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The evolution of mast cells across all vertebrate classes: The mystery continues

Stefano Bacci
Department of Biology, Research Unit of Histology and Embryology, University of Florence, Florence, Italy

Summary. The paper examines what the mast cell, a cell that arose in urochordates and reached humans with the same morphological profile, is used for. Activated mast cells contribute to the regulation of the local immune response and major inflammation and healing processes with the help of a broad range of mediators. Located primarily at the interface between the host and the external environment, mast cells are widely distributed. The local microenvironment directly affects mast cell development, phenotype, and function, which in turn affects the cells' capacity to identify and react to different stimuli by releasing a variety of physiologically active mediators. By interacting with a range of other cells involved in physiological and immunological responses, mast cells can react to changes in their surroundings and serve as first responders in dangerous situations. Consequently, the mast cell's crucial function in innate and adaptive immunity, including immunological tolerance, has come to light more frequently. On the other hand, mast cell malfunction has identified these cells as the primary culprits in a number of autoimmune illnesses, cancer, and chronic allergic/inflammatory conditions.

Key words: Evolution, Immune System, Mast Cells, Vertebrates

Introduction

Mast cells (MCs) are multifunctional cells present in all vascularized tissues and organs, and they are increasingly acknowledged as a crucial component of the host defense system (Krystel-Whittemore et al., 2016; Theoharides et al., 2019; Bacci, 2022; St John et al., 2023; Fernández-Guarino and Bacci, 2025). MCs in mammals are associated with innate and adaptive immune responses, wound healing, tissue remodeling, homeostasis, and models of inflammatory diseases. The extensive range of MC biology in mammals underscores the necessity to comprehend the mechanisms governing their growth and extensive dispersion in non-mammalian vertebrates (Krystel-Whittemore et al., 2016; Theoharides et al., 2019; Bacci, 2022; St John et al., 2023; Fernández-Guarino and Bacci, 2025). The initial identification of MCs in a vertebrate was by Friedrich von Recklinghausen in 1863. Since that time, significant advancements have been made in the morphological, histochemical, and biochemical characteristics of MCs. This information will be contrasted with the extensive data available for mammals (Krystel-Whittemore et al., 2016; Theoharides et al., 2019; Bacci, 2022; St John et al., 2023; Fernández-Guarino and Bacci, 2025). In the early twentieth century, certain authors posited that MCs were either completely absent or present in minimal quantities within the fish group. MCs were initially identified in turtles within the class Reptilia. The initial reference to MCs in avian species originated from Westphal's research in 1880, subsequently supported by findings in chicken bone marrow (Baccari et al., 2011). Electron microscope resolution elucidates the closeness of MCs to connective tissue cells, blood arteries, and nerves while offering data on microanatomic relationships between MCs and diverse cell types (cell-cell communication). MCs have been identified within nerve fascicles and brain parenchyma in many non-mammalian vertebrates, as well as in mammals, including rats and humans (Baccari et al., 2011).

The link between MCs and neurons suggests the likelihood of a reciprocal interaction through the release of their metabolic byproducts. MCs can synthesize Nerve Growth Factor (NGF), which may function through paracrine and autocrine mechanisms to facilitate

Corresponding Author: Stefano Bacci, Ph.D., D.Sci., Research Unit of Histology and Embryology, Department of Biology, University of Florence, Viale Pieraccini 6, 50134, Florence, Italy. e-mail: stefano.bacci@unifi.it
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Abbreviations. CR3, Complement receptor type 3; CTMC, Connective tissue MC; EGC, Eosinophilic granule cells; FGF, Fibroblast growth factor; MC, Mast cell; MMC, Mucosal MC; NGF, Nerve growth factor; NO, Nitric oxide; SCF, Stem cell factor; TLR, Toll-like receptor; MCT, Tryptase positive, chymase negative MC; MCTC, Tryptase positive, chymase positive MC; TNF, Tumor necrosis factor.

the release of cytokines and other mediators generated within the MC itself. Data indicate that several neuropeptides and neurokines released by nerve fibers activate MCs to secrete their chemical mediators. Electrical stimulation of cholinergic fibers in frogs prompts MCs to discharge their chemical mediators (Kritas et al., 2014; Forsythe, 2019; Mittal et al., 2019; Plum et al., 2024).

Mast cells and the evolution

The hemolymph of ascidians (marine invertebrates classified within the subphylum Urochordata of invertebrate chordates, which emerged roughly 500 million years ago) comprises various circulating cell types, some of which migrate from to the tissues to perform multiple immunological functions, including phagocytosis of self and non-self molecules, expression of cytotoxic agents, encapsulation of foreign antigens, and tissue repair (Metcalfe and Boyce, 2006; Crivellato and Ribatti, 2010; Wong et al., 2014; Saccheri et al., 2019; Chia et al., 2023). Studies have demonstrated that circulating granular hemocytes in the hemolymph of the ascidian *Styela plicata* exhibited intermediate traits of basophils and MCs (Metcalfe and Boyce, 2006; Crivellato and Ribatti, 2010; Wong et al., 2014; Saccheri et al., 2019; Chia et al., 2023). In contrast to the hemocytes of other invertebrate species, the granules of these cells contained both heparin and histamine, which are primary constituents of MC granules in mammals. MCs may have developed in stages during the development of vertebrates. The circulating granulocyte is most likely the earliest form of MC in invertebrates (Mulero et al., 2007; Crivellato et al., 2015; Theoharides, 2023). These granulocytes help with development and metabolism, immune system activities, wound healing, blood clotting, phagocytosis, and encasing pathogens, among others. It is possible that MCs evolved a long time before adaptive immune system cells did. The neutrophil found in the ascidian *Styela plicata* might be related to the earliest form of MC. It is a type of cell that is in between MCs and basophils. Like basophils, MCs may have come from a basophilic cell parent (Mulero et al., 2007; Crivellato et al., 2015; Theoharides, 2023). MCs may have lost their ability to move through the blood during development once they turned into cells that stay in one place and go to specific tissues. MC precursors travel through mammalian blood as agranular cells before they reach the tissues on the edges of the body and change into adult MCs. It is possible that basophils kept their original traits when they were circulating cells but lost their c-kit receptor when they changed into real granulocytic cells. New studies on the development of MCs support the idea that they came from a shared ancestor with basophils (Mulero et al., 2007; Crivellato et al., 2015; Theoharides, 2023). Recently, a cell population has been identified in the mouse spleen with the characteristics of a bipotent progenitor for the basophil and MC lineages. This cell population, termed basophil/MC common progenitor (BMCP), can be generated mainly from granulocyte/macrophage progenitors in the bone marrow. It should be noted, however, that these findings are not fully consistent with the results of another study, which demonstrates that a very early hematopoietic progenitor present in the mouse bone marrow can give rise to an MC-committed progenitor that appears to have the potential to produce only MCs *in vitro* or *in vivo*. These data underlie the complexity involved in reconstructing MC evolution and suggest caution in interpreting individual experimental results (Metcalfe and Boyce, 2006; Mulero et al., 2007; Crivellato and Ribatti, 2010; Wong et al., 2014; Crivellato et al., 2015; Saccheri et al., 2019; Chia et al., 2023; Theoharides, 2023; Norrby, 2024).

