

Poster Presentation

MS53.P33

Structural Characterization of Human Immunity-Related GTPase Family M (IRGM)

S. Sabboobeh¹, B. Nagar¹

¹*McGill University, Department of Biochemistry, Montreal, Canada*

The Immunity-Related GTPase Family M protein (IRGM) is involved in regulating cellular autophagy. Cellular knockdown of IRGM was shown to allow RNA viruses to hijack the autophagic immune response. Additionally, recent genetic studies have shown that underexpression of IRGM is associated with the incidence of Crohn's disease and infection by *Mycobacterium tuberculosis*. IRGM is an interferon-induced GTPase with an evolutionary conserved P-loop. It is an effector of the interferon-gamma pathway, but, unlike its protein family members, is not directly activated by the pathway. Its mechanism of action has been proposed to occur by translocation of IRGM to the mitochondria through recognition of cardiolipin, and affecting mitochondrial fission to induce autophagy. This potential interaction with cardiolipin might indicate the presence of a unique GTPase recognition and activation fold within IRGM. Our goal is to determine the X-ray crystal structure of IRGM in an effort to understand its molecular role in normal and diseased states. Additionally, we seek to test its interaction with and mechanism of recognition to mitochondrial cardiolipin as well as other autophagy-inducing binding partners. Currently, we have managed to express human IRGM in bacterial cells and have purified it to homogeneity using affinity and size-exclusion chromatography. These findings will serve to elucidate the mechanism of action of IRGM. Crucially, we hope to gain an understanding of its contributing role to Crohn's disease and tuberculosis infection at the molecular level, potentially paving the way to structure-based drug design and therapeutic opportunities.

[1] D. Petkova, C. Viret, M. Faure, *Frontiers in Immunology*, 2013, [2] Singh, S. B. et al, *Nat. Cell Biol.* 12, 1154–1165 (2010)., [3] Haldar, A. K. et al., *PLoS Pathog.* 9, e1003414 (2013)

Keywords: Crystallography, Autophagy, Crohn's