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Unique and redundant roles of class I_A PI3Kinase regulatory subunits in mast cell development

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Mast cells are effector cells of the immune system that are derived from hematopoietic stem cells.[1,2] These cells regulate both innate and adaptive immunity and have also been implicated in a variety of inflammatory diseases.[1,2] The maturation of these cells is dependent on signals regulated via the c-Kit and IL-3 receptors as well as transcription factors including MITF.[1-3] While the role of c-Kit and IL-3 receptor in mast development is known; the signaling molecules downstream from these receptors involved in regulating the growth and maturation of these cells are poorly understood.

Class 1_A phosphatidylinositol 3-kinase (PI3K) is a lipid kinase composed of heterodimer made up of p85 regulatory subunit(s) and p110 catalytic subunit(s).[4] In hematopoietic cells, class 1_A PI3K consists of four variants of p85 (p85α, p85β, p55α and p50α) and three variants of p110 (p110α, p110β and p110δ). While p85α, p55α and p50α are splice variants of a single gene, *Pik3r1,* p85β is encoded by separate gene, *Pik3r2*. The catalytic subunits p110α, p110β and p110δ are encoded by separate genes, *Pik3ca, Pik3cb* and *Pik3cd*, respectively. p85α and p85β share near 80% homology in the C terminus and only 40% homology in the N terminus. The shorter isoforms p55α and p50α completely lack N-terminal end sequences, including the SH3 and the BH domains of p85α. While the regulatory subunits mediate the binding and localization of the PI3K enzyme to activated cytokine or receptor tyrosine kinases; the catalytic subunits convert phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3).[4]

In general, it is believed that regulatory subunits of class 1_A PI3K bind with equal efficiency to all the catalytic subunits and, therefore, have redundant functions. However, Krishnan et al. have recently shown that p85α and p85β have non-redundant and opposite roles in mast cell development.[5] While loss of p85α results in reduced maturation in response to IL-3; p85β deficiency results in increased maturation compared with wild-type (WT) cells. In addition, *p85*$\alpha^{-/-}$ cells show complete loss of SCF-induced growth and survival, whereas *p85*$\beta^{-/-}$ cells show enhanced growth and survival compared with WT controls. These studies indicate that p85α functions as a positive regulator of mast cell development, whereas p85β functions as a negative regulator. Earlier studies also showed fewer mast cells in most tissues, but not all, of p85α-deficient mice, indicating the positive regulatory role of p85α in mast cell development.[6] Emerging studies also demonstrate unique role(s) for p85 in other hematopoietic cells, including lymphocytes. While deficiency of p85β results in enhanced growth and survival of T cells, p85α-deficient T cells are normal.[7,8] In contrast, p85α-deficient mice show severe defects in B cell development, but p85β-deficient mice exhibit normal B cell functions.[7,8] These studies further suggest unique functions of p85 in hematopoietic cells, and their functions might vary in different cell types.

How different p85 subunits regulate the development of mast cells or other hematopoietic cells is not well-known. Krishnan et al. have shown that p85 subunits differentially regulate the expression of MITF, which has been shown to be important for mast cell development.[3,5] While p85β-deficient cells show enhanced MITF expression, loss of p85α results in reduced MITF expression, which correlates with altered maturation. In addition, overexpression of p85β in WT cells resulted in reduced MITF expression and reduced maturation. Furthermore, overexpression of p85α in *p85*$\alpha^{-/-}$ cells restored MITF expression and maturation. These studies suggest that p85 regulatory subunits might control mast cell development through regulation of MITF expression. How precisely p85 subunits regulate MITF expression, either by directly binding to the MITF promoter or through interaction with some other intermediary molecules, is not clear.

Recently, Ma et al. have shown that shorter isoforms of p85α, such as p55α and p50α, also have redundant and unique function(s) in mast cell development.[9] In these studies, complete loss of p85α and its shorter isoforms p55α and p50α resulted in greater reduction in maturation compared with only *p85*$\alpha^{-/-}$ cells. In addition, while overexpression of p50α in *p85*$\alpha^{-/-}$ cells resulted in complete rescue of maturation, it only partially restored SCF-induced growth. Furthermore, overexpression of p85α mutants lacking either SH3 domain or BH domain completely corrected the maturation, but it only partially rescued SCF-mediated growth. These studies suggest that p85α, p55α and p50α might have redundant roles in mast cell maturation, but unique roles in mast cell growth and survival. Likewise, the sequences in the N-terminal region of p85α, including the SH3 and the BH domain, are critical for SCF-induced proliferation, but not IL-3-mediated maturation. Recent evidence also suggests distinct cellular functions for SH3 and BH domains of p85α in the activation of the cdc42/JNK pathway.[10] Since p85α and p85β subunits share only 40% homology

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in N-terminal domains, it is possible that the functional differences between these two regulatory subunits are due to differences in binding partners. Further studies are necessary to identify the different signaling molecules that interact with the SH3 and BH domains in p85α and p85β subunits. These studies will help us in understanding how p85 subunits precisely regulate hematopoietic cell development and can be used in developing novel therapeutic targets for treating hematologic malignancies including myeloproliferative neoplasms, allergy and asthma.

References

1. Metcalfe DD, et al. Physiol Rev 1997; 77:1033-79; PMID:9354811
2. Galli SJ, et al. Nat Immunol 2005; 6:135-42; PMID:15662442; http://dx.doi.org/10.1038/ni1158
3. Morii E, et al. Blood 2001; 97:2038-44; PMID:11264169; http://dx.doi.org/10.1182/blood.V97.7.2038
4. Fruman DA, et al. Annu Rev Biochem 1998; 67:481-507; PMID:9759495; http://dx.doi.org/10.1146/annurev.biochem.67.1.481
5. Krishnan S, et al. Blood 2012; 119:3951-61; PMID:22378847; http://dx.doi.org/10.1182/blood-2011-05-355602
6. Fukao T, et al. Nat Immunol 2002; 3:295-304; PMID:11850627; http://dx.doi.org/10.1038/ni768
7. Deane JA, et al. J Immunol 2004; 172:6615-25; PMID:15153476
8. Fruman DA, et al. Science 1999; 283:393-7; PMID:9888855; http://dx.doi.org/10.1126/science.283.5400.393
9. Ma P, et al. Blood 2011; 118:3459-69; PMID:21791431; http://dx.doi.org/10.1182/blood-2011-04-351809
10. Taniguchi CM, et al. Mol Cell Biol 2007; 27:2830-40; PMID:17283057; http://dx.doi.org/10.1128/MCB.00079-07