

Protective and pathological roles of mast cells and basophils

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Abstract | Mast cells and basophils are potent effector cells of the innate immune system, and they have both beneficial and detrimental functions for the host. They are mainly implicated in pro-inflammatory responses to allergens but can also contribute to protection against pathogens. Although both cell types were identified more than 130 years ago by Paul Ehrlich, their *in vivo* functions remain poorly understood. The precursor cell populations that give rise to mast cells and basophils have recently been characterized and isolated. Furthermore, new genetically modified mouse strains have been developed, which enable more specific targeting of mast cells and basophils. Such advances offer new opportunities to uncover the true *in vivo* activities of these cells and to revisit their previously proposed effector functions.

Mast cells and basophils are functionally and developmentally similar cell types that are generally associated with type 2 immune responses, which are mainly characterized by the presence of T helper 2 (T_H2) cells, high levels of IgE and eosinophilia. Type 2 immunity develops in response to allergens and multicellular parasites, such as parasitic worms (helminths) or ticks. Mast cells and basophils express an overlapping set of effector molecules, including mast cell-associated proteases, vasodilating substances (such as histamine), various cytokines, pro-inflammatory chemokines and lipid mediators (TABLE 1). Many of these effector molecules are stored in cytoplasmic granules and are rapidly released in response to activation of the high-affinity receptor for IgE (FcεRI) or other surface receptors that are expressed by mast cells and basophils^{1,2}. The *in vivo* functions of both cell types are only partially understood owing to the fact that these cells are fairly rare and are difficult to isolate as a pure population without interfering with their state of activation. Mast cells have been reported to protect the host against a range of parasitic and bacterial infections, to degrade venom toxins, to mediate tolerance to skin transplants and to contribute to tumour rejection. Conversely, they cause detrimental inflammatory responses to allergens, and they might exacerbate autoimmunity³. Basophils can contribute to protection against helminths and ticks⁴, but they can also have a non-redundant role during IgE-mediated chronic allergic inflammation of the skin and are implicated in the late-phase response of allergic asthma⁵.

In addition to their effector functions, basophils and mast cells can rapidly respond to environmental signals and might function as modulators of immune responses

by enhancing, suppressing or polarizing adaptive immunity^{2,3,6–12}. Newly developed reagents and genetically modified mouse strains have greatly improved the ‘tool box’ that is available for addressing the remaining questions and for revisiting the previously proposed functions of mast cells and basophils. This Review focuses on recent advances in our understanding of basophil and mast cell development, the contribution of these cells to protective immunity against parasites, and their role during allergic or autoimmune inflammation.

Phylogeny and lineage development

Evolutionary aspects. Paul Ehrlich originally noted that mast cells and basophils show similar metachromatic staining characteristics when they are stained with anilin dyes (reviewed in REF. 13). From our current perspective, the mostly overlapping gene expression profiles of mast cells and basophils are intriguing and indicate that these cells might have developed from a common precursor cell long before adaptive immune mechanisms and IgE evolved. A mast cell/basophil-like (MCBL) cell that contains histamine and heparin was recently identified in the haemolymph of the ascidian *Styela plicata*, which belongs to the group of invertebrate chordates (urochordates) that first appeared about 500 million years ago¹⁴ (FIG. 1). In the same organism it was reported that test cells — accessory cells that are associated with oocytes in ascidians — release histamine, heparin and tryptases when they are exposed to the compound 48/80, which is a synthetic polyamine and potent secretagogue of mast cells¹⁵. The authors proposed that test cells might protect the oocyte against microbial infections.

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Table 1 | **Selected characteristics of mast cells and basophils***

Characteristic	Mast cells	Basophils	Both mast cells and basophils
Size	5–10 µm	5–7 µm	NA
Nuclear morphology	Round	Indented or segmented	NA
Lifespan	Weeks to months	60 hours [†] (REF. 21)	NA
Proteases expressed	Chymases and tryptases	mMCP8 [†] (REF. 150) and mMCP11 [†] (REF. 145)	CPA ^{151,152} , granzymes and cathepsins
Proteoglycans expressed	Heparin	NA	Chondroitin sulphates
Cytokines produced	IL-8, IL-10, IL-25, TNF and VEGF ¹⁰	NA	IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-13, IL-15, TSLP and others ^{2,10,151}
Activating receptors expressed	KIT ¹⁵³ , FcγRI [§] and FcγRIIA [§] (REF. 51)	2B4 [†] (REF. 151), LIR7 [§] (REF. 154), leptin receptor [†] (REF. 155)	FcεRI, FcγRIIA [†] , CD200R3 [†] , C3aR, C5aR, LTB4R1, IL-3R, IL-18R, IL-33R and TSLPR ^{1–3,11,151}
Inhibitory receptors expressed	NA	LIR3 [§] (REF. 154)	CD200R1, CD300a (also known as LMIR1 in mice), FcγRIIB, GP49B1 and LIR2 [§] (REFS 1,3,151,153,154)
Survival factors expressed	BCL-X _L (REF. 156)	PIM1 kinase [§] (REF. 41)	MCL1 [†] (REF. 43) and BCL-2 (REF. 156)
Transcription factors expressed	MITF (REF. 157)	P1-RUNX1 [†] (REF. 29) and C/EBPα [†] (REF. 25)	GATA factors and STAT5 (REF. 158)
Immunomodulatory mediators produced	PGD2 and LTB4 (REF. 3)	NA	LTC4, PAF, histamine and serotonin [†] (REFS 2,3)
Other associated molecular markers	NA	CD49b [†] (REF. 151), basogranulin [§] (REF. 159) and CD203c [§] (REF. 32)	CD40L ⁷⁸ and CRTH2 (REFS 160,161)

BCL, B cell lymphoma; C3aR, complement component 3a receptor; CD200R, CD200 receptor; CD40L, CD40 ligand; C/EBPα, CCAAT/enhancer-binding protein-α; CPA, carboxypeptidase A; CRTH2, chemoattractant-receptor homologous molecule expressed by T_H2 cells; FcR, Fc receptor; GP49B1, glycoprotein 49 B1; IL, interleukin; IL-3R, IL-3 receptor; LIR, leukocyte immunoglobulin-like receptor; LMIR1, leukocyte mono-immunoglobulin-like receptor 1; LTB4, leukotriene B4; LTB4R1, LTB4 receptor 1; MCL1, myeloid cell leukaemia sequence 1; MITF, microphthalmia-associated transcription factor; mMCP, mast cell protease; NA, not applicable; P1-RUNX1, distal promoter-derived runt-related transcription factor 1; PAF, platelet-activating factor; PGD2, prostaglandin D2; STAT5, signal transducer and activator of transcription 5; TNF, tumour necrosis factor-α; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor; VEGF, vascular endothelial growth factor. *For further differences in gene expression between human and murine mast cells see also REFS 8, 162. [†]Expression reported in mice only. [§]Expression reported in humans only.

The lineage separation of mast cells and basophils probably occurred before the evolution of vertebrates, as both cell types can be found in lower vertebrates. Mast cells in zebrafish were found to express carboxypeptidase A (CPA) and an FcεRI-like receptor^{16,17}. Histamine-containing mast cells were further discovered in Perciformes, the most evolutionarily advanced order of teleost fish¹⁸. Similarly to mammalian mast cells, mast cells from Perciformes stain positively for the receptor tyrosine kinase KIT, and are mainly located around blood vessels and in tissues that form a barrier to the environment, such as the skin, the intestine and the gills. Basophils can also be detected by histology in teleost fish and reptiles. Basophils can be abundant in reptiles, and constitute more than 50% of blood leukocytes in the snapping turtle *Chelydra serpentina*¹⁹. These basophils express activating Fc receptors (FcRs) on their cell surface and can be induced to release histamine in response to stimulation with a rabbit anti-turtle immunoglobulin serum¹⁹. A rapid expansion and diversification of mast cell protease loci are found in mammalian species, which indicates that these proteases contribute to the fitness of individual species that live in different habitats (BOX 1).

Ontogeny of mast cells and basophils. The relationship between mast cell and basophil lineages found in mice and humans is incompletely understood. Mast cell

development seems to generally depend on the expression of KIT, as different mouse strains with natural mutations in the *Kit* locus or in the *Sl* (also known as *Kitl*) locus, which encodes the ligand for KIT (stem cell factor (SCF); also known as KITLG), lack mast cells, although they also have other defects (BOX 2). A mast cell-committed precursor — characterized by a THY1^{low}KIT^{hi}mMCP2 (mast cell protease 2; also known as MCPT2)⁺mMCP4 (also known as MCPT4)⁺CPA3⁺ phenotype — with the potential to repopulate the mast cell compartment in mast cell-deficient adult *Kit*^{W/W^{-v}} mice (BOX 2) was identified in the fetal blood at day 15.5 of gestation²⁰. At this stage of development, basophil-like cells (characterized by an interleukin-3 receptor-α (IL-3Rα)⁺FcεRIα⁻KIT⁻CD49b⁺ phenotype) were also detected in the fetal liver²¹. On the basis of mouse studies, it was proposed that basophils and mast cells develop from a granulocyte/monocyte progenitor (GMP) cell, and that their lineage specification is regulated by the timed expression of the transcription factors GATA-binding protein 2 (GATA2) and CCAAT/enhancer-binding protein-α (C/EBPα)²². However, others have reported that, although basophils arise from GMPs, mast cells develop from common myeloid progenitors (CMPs), which are characterized by a lineage (LIN)⁻KIT⁺ stem cell antigen 1 (SCA1)^{low}FMS-related tyrosine kinase 3 (FLT3; also known as FLK2)⁻ phenotype^{23,24} (FIG. 2).

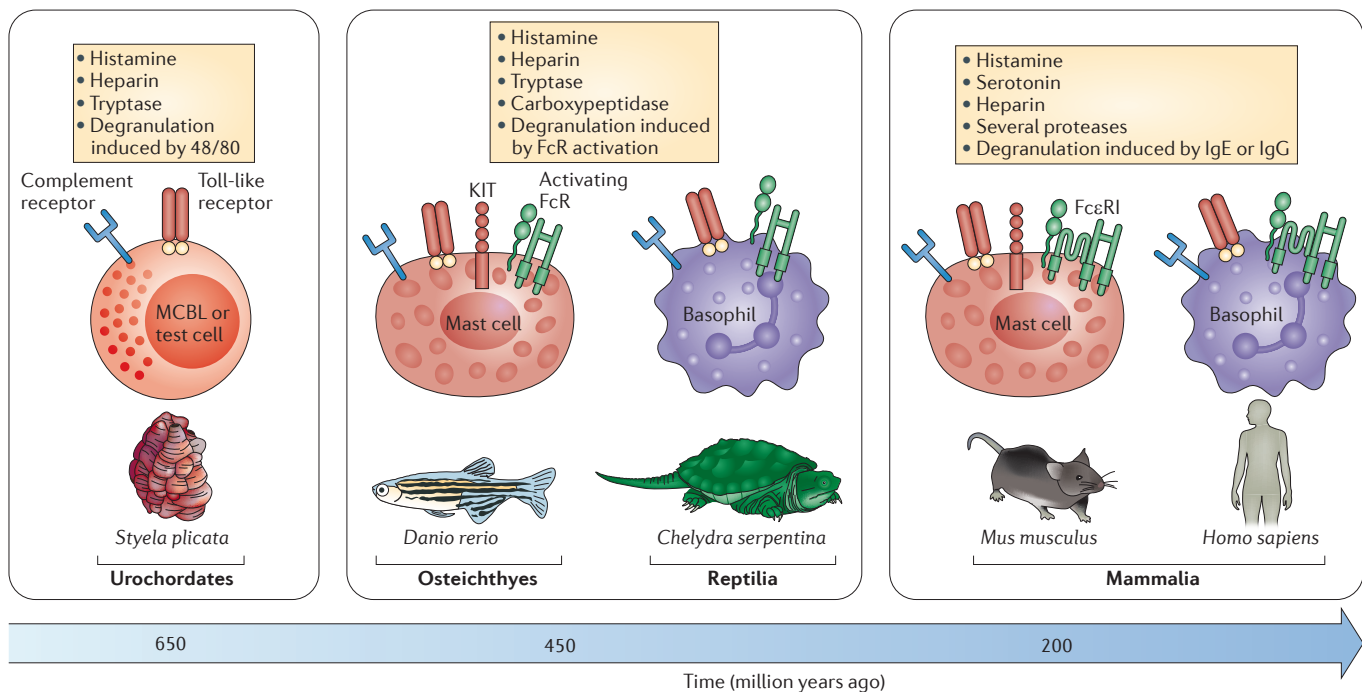


Figure 1 | Evolution of mast cells and basophils. The earliest precursor cells with features of mast cells and basophils are found in the urochordate *Styela plicata*. Mast cell/basophil-like (MCBL) cells and test cells might function as primitive antimicrobial effector cells. A separation of the mast cell and basophil lineages is seen in osteichthyes and reptilia, in which a primitive form of an activating Fc receptor (FcR) is expressed on both cell types and in which KIT could be identified on mast cells. Mammalia acquired expression of the high-affinity receptor for IgE (FcεRI) and other activating FcRs on mast cells and basophils. In addition, the mast cell protease family shows an enormous gene diversification in different mammalian species.

