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Mycobacteriophage and Human Histidine Triad Protein Homologs: Bridging Human Tumor Suppression and Bacteriophage Host Control

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The Histidine triad (HIT) protein superfamily is found in nearly all life on Earth, spanning prokaryotes, archaea, and eukaryotes. The Fragile Histidine Triad (FHIT) and Histidine Triad Nucleotide-binding Protein (HINT) are two essential proteins involved in various cellular processes and have garnered significant attention in cancer biology research. FHIT and HINT both act as tumor suppressors and are frequently deleted or downregulated in various human cancers. These proteins modulate numerous cell cycle regulation and cell death pathways. In novel bacteriophages, discovered at Purdue University, prior genome annotation has led to the identification of bacteriophage-encoded HIT proteins. This investigation explores the homology between the human and bacteriophage variants of HIT by analyzing biochemical properties, primary sequence alignments, cellular interactomes, structural conservation, and ligand binding. This study finds that multiple bacteriophage HIT proteins show high conservation to the human variants of HINT, with noteworthy similarity in tertiary structure and ligand binding. These findings suggest that bacteriophage and human HIT proteins are homologs and engage in similar biological activity. Thus far, understanding the intricate roles of FHIT and HINT in cancer oncogenesis has provided valuable insights into developing novel therapeutic strategies. Furthermore, these bacteriophage HIT proteins could offer a platform to develop novel targeted cancer therapies by leveraging innate bacteriophage infrastructure.