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Designing Defenses against Deadly Viruses

Viruses are curious life forms. Minimalistic and yet equipped with the evolvability to persist and proliferate, there’s clearly a lesson or two to be learned from them on survival. It is perhaps these very intrinsic qualities that have transformed some viruses into the deadliest known pathogens in the history of mankind. A viral epidemic has been the focus of many summer blockbuster movies, wherein identification, structural characterization, and the development of antibodies to “cure” the infection are all amazingly achieved within a matter of hours (and often by the one scientist-doctor-chemist-physicist-macho-hero, but more on that some other time). Such alacrity is desirable but perhaps not very realistic. What is truly exciting, however, is the level of insight that a number of recent studies have provided into how these deadly viruses hijack host defenses and how newer classes of drugs could protect if not potentially cure infection altogether.

One Drug to Beat Them All

With mortality rates exceeding 90%, Ebola and Marburg viruses, members of the filovirus family, are undoubtedly among the deadliest pathogens of the modern world. Infection leads to severe hemorrhagic fever, and rapid transmission occurs via physical contact or bodily fluids. Outbreaks of these and other filoviruses occur sporadically and unpredictably, and with no approved therapeutics, the most common strategy to limit the spread of the virus is to isolate and contain patients. In a breakthrough study, Bavari and colleagues identified a compound known as BCX4430, a synthetic adenosine analog that inhibits the infection of not just multiple filoviruses but a broad spectrum of other viruses such as coronaviruses, paramyxoviruses, and bunyaviruses that are causative agents of SARS, measles, and mumps among other diseases. In rodent and nonhuman primate models, this compound protects against both Ebola and Marburg viruses by significantly reducing viral titers as well as hemorrhagic manifestations of disease, all with no overt side effects. Remarkably, treatment delays of up to 48 hr were well tolerated after infection when administering BCX4430. Although the cause for the broad specificity remains to be investigated, the authors are able to determine that the compound acts as a broad inhibitor of viral RNA polymerase and functions as a nonobligate RNA chain terminator. The effect in animals is that it effectively contains the virus before severe consequences resulting from viral replication are realized. The idea of a broad-spectrum viral polymerase inhibitor is tantalizing and will potentially allow the drug to be stockpiled in outbreak-prone regions for rapid distribution and use as outbreaks are detected, regardless of which filovirus is associated with the outbreak. Studies are currently being conducted to further characterize the BCX4430 safety profile for its entry into human clinical trials.

Long-Lasting Strategy Fights HIV

Nearly three decades after its discovery as the etiological agent driving AIDS, HIV remains a global scourge, killing nearly one million people each year. Multiple attempts toward developing an AIDS vaccine have been met with limited success, but there is much promise in broadly neutralizing antibodies and stem cell transplantation as other parallel routes toward effective therapy. Further, antiretroviral cocktail therapies have successfully prolonged the lifespan and health of generations of HIV+ individuals. Importantly, prophylactic regimens involving the administration of antiretroviral medication can provide a reasonable level of protection against infection in high-risk uninfected individuals, with the limitation being the duration and adherence to this medication. Patients that fail to consume antiretroviral drugs on a daily or weekly basis are highly susceptible. Now, David Ho and colleagues develop a protocol using the drug GSK744, a long-lasting version of an HIV integrase strand-transfer inhibitor that could potentially provide long-term protection of up to 3 months from just a single injection. Though the basic drug itself is a reformulation of previous versions, its kinetic properties inside of the host, such as its solubility and slow metabolic breakdown, allow for its long-term persistence. Macaques that were repeatedly challenged with SHIV (a simian-human AIDS virus hybrid) were completely protected from infection when injected with GSK744, and preliminary evidence suggests that clearance of the drug in humans is likely to take even longer and, by extension, lead to longer periods of protection. The efficacy of this strategy in humans and whether it has any synergy or antagonism with other antiretroviral medications remain to be seen. Periodic injections would still be needed, though the study from Ho and colleagues provides a far more feasible strategy than the daily regimen of pills. Although an AIDS vaccine is still the ultimate goal, these findings provide a significantly more powerful and long-lasting strategy than current options to protect high-risk populations worldwide.

