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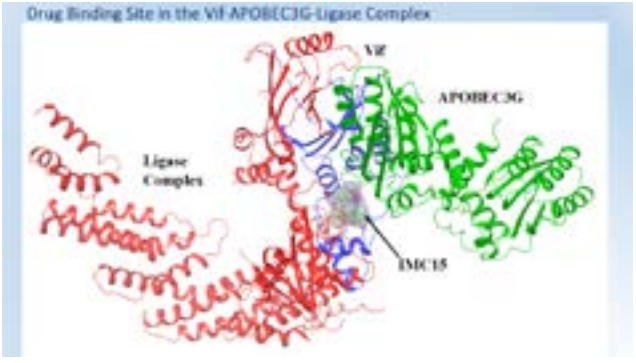
Targeting Vif regulatory Axis: developing new AIDS therapies

The human host is invaded by a wide range of microbial pathogens and has evolved a number of defensive mechanisms to survive these infections. In addition to adaptive immunity, it is becoming increasingly clear that innate immunity plays an important role in protecting host organisms from infections. One of the innate immune response mechanisms against viral infections involves a protein family, APOBEC3 (apolipoprotein B mRNA editing enzyme catalytic polypeptide 3). The APOBEC3 family of proteins can restrict replication of exogeneous retorviruses as well as Hepatitis B, a DNA virus that replicates through an RNA intermediate, and inhibit replication of retrotransposons. APOBEC3G (A3G) protein exhibits the most potent block to HIV-1 replication. To counteract host defense, HIV-1 expresses Vif protein that targets A3G for proteasomal degradation. Since HIV-1 Vif has no known cellular homologs, this protein represents an extremely attractive, yet unrealized, target for antiviral intervention. I will discuss the strategies to develop therapeutics that antagonize HIV-1 Vif function to inhibit HIV-1 replication. Further mechanistic investigation will be presented showing that Vif inhibitors' function requires Vif-A3G interactions and restores A3G function. These studies provide proof of principle that the HIV-1 Vif-A3G axis is a valid target for developing small molecule-based new therapies for AIDS or for enhancing innate immunity against viruses.



Recent Publications

1. Ali A, et al. (2012) Synthesis and structure-activity relationship studies of HIV-1 virion infectivity factor (Vif) inhibitors that block viral replication. ChemMedChem 7(7):1217-1229.

2. Mohammed I, et al., (2016) 1, 2, 3-triazoles as amide bioisosteres: discovery of a new class of potent HIV-1 Vif antagonists. Journal of medicinal chemistry 59(16):7677-7682.
3. Mohammed I, et al., (2012) SAR and lead optimization of an HIV-1 Vif-APOBEC3G axis inhibitor. ACS medicinal chemistry letters 3(6):465-469.
4. Nathans R, et al., (2008) Small-molecule inhibition of HIV-1 Vif. Nature biotechnology 26(10):1187-1192.
5. Wichroski M J, Robb G B and Rana T M (2006) Human retroviral host restriction factors APOBEC3G and APOBEC3F localize to mRNA processing bodies. PLoS pathogens 2(5): e41.

Biography

Tariq M Rana is a Scholar, Inventor, Entrepreneur and Multidisciplinary Scientist who is developing new therapies to treat infectious disease, cancer and immune disorders. He is a Professor and Chief of Genetics, V/C for Innovation in Therapeutics in the Department of Pediatrics at the University of California San Diego, School of Medicine, where his laboratory employs mechanisms and technologies of RNA, stem cells and chemical biology to discover new pathways implicated in human disease.

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