhong, J., Li, Q., Chen, J., Li, Y., Cai, D., Li, Z., 2015. Mast cells participate in corneal development in mice. Sci. Rep. 5 https://doi.org/10.1038/SREP17569.

Ljubimov, A.V., Saghizadeh, M., 2015. Progress in corneal wound healing. Prog. Retin. Eye Res. 49, 17–45. https://doi.org/10.1016/J.PRETEYERES.2015.07.002.

Lohman, R.J., Hamidon, J.K., Reid, R.C., Rowley, J.A., Yau, M.K., Halili, M.A., Nielsen, D.S., Lim, J., Wu, K.C., Loh, Z., Do, A., Suen, J.Y., Iyer, A., Fairlie, D.P., 2017. Exploiting a novel conformational switch to control innate immunity mediated by complement protein C3a. Nat. Commun. 8 https://doi.org/10.1038/S41467-017-00414-W.

Lu, L.F., Lind, E.F., Gondek, D.C., Bennett, K.A., Gleeson, M.W., Pino-Lagos, K., Scott, Z. A., Coyle, A.J., Reed, J.L., Van Snick, J., Strom, T.B., Zheng, X.X., Noelle, R.J., 2006. Mast cells are essential intermediaries in regulatory T-cell tolerance. Nature 442, 997–1002. https://doi.org/10.1038/NATURE05010.

Lubbers, R., van Essen, M.F., van Kooten, C., Trouw, L.A., 2017. Production of complement components by cells of the immune system. Clin. Exp. Immunol. 188, 183–194. https://doi.org/10.1111/CEI.12952.

Maddula, Surekha, Davis, D.K., Maddula, Soumya, Burrow, M.K., Ambati, B.K., 2011. Horizons in therapy for corneal angiogenesis. Ophthalmol. Times 118, 591–599. https://doi.org/10.1016/J.OPHTHA.2011.01.041.

Malaviya, R., Abraham, S.N., 2001. Mast cell modulation of immune responses to bacteria. Immunol. Rev. 179, 16–24. https://doi.org/10.1034/J.1600-065X.2001.790102.X.

Marone, G., Triggiani, M., Genovese, A., De Paulis, A., 2005. Role of human mast cells and basophils in bronchial asthma. Adv. Immunol. 88, 97–160. https://doi.org/10.1016/S0065-2776(05)88004-6.

Marshall, J.S., 2004. Mast-cell responses to pathogens. Nat. Rev. Immunol. 4, 787–799. https://doi.org/10.1038/NRI1460.

McMenamin, P.G., Morrison, S.M., McMenamin, C., 1996. Immunomorphologic studies of mast cell heterogeneity, location, and distribution in the rat conjunctiva. J. Allergy Clin. Immunol. 97, 1375–1386. https://doi.org/10.1016/S0091-6749(96)70207-5.

Mekori, Y.A., Metcalfe, D.D., 1999. Mast cell-T cell interactions. J. Allergy Clin. Immunol. 104, 517–523. https://doi.org/10.1016/S0091-6749(99)70316-7.

Merluzzi, S., Frossi, B., Gri, G., Parusso, S., Tripodo, C., Pucillo, C., 2010. Mast cells enhance proliferation of B lymphocytes and drive their differentiation toward IgA-secreting plasma cells. Blood 115, 2810–2817. https://doi.org/10.1182/BLOOD-2009-10-250126.

Metcalfe, D.D., Baram, D., Mekori, Y.A., 1997. Mast cells. Physiol. Rev. 77, 1033–1079. https://doi.org/10.1152/PHYSREV.1997.77.4.1033.

Micera, A., Jirsova, K., Esposito, G., Balzamino, B.O., Zazzo, A. Di, Bonini, S., 2020. Mast cells populate the corneoscleral limbus: new insights for our understanding of limbal microenvironment. Invest. Ophthalmol. Vis. Sci. 61 https://doi.org/10.1167/IOVS.61.3.43.

