May 1st, 10:00 AM - 11:00 AM

Analysis of Current Clinical Antiviral Treatment Approaches and Medications and Related Suggestions for Future Research

Daniel Sunderland
Colby College

Analysis of Current Clinical Antiviral Treatment Approaches and Medications and Related Suggestions for Future Research

Daniel Sunderland, Department of Biology, Colby College, Waterville, Maine

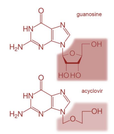
Introduction

- The term “virus” describes a group of nonliving obligatorily-pathogenic particles that are capable of infecting host cells, taking over their metabolic machinery, and reproducing at the cost of the host’s own energetic and molecular resources.
- The viral replication cycle has six basic steps:
  - adsorption,
  - penetration/uncoating,
  - viral component replication
  - assembly, and
  - release
- Treatment methods fall into discrete categories, all based on known viral infection and replication methods, to slow the replication and spread of the virus.

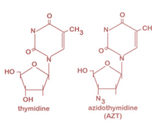
The rapid and incredibly prolific nature of viral replication allows for greater variation, and thus greater rates of resistance development. HAART and other “cocktail” treatments aim to stall viral replication at different levels, decreasing the chance that resistant strains will persist. A virus would have to have three separate resistance mechanisms simultaneously to continue unhindered in these cases.

Direct Treatment Methods

- Spike protein antagonists
  - Creating antibodies that will bind to the spike proteins or cellular receptors – expensive and incredibly time-consuming
- Disruption of Replication
  - Toxic nucleosides such as acyclovir (guanosine analogue) is used to treat the herpes simplex virus, varicella zoster, herpes zoster, and sometimes HIV[19]. Acyclovir halts DNA production because it lacks a 3’ end[12]. Azidothymidine (AZT) is a thymine analog recognized by reverse-transcriptase and used in HIV treatment[22].



  - Integrase inhibitors, including raltegravir, dolutegravir, and elvitegravir, prevent viral genes from being spliced into the host genome by selectively inhibiting the strand transfer ability of integrase[17], but side effects and/or liver dysfunction and failure have been reported[3].

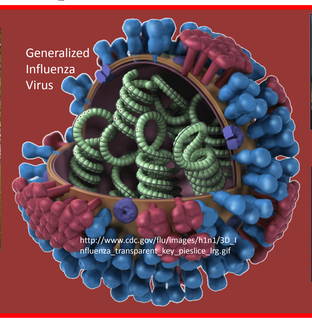


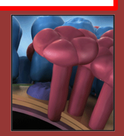
  - Protease inhibitors prevent the post-translational conversion of viral gene products to their mature form[4].
- Highly active antiretroviral therapy (HAART), used to treat HIV, is comprised of two different NRTIs and one protease or integrase[34].
  - The combination decreases viral load, decreasing the likelihood of resistance and allowing the patient’s immune system to rebuild.
- Neuraminidase inhibitors such as oseltamivir target the detachment mechanism of influenza viruses. Neuraminidase must cleave the hemagglutinin-sialic acid bond to release new virions[27].

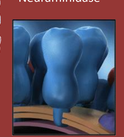
Immunomodulation

- Immunomodulatory treatments are promising because they may enhance innate immunity.
- Only interferon is prescribed for viral infection
  - Natural interferons are released by a cell infected by a viral pathogen to warn nearby cells, triggering a series of non-specific antiviral genes[8].
- GCSF is generally used to help cancer patients recover from chemotherapy[23], though it could also be used to increase immunological response, especially in advanced AIDS patients.
  - GCSF has been shown to cause Sweet’s Syndrome, an autoimmune condition[25]. Further study would be needed to confirm efficacy in a virology setting.
- Imiquimod is prescribed as a topical cream to treat warts and other skin irritations[7].
  - It activates (TLR7), acting upstream of interferon in the immune signaling pathway and triggering the release of several cytokines[6]. Its efficacy against viral infections is largely unknown.
- Sulfated polysaccharides as immunomodulatory elements
  - These compounds have been shown to increase the immune response. Sulfated polysaccharides from *Enteromorpha prolifera* and the red seaweed *Nemalion helminthoides* were shown to increase the proliferation of macrophages and stimulated nitric oxide and cytokine production[14,24].

Enteromorpha prolifera and *Nemalion helminthoides* contain sulfated polysaccharides that may increase the immune response to viruses and other pathogens.




