Poster Presentation

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Nidovirus papain-like proteases antagonize the host innate immune response

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Protein ubiquitination regulates important innate immune responses. Ubiquitin (Ub) can be attached to lysine residues on cellular proteins to promote, among other activities, the innate immune responses of the cell. These pathways can in turn be downregulated by the removal of Ub from cellular proteins by deubiquitinases (DUBs). Viruses of the order Nidovirales have positive-sense, single stranded RNA genomes. Within this order are the families Coronaviridae and Arteriviridae, which include viruses known to cause severe disease in humans and animals, respectively. Members of the families Coronaviridae and Arteriviridae share a common mechanism of gene expression, whereby the viral nonstructural proteins (nsps) are initially expressed as a single polyprotein, which is then cleaved into functional units by papain-like protease (PLP) domains encoded within. Interestingly, while also being necessary for viral replication, a number of Nidovirus PLPs have been shown to remove Ub from host proteins, in order to down-regulate the host innate immune response. Here we present the crystal structure of a Nidovirus PLP in complex with Ub. The structure allowed for the characterization of a Ub-binding interface, and identification of specific residues involved in Ub recognition that are distant from the enzyme active site. The selective inactivation of DUB activity of viral PLP enzymes verses their polyprotein cleavage activity by site directed mutagenesis is allowing us to understand the role of DUB activity in evading innate immune responses of the host, and opens the door for the development of improved live attenuated vaccines against Nidoviruses and other viruses encoding similar dual specificity proteases.

Keywords: Papain-like protease, Nidovirus