Miralda, I., Samanas, N.B., Seo, A.J., Foronda, J.S., Sachen, J., Hui, Y., Morrison, S.D., Oskeritzian, C.A., Piliponsky, A.M., 2023. Siglec-9 is an inhibitory receptor on human mast cells in vitro. J. Allergy Clin. Immunol. 152, 711–724.e14. https://doi.org/10.1016/J.JACI.2023.04.007.

Mishra, P., G, Tamboli, V., Jwala, J., Mitra, K., A, 2011. Recent patents and emerging therapeutics in the treatment of allergic conjunctivitis. Recent Pat. Inflamm. Allergy Drug Discov. 5, 26–36. https://doi.org/10.2174/187221311794474883.

Miyazaki, D., Tominaga, T., Yakura, K., Kuo, C.H., Komatsu, N., Inoue, Y., Ono, S.J., 2008. Conjunctival mast cell as a mediator of eosinophilic response in ocular allergy. Mol. Vis. 14, 1525–1532.

Mizrahi, S., Gibbs, B.F., Karra, L., Ben-Zimra, M., Levi-Schaffer, F., 2014. Siglec-7 is an inhibitory receptor on human mast cells and basophils. J. Allergy Clin. Immunol. 134 https://doi.org/10.1016/J.JACI.2014.03.031.

Molderings, G.J., Afrin, L.B., 2023. A survey of the currently known mast cell mediators with potential relevance for therapy of mast cell-induced symptoms. Naunyn-Schmiedeberg's Arch. Pharmacol. 396, 2881. https://doi.org/10.1007/S00210-023-02545-Y.

Moon, T.C., St Laurent, C.D., Morris, K.E., Marcet, C., Yoshimura, T., Sekar, Y., Befus, A. D., 2010. Advances in mast cell biology: new understanding of heterogeneity and function. Mucosal Immunol. 3, 111–128. https://doi.org/10.1038/MI.2009.136.

Muench, M.O., Cupp, J., Polakoff, J., Roncarolo, M.G., 1994. Expression of CD33, CD38, and HLA-DR on CD34+ human fetal liver progenitors with a high proliferative potential. Blood 83, 3170–3181.

Murphy, S.P., Porrett, P.M., Turka, L.A., 2011. Innate immunity in transplant tolerance and rejection. Immunol. Rev. 241, 39–48. https://doi.org/10.1111/J.1600-065X.2011.01009.X.

Nakae, S., Suto, H., Kakurai, M., Sedgwick, J.D., Tsai, M., Galli, S.J., 2005. Mast cells enhance T cell activation: importance of mast cell-derived TNF. Proc. Natl. Acad. Sci. U. S. A. 102, 6467–6472. https://doi.org/10.1073/PNAS.0501912102.

Nakae, S., Suto, H., Iikura, M., Kakurai, M., Sedgwick, J.D., Tsai, M., Galli, S.J., 2006. Mast cells enhance T cell activation: importance of mast cell costimulatory molecules and secreted TNF. J. Immunol. 176, 2238–2248. https://doi.org/10.4049/JIMMUNOL.176.4.2238.

Ng, M.F., 2010. The role of mast cells in wound healing. Int. Wound J. 7, 55–61. https://doi.org/10.1111/J.1742-481X.2009.00651.X.

Niederkorn, J.Y., 2002. Immunology and immunomodulation of corneal transplantation. Int. Rev. Immunol. 21, 173–196. https://doi.org/10.1080/08830180212064.

Noli, C., Miolo, A., 2001. The mast cell in wound healing. Vet. Dermatol. 12, 303–313. https://doi.org/10.1046/J.0959-4493.2001.00272.X.

Norrby, K., 2002. Mast cells and angiogenesis. APMIS 110, 355–371. https://doi.org/10.1034/J.1600-0463.2002.100501.X.

Otsu, K., Nakano, T., Kanakura, Y., Asai, H., Katz, H.R., Frank Austen, K., Stevens, R.L., Galli, S.J., Kitamura, Y., 1987. Phenotypic changes of bone marrow-derived mast cells after intraperitoneal transfer into W/Wv mice that are genetically deficient in mast cells. J. Exp. Med. 165, 615–627. https://doi.org/10.1084/JEM.165.3.615.