Staining of mast cells in vertebrates

Eosinophilic granule cells (EGCs) are epidermal cell types in flatfish bearing a morphological resemblance to MCs, with red granules after staining with hematoxylin and eosin. These cells might also be observed in amphibians (Fig. 1). These cells are recommended for the identification of mammalian MCs, which are now widely accepted as true MCs. EGCs described in teleost fish are MCs deprived of their basophilic granular material and resemble mammalian intestinal MCs (mucosal MC; MMC) (Bacci et al., 2009; Bacci and Romagnoli, 2010; Akin, 2014; Ribatti, 2018; Grigorev and Korzhevskii, 2021; Bacci, 2022; Fernández-Guarino and Bacci, 2025).

Specific methods for demonstrating biogenic amines with paraformaldehyde or o-phthalaldehyde failed to reveal fluorescence in carp or frog MCs. A study found that histamine fluorescence was observed in the MCs of turtles, chickens, rats, monkeys, and humans after the o-

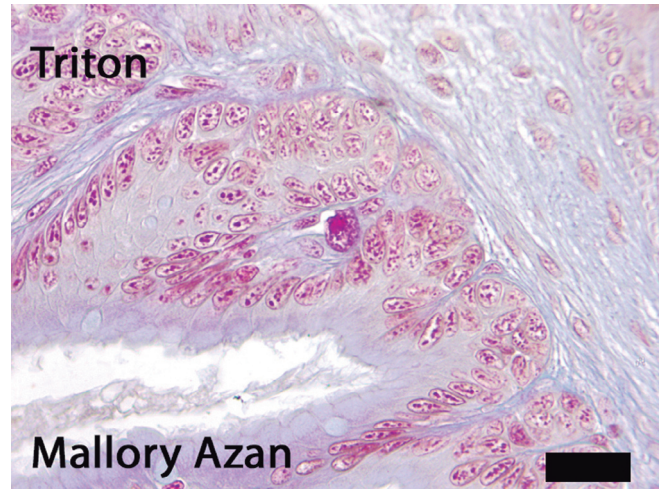

Fig. 1. Presumable eosinophilic granule cell in Triton. Light microscopy, Mallory Azan. Scale Bar: 10 μm.

phthalaldehyde reaction. Chymotrypsin-like esterase activity was observed in rat, monkey, and human MCs but not in non-mammalian species. Trypsin-like esterase was also present in turtle, monkey, and human MCs. Acid phosphatase was found in MCs only in frogs, monkeys, and humans. Beta-glucuronidase was undetectable in non-mammalian MCs except in frogs. The maximum activity of glucuronidase occurred at 4.8 pH in rats, monkeys, and humans. N-acetyl-13-glucosaminidase activity was observed in the MCs of frogs, chickens, and several mammalian species. The optimum pH for this enzyme activity did not vary significantly among species. Frog, chicken, rat, and monkey MCs displayed an optimum activity at pH 4.4 as compared with 4.8 for the human MC enzyme (Ghannadan et al., 1998; Krauth et al., 2005; Valent et al., 2010; Baccari et al., 2011; Teodosio et al., 2015; Kröger et al., 2020; Fernández-Guarino and Bacci, 2025). However, the detectability of MCs is influenced by various factors, including the type of test tissue, the dye used, the pH of the solution, the type of fixation solution, the fixation time, and the final processing technique of stained preparations. However, if immunohistochemistry is the most sensitive and selective MC identification approach, the histochemical technique of metachromatic staining is extensively employed for the identification of mastocytes in histological samples due to its simplicity, cost-effectiveness, efficiency (Ghannadan et al., 1998; Krauth et al., 2005; Valent et al., 2010; Baccari et al., 2011; Teodosio et al., 2015; Kröger et al., 2020; Fernández-Guarino and Bacci, 2025) (Fig. 2).

Structure of mast cells in mammalian

In mammalian cells, MCs are located in diverse tissues and are frequently situated near blood and lymphatic vessels, nerves, smooth muscle cells, exocrine