A bipotent basophil/mast cell progenitor (BMCP) cell that was characterized by a $\text{LIN}^- \text{CD34}^+ \text{KIT}^+ \text{FcεRI}\alpha\beta7$ integrin^{hi} and $\text{FcγRII}^{\text{hi}}$ or $\text{FcγRIII}^{\text{hi}}$ phenotype was identified in the spleens of adult C57BL/6 mice²⁵. This population expressed high levels of GATA2 and low levels of C/EBPα. The complete deletion of C/EBPα in purified BMCPs *in vitro* favoured mast cell development, whereas retroviral overexpression of C/EBPα promoted the development of the basophil lineage. However, development in the spleen probably only has a minor role in the development of the basophil lineage, as bromodeoxyuridine (BrdU) incorporation studies showed that new basophils are mainly generated in the bone marrow²¹.

Further evidence for a developmental relationship between mast cells and basophils comes from lineage-tracing studies with Cre-inducible fluorescent reporter mice. The gene *Mcpt8* (which encodes the mast cell protease mMCP8) is highly expressed in basophils but also seems to be transiently expressed during mast cell development, although it is not expressed by most other cell lineages²⁶. A basophil-specific precursor ($\text{LIN}^- \text{CD34}^+ \text{KIT}^+ \text{FcεRI}\alpha\beta7$ integrin^{low}) was found in the bone marrow²⁵, and STAT5 (signal transducer and activator of transcription 5)-mediated signals were shown to be essential for the development of basophil precursors in the bone marrow, as well as for the development of BMCPs in the spleen²⁷. Interestingly, basophils developed normally in mice that could not respond to IL-3, IL-5, granulocyte-macrophage colony-stimulating factor

(GM-CSF) and thymic stromal lymphopoietin (TSLP)²⁸. This indicates that other STAT5-associated cytokines are essential for basophil development. Surprisingly, mice deficient in the distal promoter-derived runt-related transcription factor 1 (P1-RUNX1) lack basophils, but mast cells and other cell lineages are not affected, which indicates that this transcription factor is required for the later stages of basophil development²⁹.

Two other groups found a unipotent mast cell precursor in the mouse bone marrow that could repopulate the mast cell population *in vivo*^{23,30}. This finding is consistent with previous reports that demonstrated that there was a developmental relationship between the mast cell lineage, and the megakaryocyte and erythrocyte lineages³¹. Therefore, it is possible that human basophils and mast cells might share a common precursor cell that expresses CD34, IL-3Ra and CD203c (also known as ENPP3)³². However, other reports from myeloid leukaemias, myelodysplastic syndromes and acute basophilic leukaemia provide evidence for a closer relationship between basophils, and eosinophils or megakaryocytes (reviewed in REF. 33). Most studies investigating the developmental potential of precursor cells are based on *in vitro* culture conditions with defined cytokine cocktails which do not reflect the cytokine milieu that is found *in vivo*. Moreover, instructive signals from stromal cells in the bone marrow might also be important for the development of basophils and mast cells.

Box 1 | Mast cell-associated proteases

Mast cells and basophils show overlapping expression of several characteristic genes, including a set of mast cell-associated proteases. These proteases can be categorized into three classes, namely two types of serine proteases (the chymases and the tryptases) and the metalloproteinase carboxypeptidase A (CPA3). Genes for mammalian mast cell proteases are rapidly evolving and major differences are even found between humans and other primates¹⁴¹.

The chymases are encoded by the chymase locus on chromosome 14q11.2 in mice and on 14C1/2 in humans. The human chymase locus encodes only four genes: chymase (CMA1), cathepsin G, granzyme B and granzyme H. In mice the chymase locus underwent a massive expansion and encodes six chymases: the mouse mast cell proteases mMCP1, mMCP2, mMCP4, mMCP5, mMCP9 and mMCP10, the granzyme-related gene *Mcpt8* (which encodes mMCP8) and six functional granzyme genes¹⁴². Tryptases are encoded by another locus that encodes 13 functional trypsin-like serine proteases on mouse chromosome 17A3.3 and nine proteases on human chromosome 16p13.3 (REF. 143). The human α -tryptases and β -tryptases are probably the counterparts to the murine tryptases mMCP6 and mMCP7, respectively¹⁴⁴. Interestingly, mMCP8 and the tryptase mMCP11 are highly expressed by mature basophils but not by mast cells or by any other major cell type¹⁴⁵. Therefore, the *Mcpt8* locus was chosen for the development of several different basophil-targeted mouse strains. Likewise, the *Mcpt5* (encoding mMCP5) and *Cpa3* loci were used to generate mice with targeted expression of Cre in mast cells and thereby to create Kit-independent models of mast cell deficiency (TABLE 2).

Subsets, and the homeostasis of mast cells and basophils. Like other granulocytes, basophils finish their maturation in the bone marrow, whereas mast cells enter peripheral tissues as immature cells³⁴. Two major subsets of murine mast cells have been described on the basis of their tissue localization and their expression pattern of mast cell-associated proteases (BOX 1). Connective tissue mast cells (CTMCs) are mainly located in the intestinal submucosa, the skin, the peritoneal cavity and the surrounding the blood vessels, whereas mucosal mast cells (MMC) are usually found between epithelial cells of mucosal tissues in the lung and in the intestine. CTMCs express the chymases mMCP4 and mMCP5 (also known as CMA1), the tryptases mMCP6 (also known as TPSB2) and mMCP7 (also known as TPSAB1; not expressed in

C57BL/6 mice), and CPA; however, MMCs mainly produce the chymases mMCP1 and mMCP2 (reviewed in REF. 35). A human mast cell is categorized either as a tryptase-containing mast cell (MC_T), or as a tryptase- and chymase-containing mast cell (MC_{TC})³⁶.

Basophils from allergic patients were found to express chymases, tryptases and CPA, but these proteases are not usually detected by histology in peripheral blood basophils isolated from healthy individuals³⁷. There might also be a certain degree of functional plasticity in the basophil lineage, as it has recently been shown that the production of effector molecules by basophils can be regulated by different cytokines. TSLP promotes the differentiation of basophils containing few granules but expressing high levels of IL-18R α , IL-33R (also known as T1/ST2), IL-4, IL-6, CC-chemokine ligand 3 (CCL3), CCL4, CCL12 and CXC-chemokine ligand 2 (CXCL2) compared with IL-3-elicited basophils²⁸. IL-3 promotes the accumulation of basophils in the lymph nodes³⁸, whereas TSLP was found to mediate basophil recruitment to the skin in a model of atopic dermatitis²⁸.

Basophils have a relatively short lifespan of about 60 hours in mice under steady-state conditions²¹, whereas mast cells survive for weeks to months under the same conditions³⁹. IL-3 promotes basophilia and mastocytosis during the infection of mice with gastrointestinal helminths, although IL-3 is not required for the development of basophils and mast cells under steady-state conditions *in vivo*⁴⁰. TSLP induces basophilia in the absence of IL-3, probably by increasing the lifespan of basophils²⁸. IL-3 and TSLP activate the STAT5 pathway, which reduces apoptosis, partly through the induction of the serine/threonine kinase PIM1 (REF. 41). STAT5 has also been shown to be important for mast cell development and survival⁴². The anti-apoptotic BCL-2 (B cell lymphoma 2) family member MCL1 (myeloid cell leukaemia sequence 1) also seems to be crucial for the survival of mast cells and basophils⁴³.

Box 2 | Using KIT-based mouse models to study mast cell functions

Over the past three decades the *in vivo* functions of mast cells have generally been discovered by using mouse strains with natural loss-of-function mutations at the white spotting locus (*W*), which encodes the receptor tyrosine kinase KIT. KIT is essential for mast cell development but it is also expressed by many other cell types, including haematopoietic stem cells and innate lymphoid cells. The two main mouse models used to study mast cell functions *in vivo* are WBB6F₁-Kit^{W/W-v} mice and Kit^{W-sh/W-sh} mice (also known as W-sash mice). Kit^{W/W-v} mice carry one allele (*W*) with a point mutation that produces a non-functional truncated receptor and another allele (*W-v*) that encodes a mutation in the kinase domain. This leads to the depletion of about 99% of mast cells. However, these mice have a mixed genetic background and show other defects including male sterility, anaemia, defective melanocytes, lack of interstitial cells of Cajal, reduced pacemaker activity in the intestine, impaired development of $\gamma\delta$ -T cells in the gut, neutropenia and 50–90% fewer basophils in their bone marrow, spleen and blood compared with control mice^{40,54,146}. Furthermore, mast cells can develop in WBB6F₁-Kit^{W/W-v} mice under inflammatory conditions. The *W-sh* allele results from a 3 Mb pair inversion containing 27 genes, where the 3' end of the inversion is located about 67.5 kb upstream of *Kit*¹⁴⁷. This leads to abnormal KIT expression but also disrupts the gene encoding corin, a cardiac protease, leading to mild hypertension and cardiac hypertrophy. Kit^{W-sh/W-sh} mice lack mast cells but basophil numbers are not reduced. Furthermore, they are fertile, not anaemic and have been backcrossed for more than ten generations to C57BL/6 mice. However, Kit^{W-sh/W-sh} mice show signs of abnormal haematopoiesis with neutrophilia, thrombocytosis and reduced levels of IgE^{93,147}. Adoptive transfer of bone marrow-derived mast cell cultures into Kit-mutant mice has been used to restore the mast cell population in certain tissues in order to link a given phenotype with the presence or the absence of mast cells^{148,149}. Several newly generated mouse strains have more recently been developed that can be used to study mast cell and basophil functions *in vivo*, independently of Kit mutations (TABLE 2).

The level of serum IgE or IgG1 antibodies might regulate mast cell and basophil numbers in the blood, although conflicting results have been published on this subject. It was found that certain monomeric IgE molecules could promote mast cell survival by reducing their rates of apoptosis in response to growth factor deprivation⁴⁴ and that most of these cytokinergic IgE molecules showed polyreactivity to self antigens⁴⁵. IgE was also reported to increase IL-3R expression on basophil precursors and to be crucial for basophil homeostasis under steady-state conditions⁴⁶. By contrast, another study showed normal steady-state basophilia in *FcRγ*^{-/-} mice, which do not express FcεRI or other activating FcRs⁴⁷. Others found that *FcRγ*^{-/-} mice develop impaired basophilia in response to infection with the gastrointestinal helminth *Heligmosomoides polygyrus* and that IgE or IgG1 antibodies could expand the basophil population independently of T cell-derived IL-3 (REF. 48).

Taken together, these data indicate that mast cells and basophils might have evolved from a common precursor cell type that helped to protect primitive chordates against pathogens. The diversification into mast cells and basophils could reflect the need for specialized effector functions (discussed below). Mast cells are long-lived tissue-resident cells, whereas basophils have a short lifespan and are recruited to inflamed tissues. The functional specification of mast cells and basophils is further regulated by the tissue environment and the local cytokine milieu.

