Poster Presentation

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Towards a structural characterization of the IFIT antiviral complex

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Our first line of defense against viral pathogens is the innate immune system. Interferon-induced proteins with tetratricopeptide repeats (IFITs) are innate immune effector molecules that are thought to confer antiviral defense through the formation of the IFIT 'Interactome', a multiprotein complex made up of IFIT1, IFIT2, IFIT3 and several other host factors1. Through IFIT1, this complex has the ability to distinguish self from non-self nucleic acids such as virus-derived RNA bearing 5´-triphosphate or viral mRNA lacking 2´-O methylation on the first two nucleotides1,2. We have limited information on the architecture of this complex, its role in innate immunity, and its activity downstream of RNA binding remain unclear. To better understand the mechanisms of Interactome formation, we are investigating the structure of its core, namely the IFIT1-IFIT2-IFIT3 complex. Since it is challenging to crystallize the complex as a whole, likely due to its size and heterogeneity, we are also targeting the structure of individual components and co-crystals of interacting domains. A crystal structure of human IFIT2 is available, and our lab has solved the structure of N-terminal human IFIT1 and, more recently, N-terminal IFIT3. In this study, we aim to characterize the interaction between IFIT1 and IFIT2, and between IFIT3 and IFIT2, through gel-filtration binding assays, in vitro pull-downs and deletion mutations. Preliminary results on the expression and purification of IFIT2-deletion mutants will be presented, as well as purification of IFIT subcomplexes. Understanding the molecular mechanisms behind IFIT-mediated virus elimination will help us unravel the complexities of these interactions and significantly advance our fundamental knowledge of innate immunity, paving the way for designing novel immunotherapeutics, which could potentially complement anti-cancer strategies that rely on oncolytic RNA viruses.

[1] *A. Pichlmair, C. Lassnig, C.A. Eberle, et al. Nature Immunology, 2011, 12, 624-630,* ***[2]*** *Y.M. Abbas, A. Pichlmair, M.W. Gorna, et al. Nature, 2013, 494, 60-64*

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