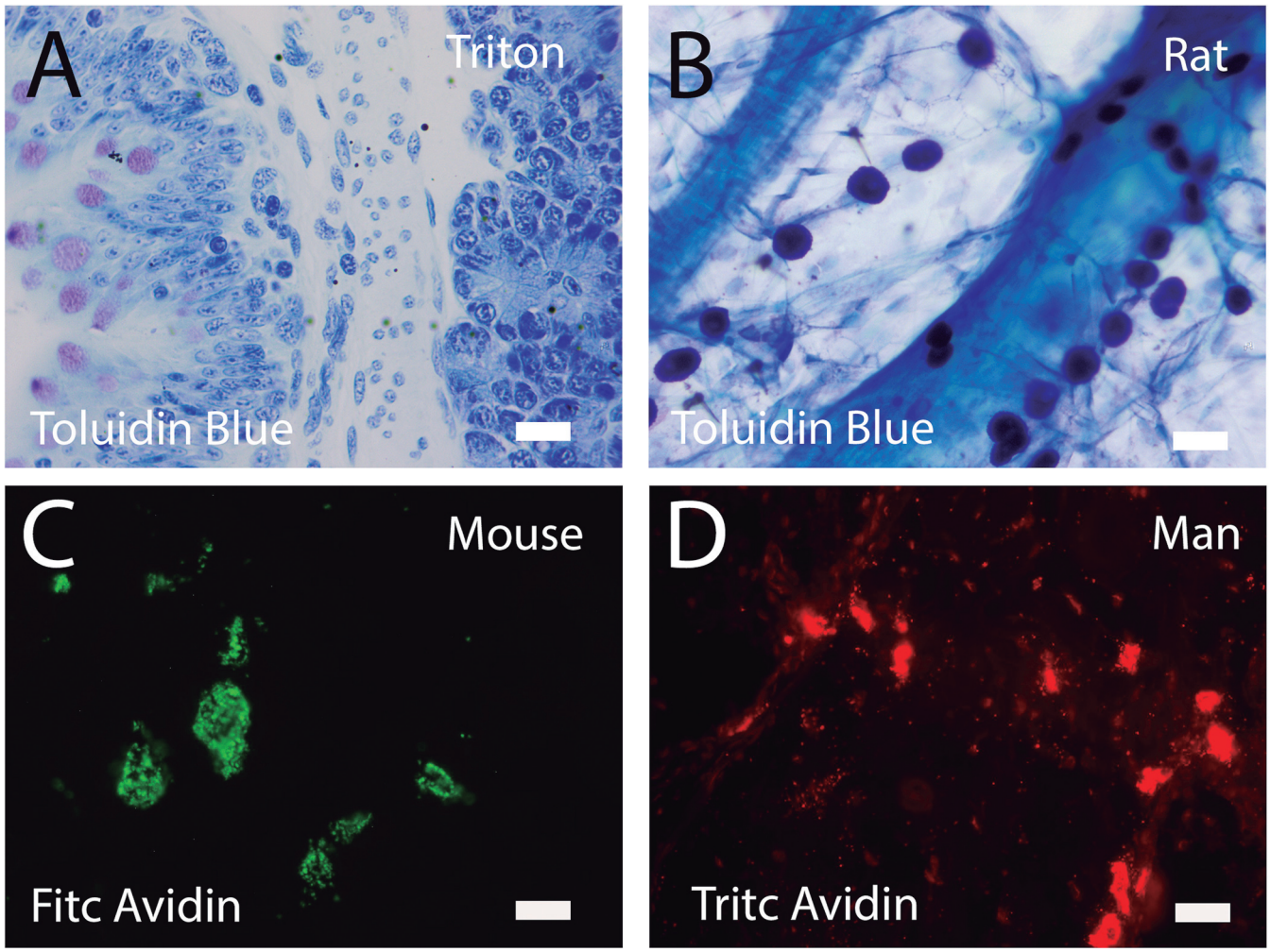

Fig. 2. Mast cells with different states of activation in various vertebrates stained respectively with Toluidine Blue or Avidin. **A, B.** Light Microscopy. **C, D.** Fluorescence Microscopy. Scale Bar: 10 μm.

glands, hair follicles, and epithelial surfaces that are exposed to environmental antigens. The cells exhibit oval, spindle, or spider morphology, with chromotropic secretion granules of 0.3-1 μm in diameter (Crivellato et al., 2004; Bacci et al., 2009; Bacci and Romagnoli, 2010; da Silva et al., 2014; Krystel-Whittemore et al., 2016; Bacci, 2022; Fernández-Guarino and Bacci, 2025). They are readily identifiable by electron microscopy and possess either a paracrystalline matrix with lamellar arrangements or whorled and scroll-like structures. Mediators that are preformed and stored in designated secretory granules can be released via several morphological secretion types, including compound exocytosis, piecemeal degranulation, and localized exocytosis (Komi et al., 2020; Dahlin et al., 2022; Norrby, 2022, 2024). Compound exocytosis typically occurs during IgE-mediated anaphylactic degranulation, leading to the rapid and extensive release of granule contents. Piecemeal degranulation entails a gradual release of granule contents through the exocytosis of shuttle vesicles that transport substances from individual granules to the cell surface, facilitating the independently regulated secretion of several compounds contained within a single granule (Bacci et al., 2009; Bacci and Romagnoli, 2010; Komi et al., 2020; Bacci, 2022; Dahlin et al., 2022; Norrby, 2022,2024; Fernández-Guarino and Bacci, 2025).

MCs possess several extremely osmiophilic lipid structures that store arachidonic acid, along with enzymes for its metabolism, and perhaps tumor necrosis factor (TNF)-alpha and basic fibroblast growth factor (FGF). MCs release lipid derivatives, such as prostaglandins, leukotrienes, thromboxanes, and platelet-activating factors. A further secretory product of MCs is nitric oxide (NO), produced in the cytosol and immediately released through the plasma membrane (Crivellato et al., 2004; Kritas et al., 2014; Wong et al., 2014; da Silva et al., 2014; Komi et al., 2020; Dahlin et al., 2022; Norrby, 2022, 2024; Bacci, 2022; Fernández-Guarino and Bacci, 2025).

Two primary subtypes of MCs exist: connective tissue MCs (CTMCs) and MMCs. CTMCs are located in the digestive tract and bone marrow, whereas MMCs are characterized by a preponderance of heparin in their secretory granules. A similar dichotomy has been seen in humans, determined by the presence of tryptase (MCT) or both tryptase and chymase (MCTC) in MCs derived from various anatomical locations (Crivellato et al., 2004; Bacci et al., 2009; Bacci and Romagnoli, 2010; Akin, 2014; da Silva et al., 2014; Krystel-Whittemore et al., 2016; Komi et al., 2020; Bacci, 2022; Dahlin et al., 2022; Norrby, 2022, 2024; Fernández-Guarino and Bacci, 2025).

MCs and basophils are two separate cell types that share identical features, including the synthesis of histamine and heparin. They also derive from a shared precursor and experienced analogous developmental stages. Basophils finalize their maturation exclusively in the bone marrow, but MCs can demonstrate a considerable lifespan, and mature MCs can proliferate under certain conditions. Stem Cell Factor (SCF) is essential for the regulation of multiple facets of MC growth and survival. It serves as the ligand for the c-kit receptor, which is part of the receptor tyrosine kinase III family of growth factor receptors. Various cytokines facilitate the activation and degranulation of basophils, whereas they induce MC movement without triggering granule release (Crivellato et al., 2004; DeBruin et al., 2015; Krystel-Whittemore et al., 2016; Varricchi et al., 2019; Bacci, 2022; Dileepan et al., 2023; Norrby, 2024; Fernández-Guarino and Bacci, 2025).

