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Title of abstract: Genetic evidence for an essential role of P38 in regulating mast cell development, chemotaxis and cytokine production.
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Abstract: Mast cells mediate a range of immune responses. However, the mechanisms by which they regulate these functions and the signaling pathways that contribute to their development remain poorly understood. Here, we provide evidence to suggest that P38 plays an essential role in regulating mast cell development, migration and cytokine production via distinct mechanisms. Induced deletion of P38 in bone marrow cells retards the maturation of mast cells in part by inhibiting the activation of CREB and expression of MITF, which encourages the generation of basophils over mast cells. In vivo, conditional deletion of P38 results in reduced numbers of mast cells in tissues and a failure to reconstitute these cells in Wsh mice transplanted with P38-/- Lin-c-kit+Sca-1+ (LSK+) cells. In fully differentiated mast cells, absence of P38 inhibits SCF-induced activation of Akt and ERK, which is associated with reduced chemotaxis and compromises antigen-induced IL-4 production by down-regulating the expression of GATA2. Our findings suggest that P38 plays a dual role by regulating the development of mast cells as well as by regulating the function of fully differentiated mast cells.