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Antiviral drugs and antiviral drug resistance

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Antiviral drugs and antiviral drug resistance can be matters of life and death for patients suffering from viral infections. They also can be valuable tools for understanding virus biology and biochemistry. Triumphs of antiviral therapy include acyclovir to treat genital herpes [1–4], triple combination chemotherapy for AIDS [5,6], and, quite recently, telaprevir or boceprivir in combination with interferon α and ribavirin for chronic hepatitis caused by hepatitis C virus (HCV) [7–11]. Triumphs of the use of antiviral drugs and drug resistance for laboratory investigation include the discovery of the M_2 ion channel of influenza A virus (amantadine) [12–15] and the UL97 protein kinase of human cytomegalovirus (HCMV) (ganciclovir) [16–19], and the first crystal structure of human immunodeficiency virus (HIV) reverse transcriptase (nevirapine) [20]. Most antiviral drugs inhibit viral functions such as viral polymerases, but increasingly host functions are being targeted for antiviral development, as exemplified by the anti-HIV drug maraviroc [21]. Thus, although antiviral drugs and resistance are relatively mature fields, there are still breakthroughs emerging in the clinic and in the laboratory.

The first highly successful antiviral drugs to be developed act against herpesviruses. Although these drugs, such as acyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) infections, and ganciclovir for HCMV infections, are widely used, they suffer a number of drawbacks. Mark Prichard and Nathan Price review these drawbacks and ongoing efforts to develop new antiherpesvirus drugs and their mechanisms of action and resistance. These newer drugs include variations on old standbys — nucleoside analogs that target viral polymerases — as well as compounds that inhibit newer targets such as a viral helicase-primase involved in HSV DNA replication, a viral terminase involved in HCMV DNA packaging, and the viral UL97 protein kinase involved in multiple stages of HCMV infection. Some of these compounds have completed phase 2 or phase 3 trials. Prichard and Price argues that the future of antiherpesvirus therapy should include drug combinations, which would likely require drugs that act against multiple targets.

Toward the end of better understanding the value of antiviral therapy for HCMV infections, Francisco Marty and Michael Boeckh detail the clinical trial of maribavir, which inhibits the UL97 protein kinase, for the management of infection in stem cell transplant populations. The importance of carefully defining primary endpoints is emphasized.

Antiviral drugs are important components for the control of influenza. Influenza causes annual epidemics of respiratory viral infections that result in significant morbidity and mortality. Influenza vaccines have been shown to reduce the risk of infection and mitigate against the virus' sequelae. Currently, there are two approved classes of antiviral drugs in the United States for the treatment of influenza: adamantanes (amantadine and rimantadine) and the neuraminidase (NA) inhibitors (NAIs; oseltamivir, and zanamivir). Several other classes of antiviral agents and immune modulators are also currently under investigation.

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Michael Ison teviews the currently approved and investigational antiviral agents and the mechanisms of resistance that impact their activity.

Certainly, one of the greatest challenges to our armamentarium of antiviral drugs is the emergence of resistant mutants. The key question is whether antiviral use or natural virus evolution will lead to the emergence of drugresistant virus with comparable or superior fitness to their drug-susceptible counterparts. Currently, NAIs are the first choice for influenza prevention and treatment. Tatiana Baranovicha, Robert Webster and Elena Govorkova review the complex process of risk assessment for the fitness of NAI-resistant seasonal H1N1 and H3N2, pandemic 2009 H1N1, and highly pathogenic H5N1 influenza A viruses: identification of antiviral susceptibility, degree of functional NA loss, molecular markers of resistance, and evaluation of explicative ability for *in vivo* virulence and transmissibility in animal studies (mouse, ferret and guinea pig models).