Ott, V.L., Cambier, J.C., Kappler, J., Marrack, P., Swanson, B.J., 2003. Mast cell-dependent migration of effector CD8+ T cells through production of leukotriene B4. Nat. Immunol. 4, 974–981. https://doi.org/10.1038/NI971.

O'Sullivan, J.A., Chang, A.T., Youngblood, B.A., Bochner, B.S., 2020. Eosinophil and mast cell Siglecs: from biology to drug target. J. Leukoc. Biol. 108, 73–81. https://doi.org/10.1002/JLB.2MR0120-352RR.

Rahkola, D., Laitala, J., Siiskonen, H., Pelkonen, J., Harvima, I.T., 2019. Mast cells are a marked source for complement C3 products that associate with increased CD11b-positive cells in keratinocyte skin carcinomas. Cancer Invest. 37, 73–84. https://doi.org/10.1080/07357907.2019.1565765.

Reber, L.L., Hernandez, J.D., Galli, S.J., 2017. The pathophysiology of anaphylaxis. J. Allergy Clin. Immunol. 140, 335–348. https://doi.org/10.1016/J.JACI.2017.06.003.

Rivera, J., Gilfillan, A.M., 2006. Molecular regulation of mast cell activation. J. Allergy Clin. Immunol. 117, 1214–1225. https://doi.org/10.1016/J.JACI.2006.04.015.

Robida, P.A., Rische, C.H., Morgenstern, N.B.B., Janarthanam, R., Cao, Y., Krier-Burris, R.A., Korver, W., Xu, A., Luu, T., Schanin, J., Leung, J., Rothenberg, M.E., Wechsler, J.B., Youngblood, B.A., Bochner, B.S., O'Sullivan, J.A., 2022. Functional and phenotypic characterization of siglec-6 on human mast cells. Cells 11. https://doi.org/10.3390/CELLS11071138.

Rodewald, H.R., Feyerabend, T.B., 2012. Widespread immunological functions of mast cells: fact or fiction? Immunity 37, 13–24. https://doi.org/10.1016/J.IMMUNI.2012.07.007.

Rönnberg, E., Guss, B., Pejler, G., 2010. Infection of mast cells with live streptococci causes a toll-like receptor 2- and cell-cell contact-dependent cytokine and chemokine response. Infect. Immun. 78, 854–864. https://doi.org/10.1128/IAI.01004-09.

Royer, D.J., Zheng, M., Conrady, C.D., Carr, D.J.J., 2015. Granulocytes in ocular HSV-1 infection: opposing roles of mast cells and neutrophils. Invest. Ophthalmol. Vis. Sci. 56, 3763–3775. https://doi.org/10.1167/IOVS.15-16900.

S, S., T, S., T, N.Y., Kanayama, Y., Kanakura, H.A., T, Y., Y, Kitamura, 1986. Development of mucosal mast cells after injection of a single connective tissue-type mast cell in the stomach mucosa of genetically mast cell-deficient W/Wv mice. J. Immunol. 137, 1319–1322. https://doi.org/10.4049/jimmunol.137.4.1319.

Sahu, S.K., Mittal, S.K., Foulsham, W., Li, M., Sangwan, V.S., Chauhan, S.K., 2018. Mast cells initiate the recruitment of neutrophils following ocular surface injury. Invest. Ophthalmol. Vis. Sci. 59, 1732–1740. https://doi.org/10.1167/IOVS.17-23398.

Schanin, J., Gebremeskel, S., Korver, W., Falahati, R., Butuci, M., Haw, T.J., Nair, P.M., Liu, G., Hansbro, N.G., Hansbro, P.M., Evensen, E., Brock, E.C., Xu, A., Wong, A., Leung, J., Bebbington, C., Tomasevic, N., Youngblood, B.A., 2021. A monoclonal antibody to Siglec-8 suppresses non-allergic airway inflammation and inhibits IgE-independent mast cell activation. Mucosal Immunol. 14, 366–376. https://doi.org/10.1038/S41385-020-00336-9.