Structure of MCs in bony fish

In numerous types of bony fish, EGC/MCs have been identified in nearly all organs and tissues, with their prevalence in the gastrointestinal tract being the most notable characteristic. EGC/MC are frequently located in the gills and epidermis. The morphology, anatomical distribution, frequency, basophilic/acidophilic staining, and heparin content of EGC/MCs among the teleostean species examined exhibit significant variation in both morphological and distributional aspects (Reite and Evensen, 2006; Mulero et al., 2007; Crivellato and Ribatti, 2010; Baccari et al., 2011; Wong et al., 2014; Prykhozhij and Berman, 2014; Sfacteria et al., 2015; Saccheri et al., 2019). No two species of bony fish possess identical distribution patterns or physical characteristics of their MCs. For instance, although EGC/MCs are prevalent in the intestines of cyprinids, such cells are not documented in the intestines of labrids. Likewise, similar cells were observed in the liver of only a limited number of species examined. In summary, EGC/MCs have only been identified in salmonid and cyprinid fish species. The fine structure of EGC/MCs in teleost fish has been examined across several tissues, including the kidney, blood, skin, gut, peritoneal exudate, and gill, in multiple species, such as trout, flounder, sucker fish, eel, and carp (Silphaduang and Noga, 2001; Noga and Silphaduang, 2003; Mulero et al., 2007; Dobson et al., 2008; Crivellato and Ribatti, 2010; Baccari et al., 2011; Saccheri et al., 2019; Romano et al., 2021; Alesci et al., 2022, 2023). The secretory granules of MCs may exhibit a densely homogeneous core, delineated from the surrounding membrane by a narrow interstice, or their matrix may present a finely granular appearance with low electron density, interspersed with occasional small membrane whorls and elongated, thin surface projections resembling a string of beads. Immunogold labeling of winter flounder EGCs using an anti-pleuricidin antibody revealed a substantial quantity of gold particles adjacent to the electron-dense granules. The granule matrix may exhibit a highly reticulated appearance with a notable electron-lucent halo surrounding it. In the eel, EGCs within the peritoneal exudate exhibit distinctive cytoplasmic rod-like formations that seem angular or hexagonal in cross-section, alongside many parallel tubular structures containing an electron-dense core. Fused granules are a

common phenomenon. In teleost fish, the substructure is predominantly homogeneous to the condition observed in rodents (Silphaduang and Noga, 2001; Noga and Silphaduang, 2003; Mulero et al., 2007; Dobson et al., 2008; Crivellato and Ribatti, 2010; Baccari et al., 2011; Saccheri et al., 2019; Romano et al., 2021; Alesci et al., 2022, 2023).

Structure of MCs in amphibians

MCs, present in amphibians such as teleost fish, display a variety of morphologies throughout different tissues and organs, especially in the tongue and nervous system. They demonstrate species-specific variations in morphology, tissue prevalence, and distribution. In amphibians, the greatest amounts of MCs were found in the tongue, stomach, small and large intestines, and mesentery. In the heart, pancreas, lung, spleen, kidney, and adrenal glands, they were poorly scattered in the interstitial connective tissue (Dobson et al., 2008; Baccari et al., 2011; Hauser et al., 2024). The tongue of *R. esculenta* exhibits the largest concentration of MCs relative to other cerebral areas. The frequency of MCs roughly doubles during larval development and metamorphic climax in the brains of developing frogs and toads. Adult toad brains exhibit a greater MC frequency compared with the brains of permanently water-bound African clawed frogs. MCs are frequently located adjacent to melanocytes and vessels. In the brain, MCs are preferentially located in the meningeal lining (*pia mater*), particularly numerous in the stroma of choroid plexuses (anterior and posterior) lying juxtaposed to blood capillaries and ventricular ependyma, and rarely in the brain parenchyma (Dobson et al., 2008; Baccari et al., 2011; McMenamin and Polla, 2013; Hauser et al., 2020, 2024a,b; Lopez et al., 2020). Secretory granules are characterized by significant heterogeneity and intricate substructural structures. They are located in frogs and toads, namely within substantial nerves such as the sciatic and brachial nerves, where they exist in the endoneurium and epineurium. In the minor nerve fascicles of the tongue, MCs are primarily situated between the perineurial layers, indicating a function in the tissue-nerve barrier. MCs also exist in proximity to nerve bundles and nerve ganglia. The fine structural level of the Harderian gland, brain, and testis in Amphibia has been examined through the lens of the MC. MCs may comprise hexagonally arranged crystalline particles, crystalline structures with parallel arrays of diverse periodicities, fusiform inclusions exhibiting a "sandwich-like" architecture, or lamellated structures (middle disk). Some authors have suggested that different ultrastructural and/or histochemical aspects of the secretory granules in MCs from the same tissue of a given species probably represent different phases of the functional cycle of a single cell type (Dobson et al., 2008; Pinelli et al., 2010; Baccari et al., 2011; McMenamin and Polla, 2013; Hauser et al., 2020; Lopez et al., 2020, 2024a,b; Voss, et al., 2021).

Structure of MCs in reptiles

As compared with other vertebrates, studies on MCs in reptiles are comparatively scarce (Sottovia-Filho, 1974; Vitiello et al., 1997; Schumacher et al., 1998; Santoro et al., 2008; Baccari et al., 2011; Onkels et al., 2020).