Strategies to study *in vivo* functions

The selective deletion of mast cells or basophils *in vivo* is a useful approach to address the role of these cell types during immune responses. Obviously, the deletion should be efficient and should only affect the cell type to be studied. Several experimental systems have been used to achieve this goal. Classical models to study mast cell functions are based on *Kit*-mutant mouse strains, which have other defects besides their lack of mast cells (BOX 2). New mouse models have been more recently developed to avoid these problems (REFS 49–51) (TABLE 2). Expression of Cre recombinase in mast cells confers their constitutive deletion after crossing these mice with R-DTA (Rosa-diphtheria toxin-α) mice, which express the diphtheria toxin α-subunit under control of a *loxP*-flanked stop cassette from the *Rosa26* locus⁵², or after crossing the Cre-expressing mice with mice that have a floxed allele of the anti-apoptotic gene *Mcl1* (REF. 43). Conditional deletion can be achieved with Cre-inducible diphtheria toxin receptor (iDTR) mice or with mast cell-specific DTR mice that express the human DTR on mast cells, which leads to the ablation of mast cells after diphtheria toxin injection^{52,53}. A rather unexpected but elegant way to delete mast cells without apparent side effects was achieved by the induction of high expression levels of Cre in mast cells⁵⁴, which leads to Cre-mediated toxicity as a result of the recognition of cryptic *loxP* sites in the genome⁵⁵.

Owing to the lack of any natural mouse mutants with basophil deficiencies, antibodies that deplete this population of cells have often been used to study the contribution of basophils in different experimental settings. These antibodies recognize either the high-affinity IgE receptor FcεRI (clone MAR-1) or the orphan activating receptor CD200 receptor 3 (CD200R3) (clone Ba103), which are both mainly expressed by basophils and mast cells. Although both antibody clones can efficiently deplete basophils, they can also activate mast cells and can cause anaphylaxis^{26,56}. Furthermore, the depletion of basophils by Ba103 is FcR-dependent and might therefore activate myeloid cells and natural killer (NK) cells⁵⁷. MAR-1 also depletes a subset of FcεRI-expressing dendritic cells (DCs)⁵⁸. Several *in vivo* functions have been attributed to basophils on the basis of studies using these depleting antibodies, and this has led to the conclusion that basophils have a crucial role as antigen-presenting cells (APCs) during T_H2 cell polarization^{59,60}, that they cause IgG1-mediated systemic anaphylaxis⁶¹, that they contribute to protective immunity against the whipworm

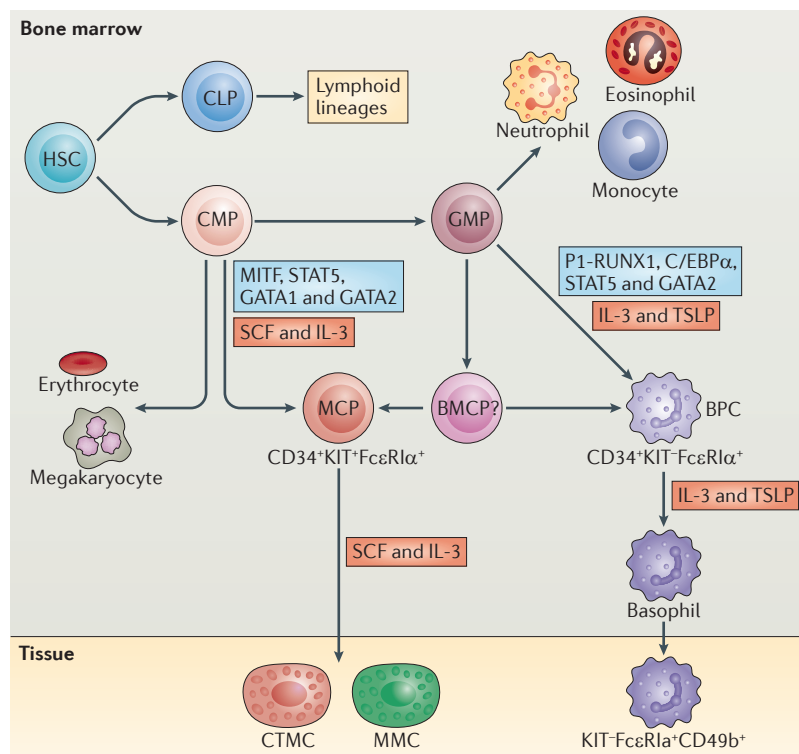


Figure 2 | Development of mast cells and basophils in the murine bone marrow. Haematopoietic stem cells (HSCs) give rise to common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). Mast cell progenitors (MCPs) might differentiate from CMPs²⁴ or from granulocyte/monocyte progenitors (GMPs) via a potential intermediate cell (known as the basophil/mast cell progenitor (BMCP)) that gives rise to basophils and mast cells but that has so far only been identified in the spleen²⁵. Mast cells enter tissues as immature cells and finish their final maturation to connective tissue mast cells (CTMCs) or mucosal mast cells (MMCs) following receipt of instructive signals from the tissue environment. Basophils develop from basophil progenitor cells (BPCs) that are derived from GMPs (or BMCPs)²⁵. They leave the bone marrow as mature cells with a lifespan of about 60 hours under steady-state conditions. Transcription factors (shown in blue) and cytokines (shown in red) that drive lineage development are indicated. C/EBPα, CCAAT/enhancer-binding protein-α; FcεRIα, high-affinity receptor for IgE; GATA, GATA-binding protein; IL-3, interleukin-3; MITF, microphthalmia-associated transcription factor; P1-RUNX1, distal promoter-derived runt-related transcription factor 1; SCF, stem cell factor; STAT5, signal transducer and activator of transcription 5; TSLP, thymic stromal lymphopoietin.

Table 2 | **New mouse models to target mast cells and basophils**

Mouse strain	Description	Reported modes of deletion	Features of deletion model	Deleted populations	Lineage tracing with reporter mice	Remarks	Refs
Mast cells							
<i>Mcpt5</i> -Cre	BAC transgene (129 kb, Cre inserted after the <i>Mcpt5</i> start codon)	Cross to Cre-iDTR mice	Cells express Cre recombinase but are not spontaneously deleted	Diphtheria toxin-induced deletion of CTMCs (>90%)	Marks CTMCs but not other cell types	MMCs and basophils are not deleted	52, 163
		Cross to R-DTA mice, which encode Cre-inducible DTA	Cells express Cre recombinase but are not spontaneously deleted	Constitutive deletion of CTMCs (>90%)			
<i>Cpa3</i> -Cre (also known as Hello Kitty)	Promoter transgene	Cross to <i>Mcl1</i> ^{fl/fl} mice causes impaired survival	Cells express Cre recombinase but are not spontaneously deleted	>90% deletion of CTMCs and MMCs, but also 60–80% deletion of basophils	Marks >80% of mast cells, 10–15% of granulocytes and 4% of TER119 ⁺ cells in the spleen	Mice develop splenic neutrophilia and macrocytic anaemia	43
<i>Chm</i> :Cre	Promoter transgene (600 bp baboon α -chymase promoter)	NR	Cells express Cre recombinase but are not spontaneously deleted	NA	Marks mast cells in the lung and the colon	No expression in the skin, heart, peritoneum or in BMMCs	164
<i>Cpa3</i> ^{Cre} (Cre-Master)	Knock-in of Cre before the first exon of <i>Cpa3</i>	Constitutive deletion due to Cre-mediated toxicity ⁵⁵ (can be partially rescued by deletion of p53)	Cells express Cre and are constitutively deleted due to Cre-mediated cytotoxicity	All CTMCs and MMCs, and 60% deletion of basophils (in the spleen)	Marks 90% of T cells and 5% of B cells but does not delete them	NA	54
Mas-TRECK	DTR transgene (under control of 5' enhancer, promoter and intronic enhancer of <i>IL4</i>)	Diphtheria toxin injection	Cells express DTR allowing inducible deletion	Diphtheria toxin-induced deletion of CTMCs, MMCs and basophils (90–100%)	NA	Basophils are restored 2 weeks after diphtheria toxin injection	53
Basophils							
Basoph8 (<i>Mcpt8</i> ^{RES-YFP-Cre})	Knock-in of IRES-YFP-Cre cassette before the <i>Mcpt8</i> start codon	Cross to R-DTA mice	Cells express Cre recombinase but are not spontaneously deleted	Constitutive deletion of basophils (>90%)	NR	NA	69
<i>Mcpt8</i> -Cre	BAC transgene (228 kb, Cre inserted after the <i>Mcpt8</i> start codon)	Constitutive deletion due to Cre toxicity	Cells express Cre and are constitutively deleted due to Cre-mediated cytotoxicity	Constitutive deletion of basophils (>90%)	Marks 80% of peritoneal mast cells	NA	26
Bas-TRECK	DTR transgene (under control of 5' enhancer, promoter and 3' proximal enhancer of <i>IL4</i>)	Diphtheria toxin injection	Cells express DTR allowing inducible deletion	Diphtheria toxin-induced deletion of basophils (>90%)	NA	NA	53
<i>Mcpt8</i> ^{DTR}	Knock-in of IRES-DTR-EGFP cassette in 3' UTR of <i>Mcpt8</i>	Diphtheria toxin injection	Cells express DTR allowing inducible deletion	Diphtheria toxin-induced deletion of basophils (>90%)	NA	NA	80
<i>P1-Runx1</i>	Knockout	<i>P1-Runx1</i> seems to be important for the basophil lineage	Strain shows constitutive deletion of basophils due to lack of the transcription factor <i>P1-RUNX1</i>	Constitutive deletion of basophils (>90%)	NA	NA	29

BAC, bacterial artificial chromosome; BMMCs, bone marrow-derived mast cells; CTMCs, connective tissue mast cells; DTR, diphtheria toxin receptor; EGFP, enhanced green fluorescent protein; iDTR, inducible DTR; *IL4*, interleukin-4; IRES, internal ribosome entry site; *P1-RUNX1*, distal promoter-derived runt-related transcription factor 1; *Mcpt*, mast cell protease; MMCs, mucosal mast cells; NA, not applicable; NR, not reported; R-DTA, ROSA-diphtheria toxin- α ; UTR, untranslated region; YFP, yellow fluorescent protein.

*Trichuris muris*⁶² and that they enhance humoral memory responses in the spleen⁶³. Several new mouse strains with constitutive or inducible depletion of basophils have recently been generated, and studies using these mice could confirm some of the previously proposed effector functions of basophils (as discussed below) (TABLE 2).

Initiation of type 2 immunity

Adaptive type 2 immunity is characterized by the polarization of T_H2 cells and by class-switch recombination (CSR) to IgE. Both events are promoted by IL-4, which can be produced with variable efficiency by many different cell types, including T_H2 cells, natural killer T (NKT) cells, type 2 innate lymphoid cells (ILC2s; which include natural helper cells, nuocytes and innate type 2 helper cells), eosinophils, basophils and mast cells. On the basis of the requirement for the addition of exogenous IL-4 for T_H2 cell polarization *in vitro*, it is widely believed that T_H2 cell polarization *in vivo* depends on an innate cell type that produces IL-4 early during the initiation of an immune response. However, antigen recognition together with IL-2-, IL-7- or TSLP-mediated signalling can lead to early T cell expression of IL-4 and the upregulation of IL-4Rα on T cells so that autocrine or paracrine IL-4 that is produced can then stabilize the T_H2 cell phenotype⁶⁴. In addition to the production of IL-4, mast cells and basophils can — at least under certain conditions — express low levels of MHC class II and co-stimulatory molecules, and can present antigen to CD4⁺ T cells^{59,60,62,65,66}. Schistosoma egg antigen (SEA) has been shown to induce basophil accumulation in the draining lymph nodes, but the depletion of basophils did not affect T_H2 cell polarization in response to SEA^{62,67}. The number of basophils in the lymph nodes increased in response to the injection of the pro-allergic cysteine protease papain before T_H2 cell polarization was observed⁶⁸. Although basophils were found to form direct contacts with T cells in the lymph nodes⁵⁹, these contacts are probably too short-lived to convey activating signals to T cells⁶⁹. T_H2 cell polarization was reduced in response to papain when basophils had been depleted with MAR-1 (REF. 68), and, furthermore, papain-induced T_H2 cell polarization was shown to depend on the cooperation between basophils and DCs⁷⁰. However, studies with mice that constitutively lack either basophils or DCs demonstrated that papain-induced T_H2 cell polarization requires DCs but not basophils²⁶. Papain has also been shown to directly induce the expression of IL-4 from naive T cells by binding to the protease-activated receptor 2 (PAR2; also known as F2RL1)⁷¹. Importantly, mice that have had their basophils genetically ablated showed normal T_H2 cell polarization in response to immunization with aluminium hydroxide (alum) in conjunction with ovalbumin (OVA), or to immunization with SEA and infection with the helminth *Nippostrongylus brasiliensis*^{26,69}. However, basophils might enhance the memory T_H2 cell response by their rapid release of IL-4 during secondary infection with helminths⁷². Human basophils were reported to express MHC class II molecules, and to promote autoantibody production and

the development of lupus nephritis^{60,73}. These findings were questioned by another study, which showed that MHC class II expression could not be detected on the cell surface of basophils that were isolated from patients with systemic lupus erythematosus (SLE). Instead, the proposed APC function of isolated human basophils could be attributed to the presence of a contaminating population of FcεRI- and IL-3R-expressing plasmacytoid DCs⁷⁴. Another study of allergic patients also found that human basophils do not express MHC class II and that the proliferation of allergen-specific T cells is not affected by the depletion of basophils⁷⁵.

