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Subcellular interactions of viral interferon antagonist proteins with host factors: Potential targets for therapeutics

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Successful viral infection depends on the virus' capacity to evade the host's interferon (IFN)-mediated innate immune response, and thereby prevent the establishment in cells of an antiviral state. Viral evasion of IFN immunity is mediated by multifunctional, virus-encoded *IFN-antagonist* proteins, which interact with diverse host factors, including intracellular signalling and effector molecules of the IFN system; thus, IFN-antagonists represent potential targets for antiviral therapies, but the molecular events underlying their functions are currently poorly defined.

Using live-cell imaging, molecular/cell biology and reverse genetics approaches with animal infection models, we have investigated the functions of the archetypal IFN-antagonist, rabies virus P protein, finding that it undergoes intricately regulated subcellular trafficking involving numerous sequences for interaction with the host cell's nuclear transport machinery, cytoskeletal components, and IFN signalling/effector molecules. Through these interactions, P-protein undergoes highly regulated nucleocytoplasmic trafficking to target host factors in specific subcellular sites, and thereby regulate the trafficking/functions of components of the IFN system by several novel mechanisms. Our *in vivo* studies have shown that P-protein trafficking is a vital component of immune evasion and pathogenicity, the first such demonstration for any virus; importantly we found that mutations affecting P-protein interactions with cellular trafficking machinery can specifically attenuate virus *in vivo*.

This work identifies IFN-antagonist subcellular trafficking/interactions as vital components in virulence, and potential therapeutic targets. IFN-antagonist trafficking has been reported for numerous human pathogenic viruses, including Nipah/Hendra, measles and Dengue, indicating that it may represent a common target for therapies for a number of highly virulent/lethal human diseases.

Biography

Following his PhD research at the University of Sheffield (UK) and WEHI (Australia), Dr Moseley was awarded a Royal Society fellowship to undertake post-doctoral research in Australia where he now heads a research team at Monash University focussed on understanding the pathogenic mechanisms of lyssaviruses including rabies, and paramyxoviruses including Nipah. His principle research interest is the role of viral protein subcellular trafficking in immune evasion, and his main research findings in this area have included the first demonstrations of a role for microtubules in viral immune evasion, and of the importance of viral protein trafficking to virulence *in vivo*.