Neuraminidase

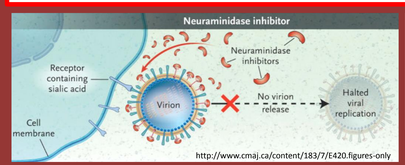

Hemagglutinin

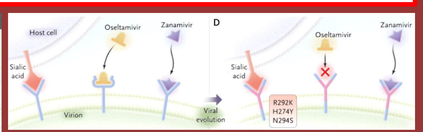
Viral Vectors

- The persistence of viral infections, such as dengue fever in the more arid parts of the world, can be directly attributed to non-human vectors in those areas.
- A recent study explored the immune response of the *Aedes aegypti* mosquito when it has been infected by dengue virus[13].
  - Two genes silenced in *A. aegypti* elevated resistance to the virus in the mosquito’s midgut, suggesting that the virus affected the immune response of the host by somehow modulating the expression of those genes.

Resistance

- Interferon modulation
  - Example: A Borna virus nucleoprotein inhibits interferon production by counteracting the TBK1–IRF3 pathway[31].
- Amantadine and rimantadine
  - Inhibits the viral M2 ion channel needed to uncoat influenza A viruses after host cell penetration[32]
  - Amantadine is no longer recommended because due to widespread resistance, particularly in all relevant strains of H1N1[9]. Amantadine was highly encouraged as both a prophylactic and a treatment as early as the 1970s[20].
- Raltegravir was hailed as major progress in the search for new integrase inhibitors[16] in 2005 and has now been approved for use in very young children[3].
  - Merck & Co. are currently researching MK-2048, a compound they refer to as a “second generation integrase inhibitor,” capable of lasting up to four hours longer than raltegravir[18].
- Oseltamivir can be seen in the very early stages of this resistance process.
  - A factsheet produced by Roche in 2006 claimed that resistance was infrequent at that time[28]. As of 2009, the WHO believes that “there is no evidence to indicate the development of widespread antiviral resistance among pandemic H1N1 viruses”[33].
- Some viruses have also developed resistance to acyclovir and penciclovir[5], which act at a very direct level on viral replication mechanisms, after decades of treatment.





Oseltamivir and zanamivir are competitive neuraminidase inhibitors. Some H1N1 oseltamivir resistance has been reported, but none for zanamivir thus far.

