OPUS 19 - ABSTRACT FOR THE GENERAL PUBLIC

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Title: Interferon-inducible anti-bacterial immunity factors of the host cell cytosol

Inflammasomes and interferons (IFNs) are one of the major means by which the innate immune system fights pathogens and promotes host survival. IFNs are a groups of signalling proteins made and released by host cells in response to the presence of infection. IFN exposure enhances intracellular immunity for efficient control of diverse intracellular pathogens through the induction of target genes. Lipopolysaccharide (LPS) is a component of the outer membrane of Gram-negative bacteria that triggers strong immune responses. LPS inside a human cell activates the protease enzyme caspase-4, which then activates the pore-forming protein gasdermin-D, leading to a form of cell death known as pyroptosis.

Pyroptotic death of infected cells in response to detection of LPS within the membrane of cytosolic bacteria is driven by assembly of a signalling platform (inflammasome) on the bacterial surface. Family of IFN-induced GTPases called guanylate-binding proteins (GBPs) assemble on the surface of cytosol-invading bacteria to create a signalling platform that recruits and activates caspase-4. The GBP-driven signalling pathway is required for caspase-4 to activate gasdermin-D and the proinflammatory cytokine interleukin-18, which is secreted to alert immune cells to the presence of infection. However, despite recent advances, the molecular details of how IFN-enhanced immunity protects the cytosol of human cells against bacterial incursion is not fully understood. Moreover, other, so far unknown, anti-bacterial defence factors may protect the host cell cytosol.

The aim of this project is to identify and analyse novel key factors of cytosolic, IFN inducible, anti-bacterial defence mechanisms of the innate immunity. We will employ large-scale state-of-the-art screening approaches to identify new host factors required for pyroptosis upon cytosolic invasion of bacteria and to find new effector proteins of known anti-bacterial restriction factors. Moreover, we will determine the specific mechanism of action of newly identified immunity factors. Finally, we will investigate the role of enzymes catalysing post-translational modifications of proteins in the GBP-CASP4 signalling platform formation.

The identification of host immunity factors may allow future development of novel therapies directed against pathogenic bacteria, including difficult to treat multidrug resistant strains e.g. to prevent from a septic shock, one of the most common causes of death. Sepsis arises from an over-activation of the immune response against infection-associated toxins, including LPS. Identification of novel GBP-CASP4 inflammasome components could provide useful targets of pharmacological inhibitors to reduce the immune response and prevent septic shock. Furthermore, since IFN plays an essential role in the development of systemic autoimmunity, understanding of the molecular mechanisms initiating pro-inflammatory processes may lead to better treatment of inflammatory diseases and hence, impact on human health.