Schlereth, S., Lee, H.S., Khandelwal, P., Saban, D.R., 2012. Blocking CCR7 at the ocular surface impairs the pathogenic contribution of dendritic cells in allergic conjunctivitis. Am. J. Pathol. 180, 2351–2360. https://doi.org/10.1016/J.AJPATH.2012.02.015.

Schultz, G.S., Davidson, J.M., Kirsner, R.S., Bornstein, P., Herman, I.M., 2011. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen. 19, 134–148. https://doi.org/10.1111/J.1524-475X.2011.00673.X.

Serhan, C.N., Chiang, N., Van Dyke, T.E., 2008. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat. Rev. Immunol. 8, 349–361. https://doi.org/10.1038/NRI2294.

Shea-Donohue, T., Stiltz, J., Zhao, A., Notari, L., 2010. Mast cells. Curr. Gastroenterol. Rep. 12, 349–357. https://doi.org/10.1007/S11894-010-0132-1.

Shelburne, C.P., Nakano, H., St John, A.L., Chan, C., McLachlan, J.B., Gunn, M.D., Staats, H.F., Abraham, S.N., 2009. Mast cells augment adaptive immunity by orchestrating dendritic cell trafficking through infected tissues. Cell Host Microbe 6, 331–342. https://doi.org/10.1016/J.CHOM.2009.09.004.

Sibilano, R., Frossi, B., Pucillo, C.E., 2014. Mast cell activation: a complex interplay of positive and negative signaling pathways. Eur. J. Immunol. 44, 2558–2566. https://doi.org/10.1002/EJI.201444546.

Singh, R., Gupta, N., Vanathi, M., Tandon, R., 2019. Corneal transplantation in the modern era. Indian J. Med. Res. 150, 7–22. https://doi.org/10.4103/IJMR.IJMR_141_19.

Siraganian, R.P., 2003. Mast cell signal transduction from the high-affinity IgE receptor. Curr. Opin. Immunol. 15, 639–646. https://doi.org/10.1016/j.coi.2003.09.010.

Steinman, R.M., Inaba, K., 1999. Myeloid dendritic cells. J. Leukoc. Biol. 66, 205–208. https://doi.org/10.1002/JLB.66.2.205.

Supajatura, V., Ushio, H., Nakao, A., Okumura, K., Ra, C., Ogawa, H., 2001. Protective roles of mast cells against enterobacterial infection are mediated by Toll-like receptor 4. J. Immunol. 167, 2250–2256. https://doi.org/10.4049/JIMMUNOL.167.4.2250.

Suurmond, J., Dorjée, A.L., Knol, E.F., Huizinga, T.W.J., Toes, R.E.M., 2015. Differential TLR-induced cytokine production by human mast cells is amplified by FcεRI triggering. Clin. Exp. Allergy 45, 788–796. https://doi.org/10.1111/CEA.12509.

Tlsty, T.D., Coussens, L.M., 2006. Tumor stroma and regulation of cancer development. Annu. Rev. Pathol. 1, 119–150. https://doi.org/10.1146/ANNUREV.PATHOL.1.110304.100224.

Trautmann, A., Toksoy, A., Engelhardt, E., Bröcker, E.B., Gillitzer, R., 2000. Mast cell involvement in normal human skin wound healing: expression of monocyte chemoattractant protein-1 is correlated with recruitment of mast cells which synthesize interleukin-4 in vivo. J. Pathol. 190, 100–106. https://doi.org/10.1002/(sici)1096-9896(200001)190:1<100::aid-path496>3.0.co;2-q.

Tsai, M., Grimbaldeston, M., Galli, S.J., 2011. Mast cells and immunoregulation/immunomodulation. Adv. Exp. Med. Biol. 716, 186–211. https://doi.org/10.1007/978-1-4419-9533-9_11.

Turner, H., Kinet, J.P., 1999. Signalling through the high-affinity IgE receptor Fc epsilonRI. Nature 402. https://doi.org/10.1038/35037021.

Villegas, B.V., Benitez-Del-castillo, J.M., 2021. Current knowledge in allergic conjunctivitis. Turk J Ophthalmol 51, 45–54. https://doi.org/10.4274/TJO.GALENOS.2020.11456.