There are more drugs against HIV than against any other virus, and also more targets against which antiviral drugs have been developed. This plethora of drugs and targets has permitted combination chemotherapy, which is necessitated by the ease with which HIV develops drug resistance. Even with combination chemotherapy, resistance has continued to be a problem, although as reviewed by Daniel Kuritzkes, the patterns of resistance have changed over the past decade. He further reviews recent developments in resistance to several newer anti-HIV drugs, including the newer non-nucleoside reverse transcriptase inhibitors, the integrase inhibitors, and the CCR5 antagonists (e.g. maraviroc), which block a host co-receptor. Of note are the detailed molecular differences in resistance mechanisms even with drugs of the same class. Even as progress in HIV therapy continues, the virus will evolve to spur the development of still more anti-HIV drugs.

The era of direct acting antiviral (DAA) therapy for HCV infection has dawned. The development of DAA therapy is an exciting advance for clinicians and patients, but it will also bring new challenges. Until 2011, the standard of care for chronic HCV was the administration of pegylated interferon α in combination with oral ribavirin, a nucleoside analogue. In 2011, the standard of care became these two agents combined with either telaprevir or boceprivir, which are inhibitors of the HCV NS3/4A protease. Although this three-drug combination is more efficacious than the previous standard of care, patients must still receive intravenous infusions of interferon, and take a drug, ribavirin, whose mechanism of action remains mysterious. Knowing more about how ribavirin abets therapy of HCV could open opportunities for more rational approaches. Jan Paeshuyse, Kai Dallmeier, and Johan Neyts review the large, perplexing, and often contradictory literature on ribavirin and HCV. The field is further complicated by the difficulty in knowing whether the drug's direct *in vitro* action against HCV is relevant to its ability to augment interferon therapy, as the drug has little if any antiviral effect by itself in patients at clinically achievable concentrations. The authors identify at least five potential mechanisms by which ribavirin can act, some of which entail direct antiviral action and others of which entail effects on acquired or innate immunity. Most of these mechanisms are not mutually exclusive. Sorting out the ribavirin puzzle should shed light on HCV biology and the HCV-host interaction.

For the first time, drug resistance has become an issue to consider in the management of HCV. Alex Thompson, Stephen Locarnini, and Michael Beard summarize the current literature concerning resistance to the HCV NS3/4A protease inhibitors, both investigational and clinical, and identify the key questions facing the field.

In the meantime, there are a variety of new drugs on the horizon for HCV. Priscilla Yang, Min Gao, Kai Lin, Qingsong Liu, and Valerie Villareal discuss these. Of interest, some of these drugs, such as R7128 and BMS-790052, directly act against viral proteins to block

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HCV replication, while others such as Debio-025, act against host factors such as cyclophilins that are important for HCV. Several other viral and host targets have been identified, and therapeutic strategies exploiting these targets are in development. Both classes of drugs and targets have provided new insights into HCV biology, particularly regarding the enigmatic NS5A protein, and both types of drugs have considerable promise for improving therapy of HCV infections, especially as resistance appears to arise much more slowly for some of these drugs than for protease inhibitors. There is considerable optimism that combinations of newer drugs could lead to cures of HCV infections without resorting to interferon or ribavirin.

The past twenty years have demonstrated the incredible abilities of viruses to evolve to become resistant to antiviral drugs, and how important it is to the effectiveness of antiviral therapy whether resistant variants are fit. Thus, drug resistance is both a spur to efforts to develop new drugs, and a key consideration in conceiving and executing drug development. It will be interesting to see how viruses and scientists adapt during the next two decades.

Biography

Don Coen is a Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School in Boston, MA, USA. His laboratory works on herpes simplex virus and human cytomegalovirus with emphasis on understanding viral proteins and microRNAs that are either actual or potential drug targets, and uncovering their roles in productive and latent infection, and on elucidating mechanisms by which drugresistant mutants evade drug action yet retain pathogenicity.

Richard Whitley is distinguished Professor, Loeb Scholar in Pediatrics and Professor of Pediatrics, Microbiology, Medicine and Neurosurgery at the University of Alabama at Birmingham. He has studied the development of antiviral drugs for herpes simplex encephalitis, neonatal herpes, varicella zoster virus infections, cytomegalovirus, influenza and west nile virus infections. In addition, he works on the engineering of herpes simplex virus for gene therapy.

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