Still, it is clear that MCs have different shapes and are found in many places and in all reptile subgroups, except for Sphenodon. These subgroups include lizards, snakes, skinks, crocodiles, and turtles. In lizards, MCs were seen in all organs, although in greater amounts in the mesentery, between the muscle fibers of the tongue, and in the submucosa of the stomach and intestines. The lung, pancreas, spleen, heart, kidney, and adrenal glands had smaller MCs; MCs were practically absent in the liver. The great majority of these cells were either confined to the adventitia of blood vessels or in close relationship with capillaries or nerve bundles. Cytoplasmic granules presented an amphoteric character; they were basophilic and metachromatic with toluidine blue and acidophilic with hematoxylin-eosin and Masson's trichrome. The cytoplasmic granules of lizard MCs are positive to Periodic acid-Schiff (PAS) and Vialli's combined technique; PAS-positive and Alcian blue-positive granules were intermingled within the same cell. In the frogs, the granules were faintly stained with PAS and Vialli's technique, only Alcian blue-stained granules could be well evidenced (Sottovia-Filho, 1974; Vitiello et al., 1997; Schumacher et al., 1998; Santoro et al., 2008; Baccari et al., 2011; Onkels et al., 2020).

In snakes, MCs were found to be relatively small (7-11 μm in diameter) compared with those of lizards (8-15 μm), dogs, and rats (9-15 μm). Among the various organs examined, MCs are described to be particularly numerous in the choroid plexus, mesentery, and tongue, underneath the serosa of the intestine and in the heart, interspersed among muscle fibers, and in the epicardium. In a study of MC ultrastructure in the reptiles *Podarcis sicula* and *Tarentola mauritanica*, the nucleus was found to be irregular, with large heterochromatin masses, and the cytoplasm was full of homogeneous, osmophilic secretory granules (Sottovia-Filho, 1974; Vitiello et al., 1997; Schumacher et al., 1998; Santoro et al., 2008; Baccari et al., 2011, Onkels et al., 2020, Kleansmith et al., 2023).

Structure of MCs in birds

MCs have been most studied in Galliformes (chicken), and much less in Columbiformes (pigeon and ring dove), and even less in Passeriformes, Anseriformes, Psittaciformes, and Strigiformes (Crivellato and Ribatti, 2010; Baccari et al., 2011; Norrby, 2024) Also in birds, MCs exhibit varying gross morphology: oval and elongated being the most common types. MC granules are found in various parts of the body, including the intestines, brain, tongue, stomach,

lung, mesentery, thyroid, liver, and oviduct. In chickens, the highest MC frequency is found in the proventriculus, duodenum, and middle and terminal intestine, followed by a lower frequency in other parts.

There is no report on MC presence in the testis, kidney, pancreas, adrenal, muscles, spinal cord, and hypophysis. Medial habenular MCs increase in number during development, peaking in peripuberal ring doves and declining thereafter. Age-related changes in MC number are observed in chicken lymphoid tissues, with the highest number recorded in the bursa of Fabricius in seven-day-old chickens.

Secretory granules in chicken, duck, and pigeon MCs have variable internal morphology, with some being electron-dense and others being composed of cords arranged in varying degrees of complexity. The central nervous system can attract and support MC differentiation. MC secretory granules in all bird species have one morphological feature in common: the presence of semicircular concavities (Takaia, 1969; Carlson and Hacking, 1972; Crivellato and Ribatti, 2010; Liu et al., 2006; Baccari et al., 2011; McMenamin and Polla, 2012; Zu et al., 2017; Saccheri et al., 2019).

Common functions of MCs in all vertebrates

The MC is primarily recognized for its crucial function in mediating detrimental allergy diseases and life-threatening anaphylaxis while having been conserved across all vertebrate species for over 500 million years, predating the emergence of adaptive immunity. This indicates that MCs possess substantial yet unidentified vital life-promoting roles. The MC is a distinctive innate immune cell due to two key characteristics: its unique mediator profile and its remarkable capacity to influence the vasculature, facilitating selective cell recruitment and permeability changes, thus preparing for an appropriate acquired response. The MC is exceptionally reactive to various injurious agents and to the major female sex hormones (Krystel-Whittemore et al., 2016; Hellman et al., 2017; Dudeck et al., 2019; Theoharides et al., 2019; Komi et al., 2020; Norrby, 2022, 2024; St John et al., 2023).

Molecular mechanisms for MC activation in non-mammalian vertebrates are not clear. While no IgEs are known in non-mammalian vertebrates, a genome map-based *in situ* hybridization study for FceRI in zebrafish appears to show the presence of FceRI receptor subunits. In amphibians, reptiles, and birds, the low molecular weight Ig is IgY, which seems to not only share some characteristics but also the phylogenetic story with mammalian IgE and IgG (Bacci and Romagnoli, 2010; Crivellato et al., 2004; Komi et al., 2020; Norrby, 2022, 2024; Theoharides, 2023; Fernández-Guarino and Bacci, 2025).

The activated MC is able to secrete multiple potent bioactive molecules, including heparin, highly efficacious extracellular matrix-degrading enzymes, mitogenic and angiogenic molecules, like histamine, heparin-binding bFGF, and VEGFA, as well as heparin-binding angiogenic inflammatory cytokines (Krystel-Whittemore et al., 2016; Komi et al., 2020; Norrby, 2022, 2024).

Research on the growth and recruitment methods of immature and developing MCs in non-mammalian vertebrates has been sparse; however, new studies on fish and avian species have yielded substantial molecular data. Tyrosine kinase proteins play a role in MC proliferation and differentiation, and comprehending the expression of adhesion molecules and chemokine receptors in these cells is essential for elucidating their migration to specific locations in the body (Crivellato and Ribatti, 2010; Baccari et al., 2011; Saccheri et al., 2019).

The host defense mechanism entails the activation of MCs and the secretion of histamine; further research is required to elucidate histamine receptors in fish and amphibians. The mechanisms of MC activation appear to be highly conserved throughout vertebrate evolution, with agents such as 48/80 inducing MC degranulation in fish, amphibians, birds, and mammals. Additionally, substance P, Concanavalin A, capsaicin, hydrocortisone, and toxins facilitate MC degranulation in certain teleost fish and mammals. Complement receptor type 3 (CR3) is involved in the response to proinflammatory mediators and chemotactic agents, promoting the chemotactic migration of MCs and eosinophils, while neurokines released from nerve fibers activate MCs to release chemical mediators (Baccari et al., 2011).

The ability of antimicrobial chemicals derived from frog skin to stimulate histamine release from rodent MCs is an additional component of this conserved MC mosaic. Given their varied morphological, developmental, and biochemical characteristics, along with experimental evidence, it is plausible to conclude that MCs in non-mammalian vertebrates exhibit a multifaceted functional repertoire (Crivellato and Ribatti, 2010; Baccari et al., 2011; Norrby, 2022, 2024).