Mast cells were found to modulate adaptive type 2 immunity in different ways. Several *in vitro* experiments have demonstrated that the expression of MHC class II and co-stimulatory molecules can be induced on mouse and human mast cells but that there is no evidence that mast cells have a crucial role as APCs for the activation of CD4⁺ T cells *in vivo*¹⁰. However, mast cells might induce the recruitment of migrating DCs and modify the quality of those DCs to induce T_H2 cell differentiation¹⁰. The factors that induce the differentiation of T_H2 cell-polarizing DCs are manifold and include tissue damage, the activation of pattern-recognition receptors, metabolic changes and the expression of proteases⁷⁶. In addition, it was found that *Kit*^{W/W^{-v} mice have a defect in the release of IL-25, IL-33 and TSLP from their tissues and that they show reduced T_H2 cell priming in response to infection with the gastrointestinal helminth *H. polygyrus*⁷⁷. These defects were attributed to the lack of mast cells, as similar results were obtained using mice in which mast cell degranulation was blocked with cromolyn sodium and because a normal response could be restored by reconstitution of the *Kit*^{W/W^{-v} mice with bone marrow cells from wild-type mice.}}

Human mast cell and basophil lines have been shown to directly induce CSR to IgE in B cells *in vitro* owing to their expression of CD40 ligand (CD40L)⁷⁸. However, murine basophils and mast cells seem to be dispensable for the induction of systemic IgE responses to allergens, to helminths or to ticks *in vivo*^{26,79,80}. These findings do not exclude the possibility that both cell types might induce IgE CSR locally in mucosal tissues⁸¹.

Protection against multicellular parasites

From an evolutionary perspective, mast cells and basophils probably developed to confer protection against a variety of pathogens. Protective mast cell functions against bacterial, viral and fungal infections have been covered by other reviews and are not discussed here^{7,8}. Helminths and blood-feeding ticks elicit a special type of immune response, as these multicellular pathogens cannot be eliminated by phagocytosis or by cytotoxic attacks. These pathogens interact with their hosts at barrier tissues, such as the skin and the intestinal mucosa, and they produce enzymes that cause considerable tissue damage. It is therefore important to rapidly control the infection and to repair the damage. The immune system handles this problem by mounting a type 2 immune response to which basophils and mast cells can contribute at different levels.

Infections with gastrointestinal helminths. Helminths infect more than two billion people worldwide, mainly in areas with low hygiene standards⁸². Furthermore, they cause major problems for livestock farming with considerable economic losses. Vaccines against helminths that infect humans are under development but are not yet available. Several murine infection models have been established to gain insights into the regulation of protective immunity against tissue-dwelling and gastrointestinal helminths⁸³. In general, the immune system either creates an inhospitable environment in the intestinal lumen so that the worms detach and are expelled from the body, or the immune system promotes the formation of granulomas to shield tissue-dwelling parasites from the rest of the tissue. IL-4 and IL-13 seem to be crucial for both processes. These cytokines induce the expression of a set of STAT6-dependent genes in different cell types, which leads to the production of IgE and IgG1; the secretion of effector molecules, including chitinase-like proteins, resistin-like molecules (RELMA and RELM β) and trefoil factor 2; the activation of smooth muscle cells; mucus production by goblet cells; collagen deposition; the differentiation of alternatively activated macrophages (AAMs); and the increased turnover of intestinal epithelial cells (reviewed in REFS 84,85) (FIG. 3). Basophils and mast cells might contribute to the protection of the host during the early phase of infection partly by their secretion of IL-4 and IL-13, either in response to helminth-derived factors such as proteases^{86,87} or in response to host-derived molecules, including anaphylatoxins and cytokines such as IL-18, IL-33, TSLP and IL-3. At later stages of the infection, or after secondary infection, both cell types can be further activated by helminth-specific antibodies.

The immune response can be different between primary and secondary infections. For example, the nematode *N. brasiliensis* lives as an adult worm in the lumen of the small intestine, from where it is normally expelled about 10 days after the primary infection of the mouse, by a process that requires CD4⁺ T cells⁸⁸, the production of IL-25 and IL-33 from tissues, the production of IL-13 from ILC2 cells⁸⁹ and STAT6 expression in epithelial cells⁹⁰. However, eosinophils⁹¹, basophils²⁶ and B cells⁹² are generally dispensable for the immune-mediated expulsion of *N. brasiliensis*. Mast cell-deficient *Kit*^{W-sh/W-sh} and *Kit*^{W/W-v} mice show slightly delayed kinetics of worm expulsion during the primary infection^{93,94}. However, these observations, along with other studies that examine gastrointestinal helminth infection in *Kit*-mutant mice, must be viewed with caution, as these mice have additional physiological defects, including changes to intestinal peristalsis (BOX 2). During secondary infection with *N. brasiliensis*, worm expulsion occurs within 5 days and operates independently of mast cells and CD4⁺ T cells, but the expulsion of worms is partially impaired in mice depleted of basophils with either the MAR-1 or the Ba103 antibodies, or in *Mcpt8*-Cre mice that have had their basophils genetically depleted^{26,93}. Another study demonstrated that the production of IL-4 or IL-13 by

basophils contributes to worm expulsion during the primary infection when both cytokines cannot be produced by T cells⁶⁹. In contrast to the *Mcpt8*-Cre mice, Basoph8 mice crossed with R-DTA mice (TABLE 2) could efficiently expel *N. brasiliensis* during the secondary infection, which indicates that compensatory mechanisms that remain to be characterized might exist under certain conditions⁶⁹. Similar to the impaired immune response to *N. brasiliensis* observed following basophil depletion, the depletion of basophils also affected worm expulsion during secondary *H. polygyrus* infection⁴⁸. In addition, the fecundity of *H. polygyrus* seemed to be inversely correlated with the number of mast cells⁹⁵. *Kit*^{W-sh/W-sh} mice and mice depleted of basophils with the MAR-1 antibody showed a partially impaired expulsion of *T. muris*, a helminth that inhabits the caecum and the colon, which indicates that mast cells and basophils contribute to host protection against *T. muris*^{62,77}. The expulsion of *Trichinella spiralis*, which lives as an adult worm in the epithelial cells of the small intestine, is also delayed in *Kit*-mutant mice⁹⁶. Furthermore, it was shown that the mast cell-derived chymase mMCP1 is required to limit the deposition of *T. spiralis* larvae in tissues and to expel adult worms in a timely manner, but that mMCP1 was not required for the expulsion of *N. brasiliensis*⁹⁷. In addition, mMCP-6 and IgE seem to be important for the recruitment of eosinophils to *T. spiralis* larval cysts in striated muscle tissue^{98,99}.

The blood fluke *S. mansoni* infects about 200 million people worldwide and causes pathological complications as a result of the toxic products produced by its deposited eggs in the lungs and liver. The eggs induce a strong type 2 immune response, and the IL-4- or IL-13-mediated differentiation of AAMs is essential to prevent severe pathology following infection¹⁰⁰. Similarly, AAMs seem to be crucial for protective immunity during secondary *H. polygyrus* infection¹⁰¹. AAMs are part of the granulomas that form around *S. mansoni* eggs and the larvae of other helminths in tissues to prevent excessive tissue damage (reviewed in REF. 85). It has been shown that IgE-deficient mice form smaller granulomas and have a higher worm burden after *S. mansoni* infection, which indicates that the IgE-mediated activation of mast cells or basophils induces their release of IL-4 or IL-13 and this contributes to host protection against this parasite¹⁰². However, another study using Fc ϵ RI-deficient mice found no difference in adult worm counts or tissue egg burden when compared with wild-type mice¹⁰³. Interestingly, basophils and mast cells can be induced to release IL-4 and IL-13 by the major antigen in *S. mansoni* eggs IgE-binding IL-4-inducing principle (IPSE)/ α 1, which functions in a similar manner to a superantigen, in that it activates cells by antigen-independent binding to IgE molecules that are bound to Fc ϵ RI¹⁰⁴. Although mast cells might contribute to the immune response during primary infection, they are not required for a protective immune response after vaccination with irradiated *S. mansoni* cercariae¹⁰⁵. The role of basophils during the course of infection remains to be determined.

