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Function of phosphatidylinositol-3-kinase-gamma and SH2-containing inositol-5-phosphatase-1 in innate immunity

Innate immunity refers to the activation of different antigen-nonspecific mechanisms, including immune components as well as the non-immune defense machinery. In this context, those cellular components of the innate immune system are designed to recognize a few highly conserved structures present in many different microorganisms, known as pathogen-associated molecular patterns. Recent studies have illustrated that gd-Tcells and NK-T cells participate in natural immunity alongside the classical cellular components such as neutrophils, macrophages and NK cells. In leukocytes, chemotaxins activate phosphatidylinositol-3-kinase-γamma (PI3Kγ), which synthetizes phosphatidylinositol-3,4,5-triphosphat (PIP3). This lipid is further metabolised by SH2-containing inositol-5-phosphatase-1 (SHIP-1) to phosphatidylinositol-3.4-bisphosphate (PI3,4P2).

Moreover there is well evidence that PI3Kγ is also a protein kinase and functions as an adaptor protein. The intention of this project is the comparative study of upstream and downstream PI3Kγ/SHIP-1 signalling pathways in γδT-cells and NK-T cells, in order to highlight the importance of this cascade in the immune system. For this approach biochemical analyses (e.g. phospholipid measurements and Akt, Rac, or Rho activation, between other molecules), macrocomplex formation (e.g. immune precipitation, lipid rafts experiments, mass spectrometry), cell studies (cytokine production, growth factor release, secretion of matrix-metalloproteinases, cytotoxicity) and animal experiments (e.g.infection with Escherichia coli) will be performed in PI3Kγ -/- and SHIP-1 -/- mice.

Our present proposal integrates different biological aspects. On one side, it is related to the study of the innate immune, one of the most important mechanisms necessary for the maintainance of the life, since its main objective is to gain fundamental knowledge about the 3-phospholipid metabolism in immune cells, in order to better understand their patho-and physiological consequences. On the other hand, PI3Kγ as well as SHIP represent, between others, a novel feature into the classical protein field. These proteins, as well as some of their downstream adaptors, show a high plasticity due to their multifunctionality, e.g. acting as enzymes or adaptor proteins, which allows a larger range of pharmacological intervention strategies, in order to modulate the immune reactions, as well as other biological processes.

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