Research with parasitized animals is crucial for elucidating the mechanisms of MC development and recruitment, demonstrating that non-mammalian MCs participate in host defense mechanisms akin to those in mammals (Crivellato and Ribatti, 2010; Baccari et al., 2011; Crivellato et al., 2015).

A possible evolutionary importance may be attributed to the trio of extracellular matrix degradation/tissue remodeling, *de novo* tissue-cell proliferation, and *de novo* angiogenesis that occurs after MC degranulation. This is because the activation of MCs is essential for the effective completion of pregnancy, as well as for the life-saving activities that occur in inflammation and wound healing, which provide humans with the ability to reach reproductive age. Hence, it would seem that this triad of tissue responses is responsible for the generation of a life-sustaining loop, which, in theory, might be a factor in the prolonged existence of vertebrates. If this is the case, the ability to elicit such a tripartite reaction can be regarded as the

fundamental purpose of MC organizations (Norrby, 2024; Fernández-Guarino and Bacci, 2025).

Remarks and conclusions

In conclusion, MCs are primordial cells, with their lineage tracing back to an MC-like progenitor from urochordates, approximately 550 million years ago. Despite the initial description of mammalian MCs over a century ago, their specific roles continue to be unclear. MCs are currently regarded as multipurpose immune cells involved in several physiological and pathological conditions. MCs demonstrate significant heterogeneity and plasticity because of their extensive distribution and the mediators or pathogens with which they interact. MC development, phenotype, and function are increasingly determined by the local milieu, which significantly influences their capacity to perceive and respond to stimuli (Metcalfe and Boyce, 2006; Crivellato and Ribatti, 2010; Wong et al., 2014; Saccheri et al., 2019).

The extensive distribution of MCs throughout tissues and their adaptability enable them to act as initial responders to dangerous events and to react to environmental changes through interactions with other cells involved in physiological and immunological responses. Their widespread distribution positions MCs to function as protectors of the immune system while also engaging in other biological processes and maintaining homeostasis. MCs possess both immunomodulatory and physiological roles, they are recognized for their role in modulating both innate and adaptive immunological responses, directly and indirectly, by interacting with other immune cells. Furthermore, MCs can influence immunological responses via their diverse mediators, surface chemicals, and co-stimulatory molecules (Norrby, 2022, 2024).

Throughout an MC's lifespan, various variables can modify its phenotype, and a combination of these alterations can dictate MC homeostatic or pathologic responses. The characteristics enabling MCe to engage with the milieu are the same as those that, when improperly regulated, can lead to severe repercussions for the organism. The role of MCs in various disease states is, therefore, the subject of ongoing evaluation (Metcalfe and Boyce, 2006; Crivellato and Ribatti, 2010; Wong et al., 2014; Saccheri et al., 2019).

Consequently, MCs can be regarded as sentinel cells that respond by secreting preformed and newly synthesized mediators upon antigen entry, activating both immediate and delayed responses to obstruct and repair potential damage. The absence of specialization for specific antigens, which distinguishes Ig-bearing MCs from lymphocytes, would optimize these cells' ability to initiate a localized reaction against any antigens entering the body. Given that MCs respond to many neurotransmitters and may be located adjacent to or in direct contact with nerve fibers, they are potential mediators of local neuro-immune interactions. The substantial quantity of these cells and their capacity to rapidly release significant amounts of strong bioactive chemicals may result in health and potentially life-threatening problems when MCs are unduly activated (Bacci et al., 2009; Bacci and Romagnoli, 2010; Dahlin et al., 2015; De Bruin et al., 2015, Dudek et al., 2019; Bacci, 2022; Fernández-Guarino and Bacci, 2025).

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Conflicts of Interest Statement. The author declares no conflicts of interest.

References

Akin C. (2014). Morphology and histologic identification of mast cells. In: Encyclopedia of medical immunology. Mackay I.R, Rose N.R., Ledford D.K., Lockey L.F. (eds). Springer. New York, NY.

Alesci A., Albano M., Savoca S., Mokhtar D.M., Fumia A., Aragona M., Lo Cascio, P., Hussein, M.M., Capillo G., Pergolizzi S., Spanò N. and Lauriano E.R. (2022). Confocal identification of immune molecules in skin club cells of zebrafish (*Danio rerio*, Hamilton 1882) and their possible role in immunity. Biology 11, 1653.

Alesci A., Pergolizzi S., Fumia A., Calabrò C., Lo Cascio P. and Lauriano E.R. (2023). Mast cells in goldfish (*Carassius auratus*) gut: Immunohistochemical characterization. Acta Zoologica 104, 366-379.

Baccari C.G., Pinelli C., Santillo A., Minucci S. and Rastegi R.K. (2011). Mast cells in nonmammalian vertebrates: An overview. Int. Rev. Cell Mol. Biol. 290, 1-53.

Bacci S. (2022). Fine regulation during wound healing by mast cells, a physiological role not yet clarified. Int. J.Mol. Sci. 23, 1820.

Bacci S. and Romagnoli P. (2010). Drugs acting on MC functions: A cell biological perspective. Inflamm. Allergy Drug Targets 9, 214-228.

Bacci S., Bonelli A. and Romagnoli P. (2009). Mast cells in injury response. In: Cell movement: New research trends. Abreu T., Silva G. (eds). Nova Science Publishers, Inc, Hauppage, NY. pp 81-121.

Carlson H.C. and Hacking M.A. (1972). Distribution of mast cells in chicken, turkey, pheasant, and quail, and their differentiation from basophils. Avian Dis. 16, 574-577.

Chia S.L., Kapoor S., Carvalho C., Bajénoff M. and Gentek R. (2023). Mast cell ontogeny: From fetal development to life-long health and disease. Immunol. Rev. 315, 31-53.

Crivellato E. and Ribatti D. (2010). The mast cell: An evolutionary perspective. Biol. Rev. Camb. Philos. Soc. 85, 347-360.

Crivellato E., Beltrami C.A., Mallardi F. and Ribatti D. (2004). The mast cell: An active participant or an innocent bystander? Histol. Histopathol. 19, 259-270.