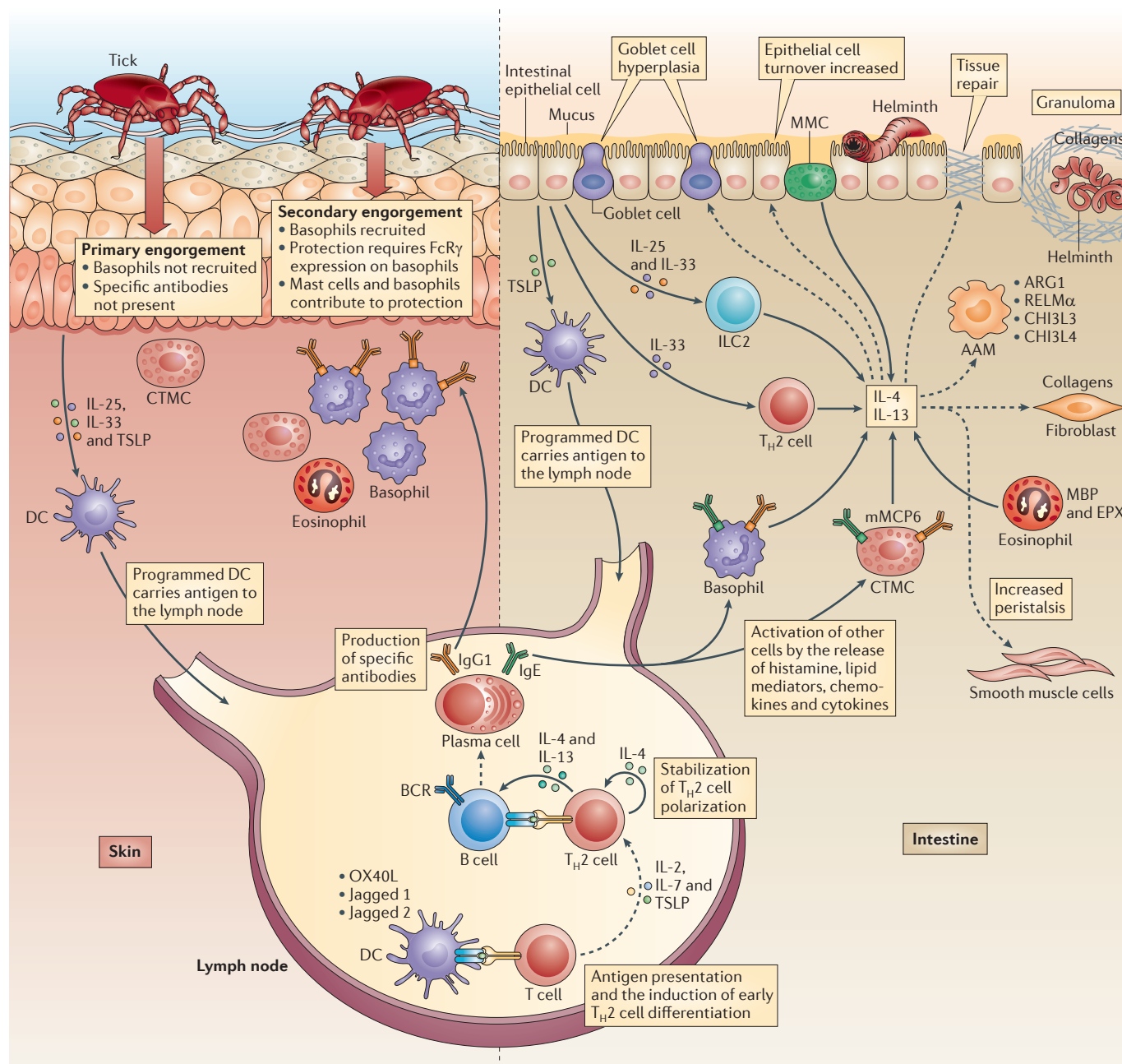


Figure 3 | Protective immunity against helminths and ticks. Parasite-derived antigens are taken up and processed by dendritic cells (DCs), which also respond to tissue-derived cytokines. Early T helper 2 (T_H2) cell polarization is promoted by signal transducer and activator of transcription 5 (STAT5)-activating cytokines and DCs that upregulate surface molecules, such as OX40L and the Notch ligands Jagged1 and Jagged2. T_H2 cells are stabilized by autocrine and/or paracrine sources of interleukin-4 (IL-4), and induce IgE and IgG1 production by plasma cells. Both isotypes bind activating receptors on basophils and mast cells, and sensitize them to rapidly respond during a secondary encounter of the same antigen. Mast cells and basophils cooperate during protective immunity against ticks by mechanisms that remain to be identified. IL-4 and IL-13 are important cytokines for protective immunity against gastrointestinal helminths as they coordinate various effector mechanisms (shown by dashed arrows) that lead to either worm expulsion or worm encapsulation in granulomas. Both cytokines can be produced by T cells and by innate cells, such as type 2 innate lymphoid cells (ILC2s), eosinophils, basophils and mast cells. ILC2s are a crucial source of IL-13 during primary infection with *Nippostrongylus brasiliensis*⁸⁹. Basophils are efficiently activated in the presence of helminth-specific antibodies and are therefore probably more important during secondary infections^{26,48}. Mast cells further induce IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) release from epithelial cells and contribute to immunity against *Trichinella spiralis* by their secretion of mast cell protease 1 (mMCP1) and mMCP6 (REFS 77,97,98). AAM, alternatively activated macrophage; ARG1, arginase 1; BCR, B cell receptor; CHI3L, chitinase-3-like protein; CTMC, connective tissue mast cell; EPX, eosinophil peroxidase; FcR, Fc receptor; MBP, major basic protein; MMC, mucosal mast cell; RELM α , resistin-like molecule- α ; TFF2, trefoil factor 2.

Antibodies can mediate protection against various helminths (reviewed in REF. 106). The antibodies might directly bind to the migrating larvae and activate the complement cascade, they might neutralize helminth-derived factors that are crucial for establishing the infection or they might sensitize cells that express activating FcRs. Human epidemiological studies show a correlation between high IgE levels and resistance to the filarial parasite *Brugia malayi*¹⁰⁷, the large intestinal roundworm *Ascaris lumbricoides*¹⁰⁸, *S. mansoni*^{109,110} and hookworms¹¹¹. Production of helminth-specific antibodies can be long-lasting. For example, people who have been infected with *B. malayi* can still contain *B. malayi*-specific IgE antibodies several years after de-worming and relocation to non-endemic areas¹¹². Although IgE is generally associated with helminth infections, there is limited evidence for a protective role for IgE. Indeed, IgM, IgG and IgA seem to be more important isotypes for mediating protective immunity against helminths in mouse models¹⁰⁶.

Acquired tick resistance. Ixodid ticks are a group of blood-feeding ectoparasites that can transmit infectious diseases, including Lyme disease and viral encephalitis. Ticks actively penetrate the skin with their mouth parts and feed for several days before they detach. Many different mammalian species show resistance to secondary infestation with ticks. Tick resistance could be conferred on naive guinea pigs by the transfer of serum or lymphocytes from infested animals^{113,114}. Some basophils, but almost no eosinophils, were recruited to the dermis and epidermis at the site of tick feeding about 1 week after primary infestation. During secondary infestation a pronounced recruitment of basophils and eosinophils was observed in the dermis but only basophils accumulated in the epidermis¹¹⁵. Basophils were indeed required for tick resistance in guinea pigs, as depletion of basophils resulted in better tick feeding and fewer eosinophils around the tick mouthparts¹¹⁶. Although tick resistance can be observed in mice, protective immunity to the tick *Haemaphysalis longicornis* seems to depend on mast cells and tick-specific antibodies, which indicates that resistance might be conferred by FcR-mediated mast cell activation¹¹⁷. Unexpectedly, a recent study demonstrated that resistance to tick infestation was still observed in *Kit^{W-sh/W-sh}* mice that were locally reconstituted with *in vitro*-generated mast cells from *Fcγ^{-/-}* mice, which indicates that activating FcRs on other cells, but not on mast cells, are crucial for resistance⁸⁰. Basophils accumulated around the tick mouthparts during secondary infestation and resistance was lost when basophils were selectively deleted in *Mcpt8^{DTT}* mice by the administration of diphtheria toxin⁸⁰. It seems probable that the expression of FcεRI or of the low-affinity FcR for IgG (FcγRIIIA) by basophils is crucial for this resistance, especially because transfer of basophils from infested mice to naive mice was sufficient to mediate resistance⁸⁰. Furthermore, it was shown that infestation of mice with pathogen-free nymphs of the tick *Ixodes scapularis* induced host resistance to transmission of

Borrelia burgdorferi by the same tick species¹¹⁸. This indicates that basophils could indeed be involved in protection against tick-transmitted diseases. It remains to be established how mast cells and basophils communicate to confer resistance to ticks (FIG. 3).

Pathology mediated by mast cells and basophils

Anaphylaxis. Systemic anaphylaxis is the most severe form of allergic reaction and occurs mainly in response to insect venoms, drugs and food allergens¹¹⁹. Anaphylaxis was first described by Paul Portier and Charles Richet in 1902 when they unexpectedly observed that dogs immunized against a toxin from the jellyfish *Physalia* were not protected but instead died after secondary injection of the toxin. An estimated 1,500 Americans die every year from anaphylactic shock¹²⁰. The classical anaphylactic reaction is caused by the crosslinking of IgE on the cell surface of mast cells and the subsequent release of histamine and other vasoactive substances. However, fatal active anaphylaxis could also be induced in *Kit^{W/W-v}* and IgE-deficient mice, which indicates that, at least in mice, mast cell- and IgE-independent pathways for anaphylaxis exist^{121,122}. On the basis of experiments using basophil-depleting antibodies, such an alternative pathway for anaphylaxis was reported to depend on basophils; it was shown that basophils release the vasoactive lipid mediator platelet-activating factor (PAF) in response to the crosslinking of IgG1 bound to the activating receptor FcγRIIIA⁶¹. However, mice in which the basophils had been genetically ablated showed a normal active and passive IgE- and IgG1-mediated anaphylactic response²⁶. Another report provides evidence that neutrophils have an important role during passive IgG- and PAF-mediated anaphylaxis, both in mice and in humans¹²³. Furthermore, in the murine system, active anaphylaxis to peanut antigens was strongly reduced when phagocytes were depleted with clodronate-containing liposomes, but depletion of basophils with Ba103 antibodies had only a minor effect on the anaphylactic response^{124,125}. Although recent studies have questioned the role of basophils in anaphylactic responses in mice, further work is needed to address the potential involvement of basophils during anaphylactic responses in humans.

Allergic asthma. Allergic asthma is characterized by airway hyper-reactivity (AHR), mucus production, eosinophilia and fibrosis in the lungs. IL-4 and IL-13 have a central role in the pathogenesis of this disease. Mouse models of allergic lung inflammation have shown that a population of FcεRI-expressing DCs is important for T_H2 cell polarization in response to the intranasal administration of house dust mite extracts, whereas depletion of basophils with Ba103 antibodies only partially reduced the T_H2 cell response and the number of eosinophils in the bronchoalveolar lavage (BAL) fluid in this model⁵⁸. In experiments using the alum-OVA model of allergic lung inflammation, AHR responses, IgE production, and the recruitment of T_H2 cells and eosinophils, were also comparable in control mice and in basophil-depleted

Bas-TRECK⁵³ or *Mcpt8*-Cre²⁶ mice (TABLE 2). However, on the basis of human studies, it seems that basophils might have an important role during the late-phase allergic asthma response (reviewed in REF. 5). Basophils are found in the airways of post-mortem cases of fatal asthma¹²⁶. Furthermore, basophils, eosinophils and lymphocytes have been shown to increase in the BAL fluid only at late time points (19 hours) following challenge of allergy patients with segmental ragweed¹²⁷. In a mouse model of chronic asthma, using mast cell reconstituted *Kit*-mutant mice, mast cells were found to promote allergic airway inflammation by inducing lung eosinophilia, collagen deposition, tissue remodelling and enhanced AHR¹²⁸. Furthermore, ablation of mast cells in Mas-TRECK mice (TABLE 2) resulted in reduced AHR responses in the same model of chronic asthma⁵³. The relative contribution of mast cells to lung inflammation depends on the model used to elicit the inflammatory response. In general, it seems that the contribution of mast cells can mainly be observed in models that omit strong adjuvants and that use low amounts of antigen for sensitization (reviewed in REF. 9). Unexpectedly, alum-OVA-induced AHR and tissue inflammation were higher in mMCP4-deficient mice compared with wild-type mice, which indicates that mast cells might also limit the pathology that occurs in the lung in this model¹²⁹.

Hypersensitivity disorders of the skin. Hypersensitivity reactions of the skin can be grouped into IgE-associated disorders, such as atopic dermatitis, urticaria and IgE-mediated chronic allergic inflammation, or into T cell-mediated responses to contact allergens which elicit a subgroup of delayed-type hypersensitivity (DTH) responses, named contact hypersensitivity (CHS) responses. Basophils have been found in lesions from patients with atopic dermatitis, prurigo, urticaria and bullous pemphigoid, but were absent in biopsy samples from patients with psoriasis or SLE¹³⁰. In a mouse model of atopic dermatitis, it was shown that basophils are recruited to the skin during disease development and that their recruitment is blocked following treatment with TSLP-specific antibodies²⁸. Whether basophils contribute to pathology in this model remains to be determined. In the mouse, basophils are essential for IgE-mediated chronic allergic inflammation, for an IgE-mediated late-phase response that leads to vascular leakage and for the infiltration of inflammatory cells into the skin¹³¹. Mast cells are well known to be mediators of early IgE-mediated inflammation of the skin, but studies in *Kit*-mutant mice have generated conflicting results regarding the role of mast cells in CHS responses. A recent study with *Mcpt5*-Cre-iDTR mice or *Mcpt5*-Cre-R-DTA mice (TABLE 2) clearly demonstrated that mast cells are required for CHS responses to dinitrofluorobenzene (DNFB) and fluorescein isothiocyanate (FITC)⁵². Surprisingly, CHS responses to DNFB were enhanced in *Kit*^{W/W-v} and *Kit*^{W-sh/W-sh} mice, and the immediate ear swelling response, which is abolished in *Mcpt5*-Cre-iDTR mice, was still intact in the *Kit*-mutant strains⁵². Further studies are necessary to clarify the mechanisms that might explain these contradictory results.

Autoimmunity. Besides their established role as pro-inflammatory cells in allergic responses, mast cells have also been reported to participate in immune responses to self antigens (reviewed in REF. 132). Experimental autoimmune encephalomyelitis (EAE) is a widely used rodent model for multiple sclerosis. Pathology can be caused by the immunization of mice with a peptide of myelin oligodendrocyte glycoprotein (MOG₃₃₋₅₅) emulsified in complete Freund's adjuvant (CFA). The use of *Kit*-mutant mice to study the role of mast cells in EAE pathogenesis has led to conflicting results. *Kit*^{W/W-v} mice were reported to develop less severe pathology in MOG₃₃₋₅₅-CFA-induced EAE compared with control mice, and their reconstitution with bone marrow-derived mast cells corrected this defect, which indicates that mast cells might be involved in EAE pathogenesis¹³³. Using the same EAE model others found that *Kit*^{W-sh/W-sh} mice developed an earlier and more severe pathology during the course of EAE, and that mast cell reconstitution reduced disease scores¹³⁴. However, another study using *Kit*^{W/W-v} and *Kit*^{W-sh/W-sh} mice showed that mast cells were dispensable for EAE pathogenesis, although they are recruited to the central nervous system in wild-type mice¹³⁵. These conflicting findings made it necessary for these experiments to be repeated using mice that were deficient in mast cells but not as a result of *Kit* mutations. A recent study using *Cpa3*^{Cre} mice (TABLE 2) found no evidence for mast cells as pro-inflammatory or anti-inflammatory modulators of pathology in MOG₃₃₋₅₅-CFA-induced EAE⁵⁴. Whether basophils are involved in EAE remains to be determined.

