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HERC5 and ISG15: Critical Modulators of the Innate Immune Response

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HERC5 and ISG15: Critical Modulators of the Antiviral Innate Immune Response

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Evolution has driven mammalian cells to develop sophisticated protein networks that identify and combat viral pathogens. For example, Interferon Stimulated Gene 15 (ISG15) is a 15.2 kDa ubiquitin-like-protein (UBL) that is used by specific E1-E2-E3 ubiquitin cascade enzymes to interfere with the activity of viral proteins. Recently, biochemical studies have determined that the E3 ligase HECT and RCC1-containing protein 5 (HERC5) ISGylates host and viral proteins in response to Hepatitis C (HCV), Influenza-A (IAV), and Human Immunodeficiency Virus (HIV-1) infection. Moving forward, structural and biophysical investigations are needed to decipher the mechanisms used by HERC5 to attach ISG15 onto its target substrates. Clarifying how HERC5 ISGylates host and viral proteins will be paramount to the development of new antiviral therapeutics that exploit HERC5 as a prominent modulator of the host antiviral response.

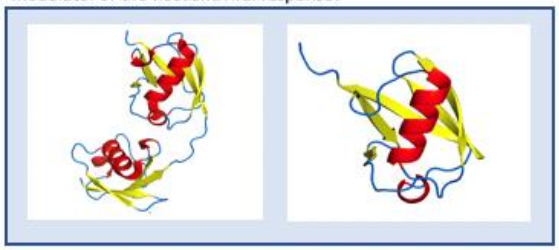

Fig 1. Left. ISG15 possesses a tandem ubiquitin like structure (PDB:1Z2M). **Right.** The crystal structure of ubiquitin (PDB:1UBQ.)

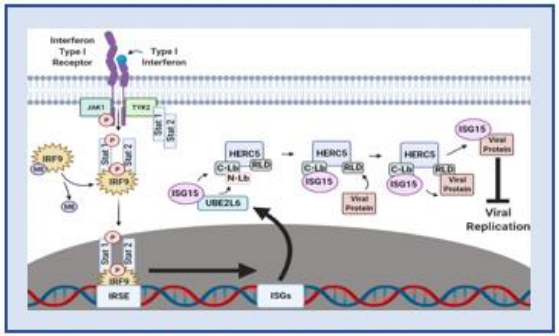

Fig 2. IRF9-dependent modes of ISG induction are initiated through an IFN-α/β surface receptor-ligand interaction that causes a conformational shift in the IFN-α/β receptor

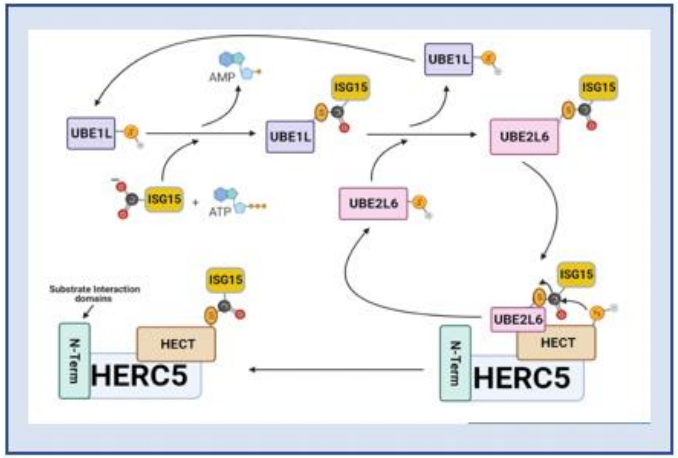

Fig 3. UBE1L (E1), UBE2L6 (E2) and HERC5 (E3) work in tandem to charge, transfer and attach ISG15 onto host and viral proteins.

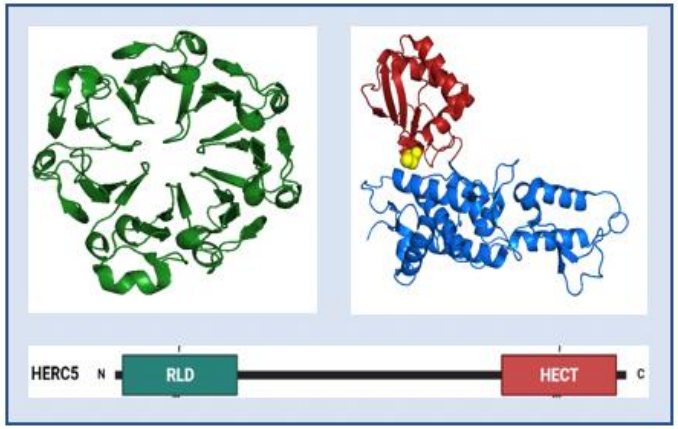

Fig 4. HERC5 uses its RCC1 like domain (RLD) to dock with viral proteins before carrying out their HECT-dependent ISGylation. **Left.** Crystal structure of the HERC1 RLD3 domain (PDB:4O2W). **Right.** Crystal structure of the E6AP HECT domain – N-lobe highlighted in marine; C-Lobe highlighted in firebrick red; Catalytic cysteine highlighted in yellow (PDB:1D5F).

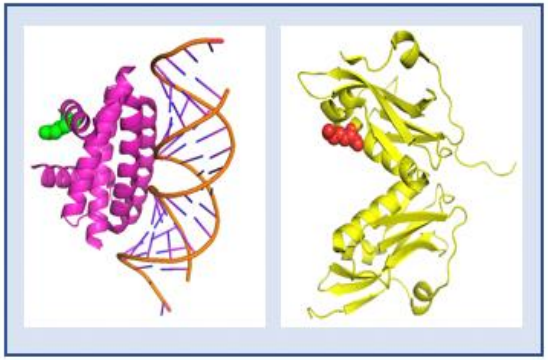

Fig 5. HERC5 ISGylates the IAV NS1 protein at Lysine 126 (K126) and Lysine 217 (K217) to stall NS1 nuclear export. **Left.** Crystal structure of the NS1 RBD domain in complex with dsRNA – K126 highlighted in TV green (PDB:2ZKO). **Right.** Crystal structure of the NS1 ED domain – K217 highlighted in TV red (PDB:3D6R).

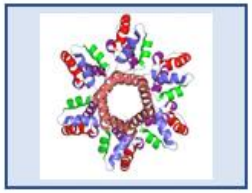

Fig 6. HERC5 prevents HIV-1 gag particle production by attaching ISG15 onto key gag precursor proteins. **Image.** Crystal structure of an immature gag particle (PDB: 5I4T)

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All work presented is part of a comprehensive review that has been submitted to journal Viruses under the special issue "Ubiquitin and ubiquitin-like pathways in viral infection".