Crivellato E., Travan L. and Ribatti D. (2015). The phylogenetic profile of mast cells. Methods Mol. Biol. 1220, 11-27.

Da Silva E.Z., Jamur M.C. and Oliver C. (2014). Mast cell function: A new vision of an old cell. J. Histochem. Cytochem. 62, 698-738.

Dahlin J.S., Maurer M., Metcalfe D.D., Pejler G., Sagi-Eisenberg R. and Nilsson G. (2022). The ingenious mast cell: Contemporary insights into mast cell behavior and function. Allergy 77, 83-99.

DeBruin E.J., Gold M., Lo B.C., Snyder K., Cait A., Lasic N., Lopez M., McNagny K.M. and Hughes M.R. (2015). Mast cells in human health and disease. Methods Mol. Biol. 1220, 93-119.

Dileepan K.N., Raveendran, V.V., Sharma, R., Abraham, H., Barua, R.,

Singh, V., Sharma, R. and Sharma M. (2023). Mast cell-mediated immune regulation in health and disease. Front. Med. 10, 1213320.

Dobson J.T., Seibert J., Teh E.M., Da'as S., Fraser R.B., Paw B.H., Lin T.J. and Berman J.N. (2008). Carboxypeptidase A5 identifies a novel mast cell lineage in the zebrafish providing new insight into mast cell fate determination. Blood 112, 2969-2972.

Dudeck A., Köberle M., Goldmann O., Meyer N., Dudeck J., Lemmens S., Rohde M., Roldán N.G., Dietze-Schwonberg K., Orinska Z., Medina E., Hendrix S., Metz M., Zenclussen A.C., von Stebut, E. and Biedermann T. (2019). Mast cells as protectors of health. J. Allergy Clin. Immunol. 144, S4-S18.

Komi E.A., Wöhrl S. and Bielory L. (2020). Mast cell biology at molecular level: A comprehensive review. Clin. Rev. Allergy Immunol. 58, 342-365.

Fernández-Guarino M. and Bacci S. (2025). Mast cells and wound healing: Still an open question. Histol. Histopathol. 40, 21-30.

Forsythe P. (2019). Mast cells in neuroimmune interactions. Trends Neurosci. 42, 43-55.

Ghannadan M., Baghestanian M., Wimazal F., Eisenmenger M., Latal D., Kargül G., Walchshofer S., Sillaber C., Lechner K. and Valent P. (1998). Phenotypic characterization of human skin MC by combined staining with toluidine blue and CD antibodies. J. Invest. Dermatol. 111, 689-695.

Grigorev I.P. and Korzhevskii D.E. (2021). Modern imaging technologies of mast cells for biology and medicine (Review). Sovrem. Tekhnologii. Med. 13, 93-107.

Hauser K.A., Popovic M., Yaparla A., Koubourli D.V., Reeves P., Batheja A., Webb R., Forzán M.J. and Leon G. (2020). Discovery of granulocyte-lineage cells in the skin of the amphibian Xenopus laevis. FACETS 571-597.

Hauser A.K., Hossainey M.R.H., Howard D.T., Koubourli D.V., Kalia N. and Grayfer L. (2024a). Granulocyes accumulate in resorbing tails of metamorphosing Xenopus laevis amphibians. Comp. Immunol. Rep. 6, 200139.

Hauser K.A., Garvey C.N., Crow R.S., Hossainey M.R.H., Howard D.T., Ranganathan N., Gentry L. K., Yaparla A., Kalia N., Zelle M., Jones E.J., Duttargi A.N., Rollins-Smith L.A., Muletz-Wolz C.R. and Grayfer L. (2024b). Amphibian mast cells serve as barriers to chytrid fungus infections. eLife 12, RP92168.

Hellman L.T., Akula S., Thorpe M. and Fu Z. (2017). Tracing the origins of IgE, mast cells, and allergies by studies of wild animals. Front. Immunol. 8, 1749.

Kleansmith L.M., Reavill D.R., Kiupel M., Hoppes S.M., Strunk A.M. and Garner M.M. (2023). Mast cell neoplasia in the green Iguana, *Iguana, Iguana*. J. Zoo Wildl. Med. 53, 864-869.

Krauth M.T., Majlesi Y., Florian S., Bohm A., Hauswirth A.W., Ghannadan M., Wimazal F., Raderer M., Wrba F. and Valent P. (2005). Cell surface membrane antigen phenotype of human gastrointestinal mast cells. Int. Arch. Allergy Immunol. 138, 111-120.

Kritas S.K., Caraffa A., Antinolfi P., Saggini A., Pantalone A., Rosati M., Tei M., Speziali A., Saggini R., Pandolfi F., Cerulli G. and Conti P. (2014). Nerve growth factor interactions with mast cells. Int. J. Immunopathol. Pharmacol. 27, 15-19.

Kröger M., Scheffel J., Nikolaev V.V., Shirshin E.A., Siebenhaar F., Schleusener J., Lademann J., Maurer M. and Darvin M.E. (2020). *In vivo* non-invasive staining-free visualization of dermal MC in healthy, allergy and mastocytosis humans using two-photon fluorescence lifetime imaging. Sci. Rep. 10, 14930.

Krystel-Whittemore M., Dileepan K.N. and Wood J.G. (2016). Mast cell: A multi-functional master cell. Front. Immunol. 6, 620.

Liu Y.H., Piao X.S., Ou D.Y., Cao Y.H., Huang D.S. and Li D.F. (2006). Effects of particle size and physical form of diets on mast cell numbers, histamine, and stem cell factor concentration in the small intestine of broiler chickens. Poult. Sci. 85, 2149-2155.

Lopez A.G., Duparc C., Naccache A., Castanet M., Lefebvre H. and Louiset E. (2020). Role of mast cells in the control of aldosterone secretion. Horm. Metab. Res. 52, 412-420.

McMenamin P.G. and Polla E. (2012). Mast cells are ubiquitously distributed in the choroid of fish, reptiles, birds, monotremes, marsupials and placental mammals. Invest. Ophthalmol. Vis. Sci. 53, 4916.

McMenamin P.G. and Polla E. (2013). Mast cells are present in the choroid of the normal eye in most vertebrate classes. Vet. Ophthalm. 16 (Suppl. 1), 73-78.