Rheumatoid arthritis is a chronic inflammatory disease of the joints. In the K/BxN mouse model of arthritis, autoantibodies against glucose-6-phosphate isomerase can transfer the disease to naive wild-type mice but not to naive *Kit*-mutant mice, which indicates that mast cells might contribute to pathogenesis¹³⁶. However, *Cpa3*^{Cre} mice showed the same disease severity and kinetics of pathology as control mice, which indicates that mast cells are dispensable in this model⁵⁴. Arthritis could not be induced in *Kit*^{W/W-v} mice in response to collagen-specific antibodies administered in combination with lipopolysaccharide (LPS), whereas *Kit*^{W-sh/W-sh} mice showed a normal response. This was attributed to a lack of neutrophilia in addition to a mast cell deficiency in *Kit*^{W/W-v} mice¹³⁷. Patients with rheumatoid arthritis who have anti-citrullinated protein antibodies (ACPAs) often develop more severe pathology compared with patients who are ACPA-negative, and IgE-ACPA-mediated activation of basophils and mast cells is positively correlated with pathogenesis¹³⁸. Conversely, basophils have been shown to ameliorate the disease by their release of IL-4 in the K/BxN mouse model¹³⁹.

SLE is an autoimmune disease that affects many different parts of the body, including the kidney, the joints and the skin. Autoreactive IgE and activated basophils have been reported to be associated with increased severity of the disease⁷³. Mice lacking the tyrosine kinase LYN, which is implicated in FcεRI signalling, develop basophilia, high IgE levels and SLE symptoms^{73,140}.

Deletion of basophils has been shown to preserve kidney function in this model, which indicates that basophils might promote lupus nephritis by enhancing autoantibody production⁷³.

Taken together, these data indicate that mast cells are the major effector cells for IgE-mediated anaphylaxis, whereas monocytes, neutrophils and basophils contribute to IgG1-mediated anaphylaxis. The late-phase allergic response in the lungs and the skin can be promoted by recruited basophils, whereas the early response is dominated by mast cells. Mast cells seem to be dispensable for MOG₃₅₋₅₅-CFA-induced EAE. Mast cells are also dispensable for the K/BxN arthritis model, whereas basophils might have a beneficial role in this model. However, basophils have been associated with disease severity in patients with SLE. This indicates that basophils might ameliorate autoimmune disorders that are driven by T_H1- and/or T_H17-type responses by producing IL-4, whereas they might enhance pathological responses in T_H2-associated autoimmune diseases, such as SLE, by further promoting the production of autoreactive IgE.

Conclusion

Basophils and mast cells are distinct cell types with overlapping effector functions. They can develop from a common precursor cell, which is found in the spleen of mice but which has not yet been identified in the bone marrow. The main function of both cell types is as effector cells, rather than as participants in the initiation of adaptive immune responses. Mast cells and basophils cooperate to protect the host against secondary infestation with ticks and to contribute, to various degrees, to immune responses against helminths. However, mast cells and basophils are also major players during systemic and local allergic responses, and they might also contribute to autoimmune pathologies. Recently developed mouse models will help to further revise and refine our current understanding of the *in vivo* functions of basophils and mast cells. An important future challenge will be to translate the findings from murine models to human diseases and to develop new strategies that can specifically interfere with mast cell and basophil functions during acute and chronic inflammation.

- Migalovich-Sheikhet, H., Friedman, S., Mankuta, D. & Levi-Schaffer, F. Novel identified receptors on mast cells. *Front. Immunol.* **3**, 238 (2012).
- Schneider, E., Thieblemont, N., De Moraes, M. L. & Dy, M. Basophils: new players in the cytokine network. *Eur. Cytokine Netw.* **21**, 142–153 (2010).
- Gilfillan, A. M. & Beaven, M. A. Regulation of mast cell responses in health and disease. *Crit. Rev. Immunol.* **31**, 475–529 (2011).
- Karasuyama, H., Mukai, K., Obata, K., Tsujimura, Y. & Wada, T. Nonredundant roles of basophils in immunity. *Annu. Rev. Immunol.* **29**, 45–69 (2011).
- Lichtenstein, L. M. & Bochner, B. S. The role of basophils in asthma. *Ann. NY Acad. Sci.* **629**, 48–61 (1991).
- Beaven, M. A. Our perception of the mast cell from Paul Ehrlich to now. *Eur. J. Immunol.* **39**, 11–25 (2009).
- Abraham, S. N. & St John, A. L. Mast cell-orchestrated immunity to pathogens. *Nature Rev. Immunol.* **10**, 440–452 (2010).
- Feger, F., Varadaradjalou, S., Gao, Z., Abraham, S. N. & Arock, M. The role of mast cells in host defense and their subversion by bacterial pathogens. *Trends Immunol.* **23**, 151–158 (2002).
- Galli, S. J. *et al.* Mast cells as “tunable” effector and immunoregulatory cells: recent advances. *Annu. Rev. Immunol.* **23**, 749–786 (2005).
- Galli, S. J., Nakae, S. & Tsai, M. Mast cells in the development of adaptive immune responses. *Nature Immunol.* **6**, 135–142 (2005).
- Falcone, F. H., Zillikens, D. & Gibbs, B. F. The 21st century renaissance of the basophil? Current insights into its role in allergic responses and innate immunity. *Exp. Dermatol.* **15**, 855–864 (2006).
- Siracusa, M. C., Comeau, M. R. & Artis, D. New insights into basophil biology: initiators, regulators, and effectors of type 2 inflammation. *Ann. NY Acad. Sci.* **1217**, 166–177 (2011).
- Crivellato, E., Beltrami, C., Mallardi, F. & Ribatti, D. Paul Ehrlich's doctoral thesis: a milestone in the study of mast cells. *Br. J. Haematol.* **123**, 19–21 (2003).
- de Barros, C. M. *et al.* The Hemolymph of the ascidian *Styela plicata* (Chordata-Tunicata) contains heparin inside basophil-like cells and a unique sulfated galactoglucan in the plasma. *J. Biol. Chem.* **282**, 1615–1626 (2007).
- Cavalcante, M. C. *et al.* Colocalization of heparin and histamine in the intracellular granules of test cells from the invertebrate *Styela plicata* (Chordata-Tunicata). *J. Struct. Biol.* **137**, 313–321 (2002).
- Dobson, J. T. *et al.* Carboxypeptidase A5 identifies a novel mast cell lineage in the zebrafish providing new insight into mast cell fate determination. *Blood* **112**, 2969–2972 (2008).
- Da'as, S. *et al.* Zebrafish mast cells possess an FcεR1-like receptor and participate in innate and adaptive immune responses. *Dev. Comparative Immunol.* **35**, 125–134 (2011).
- Mulero, I., Sepulcre, M. P., Meseguer, J., Garcia-Ayala, A. & Mulero, V. 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 (2007).
- Mead, K. F., Borysenko, M. & Findlay, S. R. Naturally abundant basophils in the snapping turtle, *Chelydra serpentina*, possess cytophilic surface antibody with reaginic function. *J. Immunol.* **130**, 334–340 (1983).
- Rodewald, H. R., Dessing, M., Dvorak, A. M. & Galli, S. J. Identification of a committed precursor for the mast cell lineage. *Science* **271**, 818–822 (1996).
- Ohnmacht, C. & Voehringer, D. Basophil effector function and homeostasis during helminth infection. *Blood* **113**, 2816–2825 (2009).
- Iwasaki, H. *et al.* The order of expression of transcription factors directs hierarchical specification of hematopoietic lineages. *Genes Dev.* **20**, 3010–3021 (2006).
- Chen, C. C., Grimbaldston, M. A., Tsai, M., Weissman, I. L. & Galli, S. J. Identification of mast cell progenitors in adult mice. *Proc. Natl Acad. Sci. USA* **102**, 11408–11413 (2005).
- Franco, C. B., Chen, C. C., Drukker, M., Weissman, I. L. & Galli, S. J. Distinguishing mast cell and granulocyte differentiation at the single-cell level. *Cell Stem Cell* **6**, 361–368 (2010).
- Arinobu, Y. *et al.* Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. *Proc. Natl Acad. Sci. USA* **102**, 18105–18110 (2005).
- Identification of a common BMCP in the spleen of adult mice. The timed expression of GATA2 and C/EBPα can direct the final maturation of BMCPs to basophils or mast cells.
- Ohnmacht, C. *et al.* Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths. *Immunity* **33**, 364–374 (2010).
- Ohmori, K. *et al.* IL-3 induces basophil expansion *in vivo* by directing granulocyte-monocyte progenitors to differentiate into basophil lineage-restricted progenitors in the bone marrow and by increasing the number of basophil/mast cell progenitors in the spleen. *J. Immunol.* **182**, 2835–2841 (2009).
- Siracusa, M. C. *et al.* TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. *Nature* **477**, 229–233 (2011).
- Mukai, K. *et al.* Critical role of P1-Runx1 in mouse basophil development. *Blood* **120**, 76–85 (2012).
- Jamur, M. C. *et al.* Identification and characterization of undifferentiated mast cells in mouse bone marrow. *Blood* **105**, 4282–4289 (2005).
- Martin, D. I., Zon, L. I., Mutter, G. & Orkin, S. H. Expression of an erythroid transcription factor in megakaryocytic and mast cell lineages. *Nature* **344**, 444–447 (1990).
- Buhring, H. J., Strebile, A. & Valent, P. The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell activation and allergy diagnosis. *Int. Arch. Allergy Immunol.* **133**, 317–329 (2004).
- Arock, M., Schneider, E., Boissan, M., Tricottet, V. & Dy, M. Differentiation of human basophils: an overview of recent advances and pending questions. *J. Leukoc. Biol.* **71**, 557–564 (2002).
- Kitamura, Y., Hatanaka, K., Murakami, M. & Shibata, H. Presence of mast cell precursors in peripheral blood of mice demonstrated by parabiosis. *Blood* **53**, 1085–1088 (1979).
- Gurish, M. F. & Austen, K. F. Developmental origin and functional specialization of mast cell subsets. *Immunity* **37**, 25–33 (2012).
- Welle, M. 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 (1997).
- Li, L. *et al.* Identification of basophilic cells that express mast cell granule proteases in the peripheral blood of asthma, allergy, and drug-reactive patients. *J. Immunol.* **161**, 5079–5086 (1998).
- Kim, S. *et al.* Cutting edge: basophils are transiently recruited into the draining lymph nodes during helminth infection via IL-3, but infection-induced Th2 immunity can develop without basophil lymph node recruitment or IL-3. *J. Immunol.* **184**, 1143–1147 (2010).
- Kiernan, J. A. Production and life span of cutaneous mast cells in young rats. *J. Anat.* **128**, 225–238 (1979).
- Lantz, C. S. *et al.* Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. *Nature* **392**, 90–93 (1998).
- Didichenko, S. A., Spiegel, N., Brunner, T. & Dahinden, C. A. IL-3 induces a Pim1-dependent antiapoptotic pathway in primary human basophils. *Blood* **112**, 3949–3958 (2008).
- Shelburne, C. P. *et al.* Stat5 expression is critical for mast cell development and survival. *Blood* **102**, 1290–1297 (2003).
- Lilla, J. N. *et al.* Reduced mast cell and basophil numbers and function in *Cpa3-Cre; Mcl-1^{fl/fl}* mice. *Blood* **118**, 6930–6938 (2011).
- Asai, K. *et al.* Regulation of mast cell survival by IgE. *Immunity* **14**, 791–800 (2001).
- Kashiwakura, J. *et al.* Most highly cytokinergic IgEs have polyreactivity to autoantigens. *Allergy Asthma Immunol. Res.* **4**, 332–340 (2012).
- Hill, D. A. *et al.* Commensal bacteria-derived signals regulate basophil hematopoiesis and allergic inflammation. *Nature Med.* **18**, 538–546 (2012).

