Title: Regulation of innate immunity and inflammation by the iRhom/iTap complex.

Supervisor: Colin Adrain

Group: Membrane Traffic Lab, ICG. www.igc.gulbenkian.pt/cadrain

Contact: cadrain@igc.gulbenkian.pt

Abstract

The inflammatory cytokine TNF (Tumour Necrosis Factor) is one of the principal driving forces behind inflammation, which underlies the pathogenesis of many serious infectious and non-communicable diseases. As a result of its extensive involvement in disease, the TNF signaling pathway is intensively studied; indeed, drugs that block the TNF pathway are the highest selling globally. TNF is synthesized as an integral membrane protein precursor, but many of the biological functions of TNF require its cleavage, hence release from the cell surface. This is catalyzed by a cell surface protease called ADAM17.

During the past few years, my lab has identified and delineated the pathway that is responsible for the trafficking and activation of ADAM17 and is hence central to the release of TNF from cells. We identified that integral membrane proteins called iRhoms are required for the trafficking of ADAM17, through the secretory pathway, from the endoplasmic reticulum to the cell surface, where it cleaves its substrates. Hence, mice null for iRhom2 exhibit pronounced inflammatory defects associated with a failure to release TNF. More recently, we also found that iRhom2 plays a central role in the mechanism whereby ADAM17 is stimulated to cleave its substrates on the cell surface. Given the importance of iRhoms in the biology of ADAM17 / TNF, my lab recently performed a screen to identify novel regulators of the iRhom pathway. This lead to the identification of a protein called iTap.

Our manuscript in revision demonstrates that when iTap is knocked out in mammalian cells or in mice, the levels of active ADAM17 are dramatically depleted and hence, the release of TNF is blocked in iTap KO cells / mice.

This master project aims to define how iTap interacts with the vesicular trafficking machinery. It will also elucidate in more detail what the physiological role of iTap is in the ADAM17 pathway. Its role in other important pathways that require iRhoms, including the STING pathway which plays a key role in antiviral defense, will also be elucidated.

References


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