Poster Presentation

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Crystal structure of N-terminal IFIT3 reveals domain-swapping dimerization

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IFIT proteins are interferon-inducible, antiviral effectors that form a multiprotein complex with the ability to recognize markers of viral infection and subsequently restrict viruses. IFIT1, IFIT2 and IFIT3 are at the heart of the complex, interacting with each other and several host factors, forming what is known as the 'IFIT interactome'. Central to their ability to mediate complex formation is the tetratricopeptide repeat (TPR) motif, a general protein-protein interaction module comprising a pair of antiparallel alpha helices. Additionally The TPR motifs of IFIT proteins have the unique ability to recognize RNA. Whereas IFIT1 interacts with virus derived ssRNA, IFIT2 has been shown to interact with dsRNA; IFIT3 is not known to bind RNA. Importantly, structural information is available for the N-terminal domain of IFIT1 and full-length IFIT2, but not for IFIT3. To gain insight into the mechanisms regulating complex formation, we are targeting the structure of human IFIT3 before incorporation into the IFIT complex. To that end, we have determined a low resolution crystal structure of N-terminal IFIT3, which reveals a domain swapped dimer. Notably, IFIT3 dimerization is similar to IFIT2, but distinct from IFIT1, which dimerizes via its C-terminus. Sequence conservation and structural analysis suggest that IFIT2 and IFIT3 evolved a similar mechanism for domain swapping. We propose that IFIT2 and IFIT3 may interact by forming domain swapped heterodimers. Current work is aimed at investigating the mechanisms of domain swapping via mutational analysis, and determining the structure of C-terminal human IFIT3.

Keywords: Tetratricopeptide Repeat, Protein engineering