47. Hida, S. *et al.* Fc receptor γ -chain, a constitutive component of the IL-3 receptor, is required for IL-3-induced IL-4 production in basophils. *Nature Immunol.* **10**, 214–222 (2009).
48. Herbst, T. *et al.* Antibodies and IL-3 support helminth-induced basophil expansion. *Proc. Natl Acad. Sci. USA* **109**, 14954–14959 (2012).
49. Reber, L. L., Marichal, T. & Galli, S. J. New models for analyzing mast cell functions *in vivo*. *Trends Immunol.* **33**, 613–625 (2012).
50. Rodewald, H. R. & Feyerabend, T. B. Widespread immunological functions of mast cells: fact or fiction? *Immunity* **37**, 13–24 (2012).
This review discusses controversial findings obtained with Kit-mutant mice and newly developed mast cell-deficient mouse strains regarding the role of mast cells in various murine disease models.
51. Jonsson, F. & Daeron, M. Mast cells and company. *Front. Immunol.* **3**, 16 (2012).
52. Dudeck, A. *et al.* Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. *Immunity* **34**, 973–984 (2011).
53. Sawaguchi, M. *et al.* Role of mast cells and basophils in IgE responses and in allergic airway hyperresponsiveness. *J. Immunol.* **188**, 1809–1818 (2012).
54. Feyerabend, T. B. *et al.* Cre-mediated cell ablation contests mast cell contribution in models of antibody- and T cell-mediated autoimmunity. *Immunity* **35**, 832–844 (2011).
55. Schmidt-Suprian, M. & Rajewsky, K. Vagaries of conditional gene targeting. *Nature Immunol.* **8**, 665–668 (2007).
This review points out that high expression levels of Cre can lead to Cre toxicity in certain cell types owing to recognition of cryptic loxP sites in the genome.
56. Kojima, T. *et al.* Mast cells and basophils are selectively activated *in vitro* and *in vivo* through CD200R3 in an IgE-independent manner. *J. Immunol.* **179**, 7093–7100 (2007).
57. Obata, K. *et al.* Basophils are essential initiators of a novel type of chronic allergic inflammation. *Blood* **110**, 913–920 (2007).
58. Hammad, H. *et al.* Inflammatory dendritic cells — not basophils — are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J. Exp. Med.* **207**, 2097–2111 (2010).
59. Sokol, C. L. *et al.* Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. *Nature Immunol.* **10**, 713–720 (2009).
60. Yoshimoto, T. *et al.* Basophils contribute to T_H2-IgE responses *in vivo* via IL-4 production and presentation of peptide-MHC class II complexes to CD4⁺ T cells. *Nature Immunol.* **10**, 706–712 (2009).
61. Tsujimura, Y. *et al.* Basophils play a pivotal role in immunoglobulin-G-mediated but not immunoglobulin-E-mediated systemic anaphylaxis. *Immunity* **28**, 581–589 (2008).
62. Perrigoue, J. G. *et al.* MHC class II-dependent basophil-CD4⁺ T cell interactions promote T_H2 cytokine-dependent immunity. *Nature Immunol.* **10**, 697–705 (2009).
63. Denzel, A. *et al.* Basophils enhance immunological memory responses. *Nature Immunol.* **9**, 733–742 (2008).
64. Paul, W. E. & Zhu, J. How are T_H2-type immune responses initiated and amplified? *Nature Rev. Immunol.* **10**, 225–235 (2010).
65. Kambayashi, T. *et al.* Inducible MHC class II expression by mast cells supports effector and regulatory T cell activation. *J. Immunol.* **182**, 4686–4695 (2009).
66. Fox, C. C., Jewell, S. D. & Whitacre, C. C. Rat peritoneal mast cells present antigen to a PPD-specific T cell line. *Cell. Immunol.* **158**, 253–264 (1994).
67. Phytian-Adams, A. T. *et al.* CD11c depletion severely disrupts Th2 induction and development *in vivo*. *J. Exp. Med.* **207**, 2089–2096 (2010).
68. Sokol, C. L., Barton, G. M., Farr, A. G. & Medzhitov, R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nature Immunol.* **9**, 310–318 (2008).
69. Sullivan, B. M. *et al.* Genetic analysis of basophil function *in vivo*. *Nature Immunol.* **12**, 527–535 (2011).
70. Tang, H. *et al.* The T helper type 2 response to cysteine proteases requires dendritic cell-basophil cooperation via ROS-mediated signaling. *Nature Immunol.* **11**, 608–617 (2010).
71. Liang, G. *et al.* Naive T cells sense the cysteine protease allergen papain through protease-activated receptor 2 and propel T_H2 immunity. *J. Allergy Clin. Immunol.* **129**, 1377–1386.e13 (2012).
72. Khodoun, M. V., Orekhova, T., Potter, C., Morris, S. & Finkelman, F. D. Basophils initiate IL-4 production during a memory T-dependent response. *J. Exp. Med.* **200**, 857–870 (2004).
73. Charles, N., Hardwick, D., Daugas, E., Illei, G. G. & Rivera, J. Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nature Med.* **16**, 701–707 (2010).
74. Dijkstra, D., Hennig, C., Witte, T. & Hansen, G. Basophils from humans with systemic lupus erythematosus do not express MHC-II. *Nature Med.* **18**, 488–490 (2012).
75. Eckl-Dorna, J. *et al.* Basophils are not the key antigen-presenting cells in allergic patients. *Allergy* **67**, 601–608 (2012).
76. Pulendran, B. & Artis, D. New paradigms in type 2 immunity. *Science* **337**, 431–435 (2012).
77. Hepworth, M. R. *et al.* Mast cells orchestrate type 2 immunity to helminths through regulation of tissue-derived cytokines. *Proc. Natl Acad. Sci. USA* **109**, 6644–6649 (2012).
78. Gauchat, J. F. *et al.* Induction of human IgE synthesis in B cells by mast cells and basophils. *Nature* **365**, 340–343 (1993).
79. Ha, T. Y., Reed, N. D. & Crowle, P. K. Immune response potential of mast cell-deficient W/W^m mice. *Int. Arch. Allergy Appl. Immunol.* **80**, 85–94 (1986).
80. Wada, T. *et al.* Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. *J. Clin. Invest.* **120**, 2867–2875 (2010).
This study demonstrates that basophils and mast cells cooperate to provide protection against secondary infestation with ticks.
81. Durham, S. R., Gould, H. J. & Hamid, Q. A. Local IgE production in nasal allergy. *Int. Arch. Allergy Immunol.* **113**, 128–130 (1997).
82. Bethony, J. *et al.* Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet* **367**, 1521–1532 (2006).
83. Gause, W. C., Urban, J. F. Jr & Stadecker, M. J. The immune response to parasitic helminths: insights from murine models. *Trends Immunol.* **24**, 269–277 (2003).
84. Allen, J. E. & Maizels, R. M. Diversity and dialogue in immunity to helminths. *Nature Rev. Immunol.* **11**, 375–388 (2011).
85. Anthony, R. M. *et al.* Protective immune mechanisms in helminth infection. *Nature Rev. Immunol.* **7**, 975–987 (2007).
86. Phillips, C., Coward, W. R., Pritchard, D. I. & Hewitt, C. R. Basophils express a type 2 cytokine profile on exposure to proteases from helminths and house dust mites. *J. Leukoc. Biol.* **73**, 165–171 (2003).
87. Machado, D. C., Horton, D., Harrop, R., Peachell, P. T. & Helm, B. A. Potential allergens stimulate the release of mediators of the allergic response from cells of mast cell lineage in the absence of sensitization with antigen-specific IgE. *Eur. J. Immunol.* **26**, 2972–2980 (1996).
88. Katona, I. M., Urban, J. F. Jr & Finkelman, F. D. The role of L3T4⁺ and Lyt-2⁺ T cells in the IgE response and immunity to *Nippostrongylus brasiliensis*. *J. Immunol.* **140**, 3206–3211 (1988).
89. Neill, D. R. *et al.* Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* **464**, 1367–1370 (2010).
90. Urban, J. F. Jr *et al.* IL-13, IL-4R α , and Stat6 are required for the expulsion of the gastrointestinal nematode parasite *Nippostrongylus brasiliensis*. *Immunity* **8**, 255–264 (1998).
91. Voehringer, D., Reese, T. A., Huang, X., Shinkai, K. & Locksley, R. M. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. *J. Exp. Med.* **203**, 1435–1446 (2006).
92. Liu, Q. *et al.* B cells have distinct roles in host protection against different nematode parasites. *J. Immunol.* **184**, 5213–5223 (2010).
93. Ohnmacht, C. & Voehringer, D. Basophils protect against reinfection with hookworms independently of mast cells and memory Th2 cells. *J. Immunol.* **184**, 344–350 (2010).
This study demonstrates that basophils contribute to the protective memory response against *N. brasiliensis*.
94. Crowle, P. K. & Reed, N. D. Rejection of the intestinal parasite *Nippostrongylus brasiliensis* by mast cell-deficient W/W^m anemic mice. *Infect. Immun.* **33**, 54–58 (1981).
95. Hashimoto, K. *et al.* Immunity-mediated regulation of fecundity in the nematode *Heligmosomoides polygyrus*—the potential role of mast cells. *Parasitology* **137**, 881–887 (2010).
96. Ha, T. Y., Reed, N. D. & Crowle, P. K. Delayed expulsion of adult *Trichinella spiralis* by mast cell-deficient W/W^m mice. *Infect. Immun.* **41**, 445–447 (1983).
97. Knight, P. A., Wright, S. H., Lawrence, C. E., Paterson, Y. Y. & Miller, H. R. Delayed expulsion of the nematode *Trichinella spiralis* in mice lacking the mucosal mast cell-specific granule chymase, mouse mast cell protease-1. *J. Exp. Med.* **192**, 1849–1856 (2000).
98. Shin, K. *et al.* Mouse mast cell tryptase mMCP-6 is a critical link between adaptive and innate immunity in the chronic phase of *Trichinella spiralis* infection. *J. Immunol.* **180**, 4885–4891 (2008).
99. Gurish, M. F. *et al.* IgE enhances parasite clearance and regulates mast cell responses in mice infected with *Trichinella spiralis*. *J. Immunol.* **172**, 1139–1145 (2004).
100. Herbert, D. R. *et al.* Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. *Immunity* **20**, 623–635 (2004).
101. Anthony, R. M. *et al.* Memory T_H2 cells induce alternatively activated macrophages to mediate protection against nematode parasites. *Nature Med.* **12**, 955–960 (2006).
102. King, C. L. *et al.* Mice with a targeted deletion of the IgE gene have increased worm burdens and reduced granulomatous inflammation following primary infection with *Schistosoma mansoni*. *J. Immunol.* **158**, 294–300 (1997).
103. Jankovic, D. *et al.* Fc epsilonRI-deficient mice infected with *Schistosoma mansoni* mount normal Th2-type responses while displaying enhanced liver pathology. *J. Immunol.* **159**, 1868–1875 (1997).
104. Schramm, G. *et al.* Cutting edge: IPSE/alpha-1, a glycoprotein from *Schistosoma mansoni* eggs, induces IgE-dependent, antigen-independent IL-4 production by murine basophils *in vivo*. *J. Immunol.* **178**, 6023–6027 (2007).
105. Sher, A., Correia-Oliveira, R., Hieny, S. & Hussain, R. Mechanisms of protective immunity against *Schistosoma mansoni* infection in mice vaccinated with irradiated cercariae. IV. Analysis of the role of IgE antibodies and mast cells. *J. Immunol.* **131**, 1460–1465 (1983).
106. Harris, N. & Gause, W. C. To B or not to B: B cells and the Th2-type immune response to helminths. *Trends Immunol.* **32**, 80–88 (2011).
107. Lobos, E., Nutman, T. B., Hotherhall, J. S. & Moncada, S. Elevated immunoglobulin E against recombinant *Brugia malayi* γ -glutamyl transpeptidase in patients with bancroftian filariasis: association with tropical pulmonary eosinophilia or putative immunity. *Infect. Immun.* **71**, 747–753 (2003).
108. Turner, J. D. *et al.* Allergen-specific IgE and IgG4 are markers of resistance and susceptibility in a human intestinal nematode infection. *Microbes Infect.* **7**, 990–996 (2005).
109. Rihet, P., Demeure, C. E., Bourgois, A., Prata, A. & Dessein, A. J. Evidence for an association between human resistance to *Schistosoma mansoni* and high anti-larval IgE levels. *Eur. J. Immunol.* **21**, 2679–2686 (1991).
110. Dunne, D. W. *et al.* Immunity after treatment of human schistosomiasis: association between IgE antibodies to adult worm antigens and resistance to reinfection. *Eur. J. Immunol.* **22**, 1483–1494 (1992).
111. Bethony, J. *et al.* Antibodies against a secreted protein from hookworm larvae reduce the intensity of hookworm infection in humans and vaccinated laboratory animals. *FASEB J.* **19**, 1743–1745 (2005).
112. Mitre, E. & Nutman, T. B. IgE memory: persistence of antigen-specific IgE responses years after treatment of human filarial infections. *J. Allergy Clin. Immunol.* **117**, 939–945 (2006).
This human study provides evidence for the existence of long-lived IgE-producing plasma cells that developed in response to *Brugia malayi* infection and persisted for several years after de-worming and relocation to non-endemic areas.