Works Cited

1. AIDSinfo. (2013, August 23). *Dolutegravir*. Retrieved from AIDSinfo Drug Database: http://aidsinfo.nih.gov/drugs/509/dolutegravir/0/patient
2. AIDSinfo. (2013, May 29). *Elvitegravir*. Retrieved from AIDSinfo Drug Database: http://aidsinfo.nih.gov/drugs/421/elvitegravir/0/patient
3. AIDSinfo. (2014, February 4). *Raltegravir*. Retrieved from AIDSinfo Drug Database: http://aidsinfo.nih.gov/drugs/420/raltegravir/0/patient
4. Anderson, J. e. (2009). Viral Protease Inhibitors. In H.-G. &. Krausslich (Ed.), *Antiviral Strategies* (Vol. 189, pp. 85-110). Heidelberg, Germany: Springer.
5. Bacon, T. H. (2003, January). Herpes Simplex Virus Resistance to Acyclovir and Penciclovir after Two Decades of Antiviral Therapy. *Clinical Microbiology Reviews*, 114-128.
6. Bilu, D., & Sauder, D. N. (2003). Imiquimod: modes of action. *Br J Dermatol.*, Supplement 5-8.
7. Daily Med Website. (2007, April). *aldara (imiquimod) cream for topical use*. (National Institutes of Health) Retrieved from Daily Med Website: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7fccca4e-fb8f-42b8-9555-8f78a5804ed3
8. Feld, J. J., & Hoofnagle, J. H. (2005, August 18). Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature, 436*, 967-972.
9. Fiore, A. E. (2011, January 21). *Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza*. Retrieved February 1, 2014, from Centers for Disease Control and Prevention: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm
10. Fleming, A. (1945, December 11). *Penicillin*. Retrieved from Nobel Prize Website: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf
11. Furman, P. A. (1986, November). Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. *Proceedings of the National Academy of Science, 83*, 8333-8337.
12. Gnann, J. W. (1983). Acyclovir: Mechanism of Action, Pharmokinetics, Safety and Clinical Applications. *Pharmacotherapy*, 275-283.
13. Jupatanakul, N. e. (2013, October 3). Aedes aegypti ML and Niemann-Pick type C family members are agonists of dengue virus infection. *Developmental and Comparitive Immunology*, 1-9.
14. Kim, J.-K. e. (2011, September 2). In vitro and in vivo immunomodulatory activity of sulfated polysaccharides from Enteromorpha prolifera. *International Journal of Biological Macromolecules*, 1051-1058.
15. Kramer, M. e. (2003). Metabolic engineering for microbial production of shikimic acid. *Metabolic Engineering*, 277-283.
16. Levin, J. (2005). *MK-0518, the first Integrase Inhibitor for HIV, No Blarney.* Dublin: National AIDS Treatment Advocacy Project.
17. Malet, I. e. (2012). The future of integrase inhibitors of HIV-1. *Current Opinion in Virology*, 580-587.
18. Mascolini, M. (2009). *Merck Offers Unique Perspective on Second-Generation Integrase Inhibitor.* Amsterdam: National AIDS Treatment Advocacy Project.
19. Mascolini, M., & Kort, R. (2010). 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention: summary of key research and implications for policy and practice - Biomedical prevention. *Journal of the International AIDS Society*, Supplement1.
20. Maugh, T. H. (1979, November). Panel Urges Wide Use of Antiviral Drug. *Science, 26*(4422), 1058-1060.
21. Medline Plus. (2010, September 1). *Acyclovir*. Retrieved from Medline Plus: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a681045.html#side-effects
22. Mitsuya, H. e. (1990, September 28). Molecular Targets for AIDS Therapy. *Science, 249*(4976), 1533-1544. Retrieved February 3, 2014, from http://www.jstor.org/stable/2877810
23. Parry, T. (2009). *Network GCSF Guidelines.* North Wales Cancer Network.
24. Pérez-Recalde, M. e. (2013, October 26). In vitro and in vivo immunomodulatory activity of sulfated polysaccharides from red seaweed Nemalion helminthoides. *International Journal of Biological Macromolecules*, 38-42.
25. Paydaş S. et al. (September 1993). "Sweet's syndrome associated with G-CSF". Br. J. Haematol. 85 (1): 191–2.
26. Song, W. e. (2013, August 11). Borna disease virus nucleoprotein inhibits type I interferon induction through the interferon regulatory factor 7 pathway. *Biochemical and Biophysical Research Communications*, 619-623.
27. Svitil, K. (2010, June 3). *Caltech Biologists Provide Molecular Explanation for the Evolution of Tamiflu Resistance*. Retrieved from CalTech Website: http://www.caltech.edu/content/caltech-biologists-provide-molecular-explanation-evolution-tamiflu-resistance
28. The Roche Group. (2006, November 17). *Factsheet Tamiflu*. Retrieved November 14, 2013, from Roche Website: http://www.roche.com/med_mbTAMIFLU05e.pdf
29. United States Food and Drug Administration. (1999). *NDA 21-087*. Rockville, MD: United States Food and Drug Association.
30. United States Food and Drug Administration. (2012, December 21). *FDA expands Tamiflu's use to treat children younger than 1 year*. Retrieved February 2, 2014, from Food and Drug Administration Website: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333205.htm
31. Unterstab, G. e. (2005, September 20). Viral targeting of the interferon-β-inducing Traf family member-associated NF-κB activator (TANK)-binding kinase-1. *Proceedings of the National Academy of Sciences, 102*(38), 13640-13645.
32. Wang, C. e. (1993, September). Ion Channel Activity of Influenza A Virus M2 Protein: Characterization of the Amantadine Block. *Journal of Virology, 67*(9), 5585-5594.
33. World Health Organization. (2009, July 8). *Viruses resistant to oseltamivir (Tamiflu) identified*. Retrieved November 14, 2013, from World Health Organization Website: http://www.who.int/csr/disease/swineflu/notes/h1n1_antiviral_resistance_20090708/en/
34. World Health Organization. (2013, June). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach*. Retrieved from World Health Organization Website: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1

Acknowledgements

I would like to thank Professor of Biology Frank Fekete for sponsoring this independent study and the librarians who helped me acquire journal articles outside the normal scope of what is available at Colby College.