Metcalfe D.D. and Boyce J.A. (2006). Mast cell biology in evolution. J. Allergy Clin. Immunol. 117, 1227-1229.

Mittal A., Sagi V., Gupta M. and Gupta K. (2019). Mast cell neural interactions in health and disease. Front. Cell. Neurosci. 13, 110.

Mulero I., Sepulcre M.P., Meseguer J., García-Ayala A. and Mulero V. (2007). Histamine is stored in mast cells of most evolutionarily advanced fish and regulates the fish inflammatory response. Proc. Natl. Acad. Sci. USA 104, 19434-19439.

Noga E.J. and Silphaduang U. (2003). Piscidins: A novel family of peptide antibiotics from fish. Drug News Perspect, 16, 87-92.

Norrby K. (2022). Do mast cells contribute to the continued survival of vertebrates? APMIS 130, 618-624.

Norrby K. (2024). On connective tissue mast cells as protectors of life, reproduction, and progeny Int. J. Mol. Sci. 25, 4499.

Onkels A.K., Stadler C., Hetzel U., Mueller J. and Herden C. (2020). Multiple cutaneous mast cell tumours in a *Boa imperator*. Vet. Record 8, e001040.

Pinelli C., Santillo A., Baccari G.C., Monteforte R. and Rastogi R.K. (2010). Mast cells in the amphibian brain during development. J. Anat. 216, 397-406.

Plum T., Feyerabend T.B. and Rodewald H.R. (2024). Beyond classical immunity: MC as signal converters between tissues and neurons. Immunity 57, 2723-2736.

Prykhozhij S.V. and Berman J.N. (2014). The progress and promise of zebrafish as a model to study mast cells. Dev. Comp. Immunol. 46, 74-83.

Reite O.B. and Evensen O. (2006). Inflammatory cells of teleostean fish: A review focusing on Mast cells /eosinophilic granule cells and rodlet cells. Fish Shellfish Immunol. 20, 192-208.

Ribatti D. (2018). The Staining of Mast cells: A historical overview. Int. Arch. Allergy Immunol. 176, 55-60.

Romano L.A., Oliveira F.P.S. and Pedrosa V.F. (2021). Mast cells and eosinophilic granule cells in *Oncorhynchus mykiss*: Are they similar or different? Fish Shellfish Immunol. Rep. 2, 100029.

Saccheri P., Travan L., Ribatti D. and Crivellato E. (2019). Mast cells, an evolutionary approach. Ital. J. Anat. Embryol. 99, 124, 271-287.

Santoro M., Stacy B.A., Morales J.A., Gastezzi-Arias P., Landazuli S. and Jacobson E.R. (2008). Mast cell tumour in a giant Galapagos tortoise (*Geochelone nigra vicina*). J. Comp. Pathol. 138, 156-159.

Schumacher J., Bennett R.A., Fox L.E., Deem S.L., Neuwirth L. and Fox J.H. (1998). Mast cell tumor in an eastern kingsnake (Lampropeltis getulus getulus). J. Vet. Diagn. Invest. 10, 101-104.

Sfacteria A., Brines M. and Blank U. (2015). The mast cell plays a

central role in the immune system of teleost fish. Mol. Immunol. 63, 3-8.

Silphaduang U., Noga E.J. (2001). Peptide antibiotics in mast cells of fish. Nature 414, 268-269.

Sottovia-Filho D. (1974). Morphology and histochemistry of the mast cells of snakes. J. Morphol. 142, 109-116.

St John A.L., Rathore A.P.S. and Ginhoux F. (2023). New perspectives on the origins and heterogeneity of mast cells. Nat. Rev. Immunol. 23, 55-68.

Takaya K. (1969). The relation between mast cells and histamine in phylogeny with special references to reptiles and birds. Arch. Histol. Jpn. 30, 401-420.

Teodosio C., Mayado A., Sánchez-Muñoz L., Morgado J.M., Jara-Acevedo M., Álvarez-Twose I., García-Montero A.C., Matito A., Caldas C., Escribano L. and Orfao A. (2015). The immunophenotype of mast cells and its utility in the diagnostic work-up of systemic mastocytosis. J. Leuk. Biol. 97, 49-59.

Theoharides T.C. (2023). The role of mast cells and their inflammatory mediators in immunity. Int. J. Mol. Sci. 24, 12130.

Theoharides T.C., Tsilioni I. and Ren H. (2019). Recent advances in our understanding of mast cell activation - or should it be mast cell mediator disorders? Expert Rev. Clin. Immun.15, 639-656.

Valent P., Cerny-Reiterer S., Herrmann H., Mirkina I., George T.I., Sotlar K., Sperr W.R. and Horny H.P. (2010). Phenotypic heterogeneity, novel diagnostic markers, and target expression profiles in normal and neoplastic human mast cells. Best Pract. Res. Clin. Haematol. 23, 369-378.

Varricchi G., Rossi F.W., Galdiero M.R., Granata F., Criscuolo G., Spadaro G., de Paulis A. and Marone G. (2019). Physiological roles of mast cells: Collegium internationale allergologicum update. Int. Arch. Allergy Immunol. 179, 247-261.

Vitiello I.I., Baccari G.C., Di Matteo L., Rusciani A., Chieffi P. and Minucci S. (1997). Number of mast cells in the Harderian gland of the lizard Podarcis sicula sicula (Raf): The annual cycle and its relation to environmental factors and estradiol administration. Gen. Comp. Endocrinol. 107, 394-400.

Voss M., Kotrba J., Gaffal E., Katsoulis-Dimitriou K. and Dudeck A. (2021). Mast cells in the skin: Defenders of integrity or offenders in inflammation? Int. J. Mol. Sci. 22, 4589.

Wong G.W., Zhuo L., Kimata K., Lam B.K., Satoh N. and Stevens R.L. (2014). Ancient origin of mast cells. Biochem. Biophys. Res. Commun. 451, 314-318.

Zu R., Meng C., Umar S., Mahrose K.M., Ding C. and Munir M. (2017). Mast cells and innate immunity: Master troupes of the avian immune system. J. World's Poult. Sci. 73, 621-632.

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