113. Wikel, S. K. & Allen, J. R. Acquired resistance to ticks. I. Passive transfer of resistance. *Immunology* **30**, 311–316 (1976).
114. Brown, S. J. & Askenase, P. W. Cutaneous basophil responses and immune resistance of guinea pigs to ticks: passive transfer with peritoneal exudate cells or serum. *J. Immunol.* **127**, 2163–2167 (1981).
115. Allen, J. R. Tick resistance: basophils in skin reactions of resistant guinea pigs. *Int. J. Parasitol.* **3**, 195–200 (1973).
116. Brown, S. J., Galli, S. J., Gleich, G. J. & Askenase, P. W. Ablation of immunity to *Amblyomma americanum* by anti-basophil serum: cooperation between basophils and eosinophils in expression of immunity to ectoparasites (ticks) in guinea pigs. *J. Immunol.* **129**, 790–796 (1982).
117. Matsuda, H. *et al.* Necessity of IgE antibodies and mast cells for manifestation of resistance against larval *Haemaphysalis longicornis* ticks in mice. *J. Immunol.* **144**, 259–262 (1990).
118. Wikel, S. K., Ramachandra, R. N., Bergman, D. K., Burkot, T. R. & Piesman, J. Infestation with pathogen-free nymphs of the tick *Ixodes scapularis* induces host resistance to transmission of *Borrelia burgdorferi* by ticks. *Infect. Immun.* **65**, 335–338 (1997).
119. Simons, F. E. Anaphylaxis. *J. Allergy Clin. Immunol.* **125**, S161–S181 (2010).
120. Matasar, M. J. & Neugut, A. I. Epidemiology of anaphylaxis in the United States. *Curr. Allergy Asthma Rep.* **3**, 30–35 (2003).
121. Oettgen, H. C. *et al.* Active anaphylaxis in IgE-deficient mice. *Nature* **370**, 367–370 (1994).
122. Jacoby, W., Cammarata, P. V., Findlay, S. & Pincus, S. H. Anaphylaxis in mast cell-deficient mice. *J. Invest. Dermatol.* **83**, 302–304 (1984).
123. Jonsson, F. *et al.* Mouse and human neutrophils induce anaphylaxis. *J. Clin. Invest.* **121**, 1484–1496 (2011).
124. Arias, K. *et al.* Distinct immune effector pathways contribute to the full expression of peanut-induced anaphylactic reactions in mice. *J. Allergy Clin. Immunol.* **127**, 1552–1561.e1 (2011).
125. Khodoun, M. *et al.* Peanuts can contribute to anaphylactic shock by activating complement. *J. Allergy Clin. Immunol.* **123**, 342–351 (2009).
126. Koshino, T. *et al.* Identification of basophils by immunohistochemistry in the airways of post-mortem cases of fatal asthma. *Clin. Exp. Allergy* **23**, 919–925 (1993).
127. Liu, M. C. *et al.* Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics. Cellular, mediator, and permeability changes. *Am. Rev. Respir. Dis.* **144**, 51–58 (1991).
128. Yu, M. *et al.* Mast cells can promote the development of multiple features of chronic asthma in mice. *J. Clin. Invest.* **116**, 1633–1641 (2006).
129. Waern, I. *et al.* Mouse mast cell protease 4 is the major chymase in murine airways and has a protective role in allergic airway inflammation. *J. Immunol.* **183**, 6369–6376 (2009).
130. Ito, Y. *et al.* Basophil recruitment and activation in inflammatory skin diseases. *Allergy* **66**, 1107–1113 (2011).
131. Mukai, K. *et al.* Basophils play a critical role in the development of IgE-mediated chronic allergic inflammation independently of T cells and mast cells. *Immunity* **23**, 191–202 (2005).
132. Benoist, C. & Mathis, D. Mast cells in autoimmune disease. *Nature* **420**, 875–878 (2002).
133. Secor, V. H., Secor, W. E., Gutekunst, C. A. & Brown, M. A. Mast cells are essential for early onset and severe disease in a murine model of multiple sclerosis. *J. Exp. Med.* **191**, 813–822 (2000).
134. Li, H. *et al.* Kit (W^{sh}) mice develop earlier and more severe experimental autoimmune encephalomyelitis due to absence of immune suppression. *J. Immunol.* **187**, 274–282 (2011).
135. Bennett, J. L. *et al.* Bone marrow-derived mast cells accumulate in the central nervous system during inflammation but are dispensable for experimental autoimmune encephalomyelitis pathogenesis. *J. Immunol.* **182**, 5507–5514 (2009).
136. Lee, D. M. *et al.* Mast cells: a cellular link between autoantibodies and inflammatory arthritis. *Science* **297**, 1689–1692 (2002).
137. Zhou, J. S., Xing, W., Friend, D. S., Austen, K. F. & Katz, H. R. Mast cell deficiency in *KitW^{sh}* mice does not impair antibody-mediated arthritis. *J. Exp. Med.* **204**, 2797–2802 (2007).
138. Schuerwegh, A. J. *et al.* Evidence for a functional role of IgE antitruncated protein antibodies in rheumatoid arthritis. *Proc. Natl Acad. Sci. USA* **107**, 2586–2591 (2010).
139. Anthony, R. M., Kobayashi, T., Wermeling, F. & Ravetch, J. V. Intravenous gammaglobulin suppresses inflammation through a novel T_H2 pathway. *Nature* **475**, 110–113 (2011).
140. Charles, N. *et al.* Lyn kinase controls basophil GATA-3 transcription factor expression and induction of Th2 cell differentiation. *Immunity* **30**, 533–543 (2009).
141. Trivedi, N. N., Raymond, W. W. & Caughey, G. H. Chimerism, point mutation, and truncation dramatically transformed mast cell delta-tryptases during primate evolution. *J. Allergy Clin. Immunol.* **121**, 1262–1268 (2008).
142. Gallwitz, M., Reimer, J. M. & Hellman, L. Expansion of the mast cell chymase locus over the past 200 million years of mammalian evolution. *Immunogenetics* **58**, 655–669 (2006).
143. Wong, G. W., Yasuda, S., Morokawa, N., Li, L. & Stevens, R. L. Mouse chromosome 17A3.3 contains 13 genes that encode functional tryptic-like serine proteases with distinct tissue and cell expression patterns. *J. Biol. Chem.* **279**, 2438–2452 (2004).
144. Pejler, G., Ronnberg, E., Waern, I. & Wernersson, S. Mast cell proteases: multifaceted regulators of inflammatory disease. *Blood* **115**, 4981–4990 (2010).
145. Ugajin, T. *et al.* Basophils preferentially express mouse Mast Cell Protease 11 among the mast cell tryptase family in contrast to mast cells. *J. Leukoc. Biol.* **86**, 1417–1425 (2009).
146. Mancardi, D. A. *et al.* Cutting Edge: The murine high-affinity IgG receptor FcγRIV is sufficient for autoantibody-induced arthritis. *J. Immunol.* **186**, 1899–1903 (2011).
147. Nigrovic, P. A. *et al.* Genetic inversion in mast cell-deficient W^{sh} mice interrupts *Corin* and manifests as hematopoietic and cardiac aberrancy. *Am. J. Pathol.* **173**, 1693–1701 (2008).
148. Tsai, M., Grimbaldston, M. A., Yu, M., Tam, S. Y. & Galli, S. J. Using mast cell knock-in mice to analyze the roles of mast cells in allergic responses *in vivo*. *Chem. Immunol. Allergy* **87**, 179–197 (2005).
149. Grimbaldston, M. A. *et al.* Mast cell-deficient *W-sash c-kit* mutant *Kit^{W-sh/W-sh}* mice as a model for investigating mast cell biology *in vivo*. *Am. J. Pathol.* **167**, 835–848 (2005).
150. Lutzelschwab, C., Huang, M. R., Kullberg, M. C., Aveskogh, M. & Hellman, L. Characterization of mouse mast cell protease-8, the first member of a novel subfamily of mouse mast cell serine proteases, distinct from both the classical chymases and tryptases. *Eur. J. Immunol.* **28**, 1022–1033 (1998).
151. Voehringer, D., Shinkai, K. & Locksley, R. M. Type 2 immunity reflects orchestrated recruitment of cells committed to IL-4 production. *Immunity* **20**, 267–277 (2004).
152. Reynolds, D. S. *et al.* Isolation and molecular cloning of mast cell carboxypeptidase A. A novel member of the carboxypeptidase gene family. *J. Biol. Chem.* **264**, 20094–20099 (1989).
153. Kitamura, Y., Go, S. & Hatanaka, K. Decrease of mast cells in W/W^v mice and their increase by bone marrow transplantation. *Blood* **52**, 447–452 (1978).
154. Sloane, D. E. *et al.* Leukocyte immunoglobulin-like receptors: novel innate receptors for human basophil activation and inhibition. *Blood* **104**, 2832–2839 (2004).
155. Suzukawa, M. *et al.* Leptin enhances survival and induces migration, degranulation, and cytokine synthesis of human basophils. *J. Immunol.* **186**, 5254–5260 (2011).
156. Okayama, Y. & Kawakami, T. Development, migration, and survival of mast cells. *Immunol. Res.* **34**, 97–115 (2006).
157. Tsujimura, T. *et al.* Involvement of transcription factor encoded by the *mi* locus in the expression of c-kit receptor tyrosine kinase in cultured mast cells of mice. *Blood* **88**, 1225–1233 (1996).
158. Tshori, S. & Nechushtan, H. Mast cell transcription factors—regulators of cell fate and phenotype. *Biochim. Biophys. Acta* **1822**, 42–48 (2012).
159. McEuen, A. R., Buckley, M. G., Compton, S. J. & Walls, A. F. Development and characterization of a monoclonal antibody specific for human basophils and the identification of a unique secretory product of basophil activation. *Lab. Invest.* **79**, 27–38 (1999).
160. Boehme, S. A. *et al.* Murine bone marrow-derived mast cells express chemoattractant receptor-homologous molecule expressed on T-helper class 2 cells (CRTh2). *Int. Immunol.* **21**, 621–632 (2009).
161. Hirai, H. *et al.* Prostaglandin D2 selectively induces chemotaxis in T helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor Crth2. *J. Exp. Med.* **193**, 255–261 (2001).
162. Bischoff, S. C. Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. *Nature Rev. Immunol.* **7**, 93–104 (2007).
163. Scholten, J. *et al.* Mast cell-specific Cre/loxP-mediated recombination *in vivo*. *Transgenic Res.* **17**, 307–315 (2008).
164. Musch, W., Wege, A. K., Mannel, D. N. & Hehlhans, T. Generation and characterization of alpha-chymase-Cre transgenic mice. *Genesis* **46**, 163–166 (2008).

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Competing interests statement

The author declares no competing financial interests.

FURTHER INFORMATION

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