Wang, S., Kahale, F., Naderi, A., Surico, P., Yin, J., Dohlman, T., Chen, Y., Dana, R., 2024. Therapeutic effects of stimulating the melanocortin pathway in regulating ocular inflammation and cell death. Biomolecules 14, 169. https://doi.org/10.3390/BIOM14020169.

Welle, M., 1997. Development, significance, and heterogeneity of mast cells with particular regard to the mast cell-specific proteases chymase and tryptase. J. Leukoc. Biol. 61, 233–245. https://doi.org/10.1002/JLB.61.3.233.

Weller, K., Foitzik, K., Paus, R., Syska, W., Maurer, M., Weller, K., Foitzik, K., Paus, R., Syska, W., Maurer, M., 2006. Mast cells are required for normal healing of skin wounds in mice. Faseb. J. 20, 2366–2368. https://doi.org/10.1096/FJ.06-5837FJE.

Wilson, S.E., 2020. Corneal wound healing. Exp. Eye Res. 197 https://doi.org/10.1016/J.EXER.2020.108089.

Xie, Y., Zhang, H., Liu, S., Chen, G., He, S., Li, Z., Wang, L., 2018. Mast cell activation protects cornea by promoting neutrophil infiltration via stimulating ICAM-1 and vascular dilation in fungal keratitis. Sci. Rep. 8 https://doi.org/10.1038/S41598-018-26798-3.

Y, K., 1989. Heterogeneity of mast cells and phenotypic change between subpopulations. Annu. Rev. Immunol. 7, 59–76. https://doi.org/10.1146/ANNUREV.IY.07.040189.000423.

Yokoi, H., Myers, A., Matsumoto, K., Crocker, P.R., Saito, H., Bochner, B.S., 2006. Alteration and acquisition of Siglecs during in vitro maturation of CD34+ progenitors into human mast cells. Allergy 61, 769–776. https://doi.org/10.1111/J.1398-9995.2006.01133.X.

Yokoi, H., Choi, O.H., Hubbard, W., Lee, H.S., Canning, B.J., Lee, H.H., Ryu, S.D., von Gunten, S., Bickel, C.A., Hudson, S.A., MacGlashan, D.W., Bochner, B.S., 2008. Inhibition of FcepsilonRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. J. Allergy Clin. Immunol. 121 https://doi.org/10.1016/J.JACI.2007.10.004.

Younan, G.J., Heit, Y.I., Dastouri, P., Kekhia, H., Xing, W., Gurish, M.F., Orgill, D.P., 2011. Mast cells are required in the proliferation and remodeling phases of microdeformational wound therapy. Plast. Reconstr. Surg. 128 https://doi.org/10.1097/PRS.0B013E318230C55D.

Youngblood, B.A., Brock, E.C., Leung, J., Falahati, R., Bochner, B.S., Rasmussen, H.S., Peterson, K., Bebbington, C., Tomasevic, N., 2019. Siglec-8 antibody reduces eosinophils and mast cells in a transgenic mouse model of eosinophilic gastroenteritis. JCI Insight 4. https://doi.org/10.1172/JCI.INSIGHT.126219.

Zhang, Y., Ramos, B.F., Jakschik, B.A., 1992. Neutrophil recruitment by tumor necrosis factor from mast cells in immune complex peritonitis. Science 258, 1957–1959. https://doi.org/10.1126/SCIENCE.1470922.

Zhu, J., Inomata, T., Di Zazzo, A., Kitazawa, K., Okumura, Y., Coassin, M., Surico, P.L., Fujio, K., Yanagawa, A., Miura, M., Akasaki, Y., Fujimoto, K., Nagino, K.,

Midorikawa-Inomata, A., Hirosawa, K., Kuwahara, M., Huang, T., Shokirova, H., Eguchi, A., Murakami, A., 2021. Role of immune cell diversity and heterogeneity in corneal graft survival: a systematic review and meta-analysis. J. Clin. Med. 10 https://doi.org/10.3390/JCM10204667.