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Marburg Keaps Antioxidant Defenses On

Pathogens consistently hijack cellular defenses and repurpose them for their own growth and survival. In particular, a number of viruses have been shown to augment or dampen gene expression regulated by Nrf2, a master regulator of cellular antioxidant responses. Under physiological conditions, the binding of Nrf2 to the cellular adaptor Keap1 directs its proteasomal degradation; however, a disruption of this interaction during conditions of oxidative stress leads to Nrf2 nuclear translocation and the activation of antioxidant, detoxification, and cell survival programs. Marburg virus infection is characterized by hemorrhagic fever and a high fatality rate. Two fascinating studies by the groups of Christopher Basler and Viktor Volchkov discover that a key protein required for Marburg virus replication competitively binds to the Nrf2-binding site in Keap1 and promotes the activation of Nrf2 transcriptional programs. This protein, mVP24, is thought to play a multifunctional role in Marburg virus replication and infectivity and bears some functional homology to eVP24, its more well-characterized counterpart in Ebola. Structure-function insights collectively reveal that Marburg, but not Ebola, VP24 induces Nrf2 activation through Keap1 binding, and the data suggest that activation of Nrf2 promotes virus survival in both bats and humans, the former being the main reservoirs for the virus. An acidic motif found in mVP24, but not eVP24, confers this binding specificity, with swapping experiments conclusively conferring Keap1 binding affinity to Ebola. Although control animals exhibit close to 100% lethality while challenged with Marburg, Nrf2−/− mice were remarkably protected, with surviving mice managing to completely clear the virus from their systems. Both studies speculate that Marburg virus ensures its survival in the host through the dysregulation of host inflammatory responses. Given the broad repertoire of Nrf2 targets, it remains to be seen which specific genes or downstream pathways as well as which tissues in the host ultimately drive the survival and replication of this deadly virus. Small-molecule Nrf2 inhibitors have been studied in the context of cancer, and it will also be interesting whether these confer any protection in response to Marburg or other viral infections.

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The Many Faces of a Flavivirus Weapon

Flaviviruses are the etiological agents of dengue fever, West Nile fever, yellow fever, and other life-threatening infections. The RNA genome encodes a single polyprotein that is processed into ten mature proteins. One of these, the glycosylated NS1 protein, associates with host membranes and is known to modulate host immune responses at multiple levels. Dimeric NS1 facilitates viral genome replication intracellularly, but interestingly, NS1 is found systemically as a secreted hexamer that sequesters lipids. The lack of homology with any other protein has provided little structural or mechanistic insight into NS1 function. Janet Smith and colleagues solved crystal structures for NS1 from West Nile and dengue viruses, unraveling some surprising functional insights into how this protein facilitates virus survival. The NS1 dimer has distinct hydrophobic and polar faces, and the recombinant protein is capable of directly remodeling liposomes without cellular factors, evidently by lipid association with the NS1 hydrophobic face. The dimer hydrophobic face also likely associates with the lumen side of the ER membrane, where NS1 interacts with transmembrane proteins of the cytoplasmic viral replication complex. Three NS1 dimers form the hexamer, with hydrophobic faces on the interior for lipid association and the glycosylated polar faces outward for interaction with the immune system. NS1 dimers on the cell surface or secreted hexamers likely allow modulation of extracellular immune surveillance. High levels of NS1 can be detected in the sera of dengue patients, with some correlation between serum levels and disease severity. The authors find homology between an NS1 structural domain and the helicase domains of mammalian antiviral RIG-I and MDA-5 proteins, speculating that this may allow NS1 to modulate host immune defenses through molecular mimicry. The wealth of structural information gleaned from this study suggests multiple strategies to target NS1 using small molecules, as well as approaches to vaccine development. That all flaviviruses rely on this central protein is likely to make it the fulcrum of efforts toward fighting viral disease in the years to come.

Akey, D.L., et al. (2014). Science 343, 881–885.

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