Universität Basel

Research Project

Distinct PI3Kgamma Complexes in Inflammation, Allergy and Metabolic Control

Third-party funded project

Project title Distinct PI3Kgamma Complexes in Inflammation, Allergy and Metabolic Control
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Phosphoinositide 3-kinase (PI3K) family members comprising the class I PI3Ks integrate signals from cell surface receptors and produce PtdIns(3,4,5)P3. The latter serves as a docking site for multiple effector proteins, such as protein kinase B/Akt (PKB/Akt), eliciting activation of the mechanistic target of rapamycin (mTOR). Consequently, PI3Ks promote cell growth, proliferation, migration and counteract apoptosis, and have been identified as valuable targets in oncology. Mechanistic, genetic and pharmacological data have associated specific class I PI3K isoforms with cancer, immunity and inflammation, allergy, metabolic control and cardiovascular disease. While the activation of class IA PI3Ks (PI3Ka, ß , and d, which are associated with p85-like regulatory subunits), is well described, the activation of class IB PI3K? has not been fully elucidated.The dogmatic activation of PI3K occurs downstream of G protein-coupled receptors (GPCRs), and is mediated by trimeric G proteins. PI3K? is a heterodimeric complex of the catalytic p110? subunit, and one adapter subunit, comprising of either p84 or p101. As we have demonstrated earlier, p84 and p101 operate non-redundantly, and the p84- and p101-PI3K? complexes produce distinguishable PtdIns(3,4,5)P3 submembrane pools with distinct cellular functions. Moreover, we have shown that p110 is phosphorylated and activated by protein kinase Cß (PKCß) in IgE-stimulated mast cells.Here we propose to investigate PI3K? adapter dependencies in mouse models for allergy, obesity, and loss of PI3Kd-induced (auto-) immunity. The approach builds on mouse models we have previously explored using p110? null mice. As PI3K? complexes occur in hematopoietic cells in different p84/p101 ratios, adapter protein contributions to specific cell responses are not well understood.The planned experiments aim to define cellular networks and cell types required in the above-mentioned disease states, and to explore if specific PI3K? complexes relay cell-specific responses. In allergy, FceRI-expressing mast cells express p84, in obesity macrophages with p84 and p101 contribute to insulin resistance, and an ill-defined cellular compartment modulates thermogenesis maintaining a lean phenotype in PI3K? mice. Lymphocytes seem dominated by p101, but also here non-cell autonomous processes influence lymphocyte development and the progression of autoimmunity.Moreover, sometimes controversial PI3K? interactions have been claimed to redefine anti-inflammatory PI3K? as a target in cancer. Novel approaches are proposed to validate and map current and novel PI3K? interactions at the membrane to further elucidate PI3K?-adapter protein function.

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