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Mini review

Human viral infections: an expanding frontier[1]

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1. Introduction

During the past 15 years, we have witnessed the appearance of more than 40 new viruses capable of infecting humans, sometimes inapparently (e.g. hepatitis G virus) but in other cases with devastating consequences (e.g. human immunodeficiency virus (HIV)). At the same time, there has been a resurgence of previously known virus diseases, such as Ebola and dengue hemorrhagic fevers. The result of these changes is a considerable expansion of potential targets for antiviral drugs. The causes underlying virus disease emergence and reemergence, which are complex and not fully understood, have been discussed elsewhere (Institute of Medicine, 1992; Hughes et al., 1993; Mahy and Peters, 1996; Mahy and Murphy, 1997). In this short review, the expanding frontier of virus infections will be described with respect to the four main causes: virus evolution; human host modifications; new technologies for detection and disease diagnosis; and changes in vector populations.

2. Virus evolution

Virus evolution includes not only point mutational changes in the sequence of the genome, but also other genetic exchanges, such as recombination and for segmented virus genomes, reassortment. Evolution of DNA genomes occurs relatively slowly due to the presence of host cellular enzymes which correct 'mistakes' that occur during DNA replication. However, for RNA genomes no such cellular enzymes exist and therefore mutations occur up to a million-fold more frequently. The concept has developed that during RNA virus replication the mutation rate is so

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high that a very large population of genomes with slightly differing sequence (termed quasispecies) is generated. Maintenance of the virus species results from constraints on replication so that only those viruses with genomes which fit the particular host environment will multiply. For example, it has been shown that during replication of HIV, the quasispecies population includes variants which have the ability to replicate in the presence of the antiviral drug azidothymidine (AZT), whether or not the human host has received the drug. This rapidity of RNA virus evolution means that new viruses will continue to appear and where there are few host constraints, multiple antigenic variants will continue to emerge from the quasispecies population, as occurs with viruses such as influenza, hepatitis C, or HIV. This makes vaccination problematic for these viruses. Fortunately, some RNA virus vaccines (e.g. vaccines against polio, measles, or mumps) succeed because they target antigenic epitopes which cannot change significantly without compromising virus fitness.

Evolution of viruses through recombination occurs with both DNA and RNA viruses and this can result in the emergence of a new virus with altered pathogenic potential or host range as compared with the parent viruses (Table 1). In the case of influenza virus, mutation affecting the hemagglutinin (HA) cleavage site may significantly alter virulence, since cleavage of the HA is essential for infectivity and may affect the ability of the virus to enter certain cell types, thus influencing virulence (Horimoto and Kawaoka, 1994). Western equine encephalitis virus (WEEV) probably arose as a recombinant between Eastern equine encephalitis virus (EEEV) and Sindbis virus (Strauss and Strauss, 1994). WEEV produces a milder disease in both horses and humans than does EEEV. The nucleotide sequence of rubella virus suggests that this virus may have arisen by rearrangement of an ancestral alphavirus genome (Frey, 1994). Rubella virus occupies a unique taxonomic niche, but within the alphavirus superfamily, it is related to hepatitis E virus and to a plant furovirus, beet necrotic yellow vein virus. Whether it arose by rearrangement or recombination between an alphavirus and hepatitis E virus or a plant virus remains unknown, but evolution through rearrangement is consistent with computer predictions (Frey, 1996).

Table 1
Virus evolution changes in virulence

Mechanism	Example	Disease
Point mutation	Influenza virus	Fowl plague
Recombination	Eastern equine encephalitis virus and alphavirus	Western equine encephalitis
Rearrangement	Rubivirus	Rubella
Hypermutation	Measles virus	Subacute sclerosing panencephalitis
Reassortment	Influenza virus	Pandemic influenza

The phenomenon of hypermutation has been described in measles viruses isolated from the brains of patients that died from subacute sclerosing panencephalitis (SSPE), but it is unclear whether or how these mutations are related to the persistent measles virus infection in the brain that precedes onset of SSPE (Cattaneo et al., 1988).

Reassortment is clearly an important means of generating new viruses and especially in the case of influenza virus, which has its genome in eight segments, appears to be the way in which new human pandemic strains are generated. Influenza virus is the only known example in which an animal virus can move into the human population and result in extensive human-to-human transmission (Mims, 1991). Since reassortment can occur between human and avian influenza viruses, replacement of the segment encoding the surface HA antigen can dramatically alter the antigenic properties of the virus, as apparently occurred in 1957 (Asian 'flu) and 1968 (Hong Kong 'flu). It is certain that a similar event will occur again—the only uncertainty is when. Consequently, many nations are developing strategic plans to respond to the emergence of the next influenza pandemic. One aspect of these plans is the use of antiviral drugs, especially amantadine and rimantadine and adequate stocks will need to be appropriately deployed. There is also a need for other anti-influenza virus drugs; several candidates are in the process of development.

3. Host modifications

Changes in human population and social behavior are important factors in the emergence and reemergence of virus diseases. The world population continues to increase by some 70 million annually, but more importantly, people are moving from rural into high-density urban areas. It has been estimated that by 2000, half the world's population will live in urban environments. The opportunities for virus spread in these settings are greatly increased, especially when accompanied by any breakdown in the public health infrastructure. For example, the resurgence of measles in the USA in 1989–1990 occurred primarily in inner-city populations in which infant vaccination rates had declined.

Social behavioral changes are also important to disease emergence and undoubtedly contributed to the spread of HIV when it first was recognized in the late 1970s. Not only HIV infection, but also the use of immunosuppressive drugs in cancer patients and transplant recipients has resulted in a significant population worldwide that is immunocompromised. In sub-Saharan Africa alone, more than 14 million persons are infected with HIV and will develop AIDS and in such populations new viruses are likely to emerge. In addition, common virus diseases are frequently of greatly increased severity in immunocompromised individuals. It is sobering to note that whilst in 1850 it took almost 1 year for a person to travel round the globe, it now takes just 1 day; thus, viruses which emerge in one part of the world can soon become problems elsewhere (Murphy and Nathanson, 1994).

Some new diseases have emerged directly through human actions that were taken in ignorance of the consequences. For example, raccoons with inapparent rabies virus infection were transferred from Florida to West Virginia, in the 1970s by game hunters who inadvertently seeded rabies virus into the raccoon population. From this focus in Virginia, rabies in raccoons has spread in the last 20 years throughout the eastern USA and is now moving west, threatening Ohio (Centers for Disease Control and Prevention, 1997). Surprisingly, no human rabies case caused by the raccoon variant of rabies virus has been described to date. This is undoubtedly attributable to the effectiveness of postexposure prophylaxis, which has increased considerably in the eastern USA since 1977 in conjunction with the advancing rabies epizootic.

Human intervention, changing the process by which cattle feed is manufactured, undoubtedly contributed to the appearance of bovine spongiform encephalopathy (BSE) in the UK and other European countries starting around 1986. In Britain, cattle were fed meat-and-bone meal prepared from sheep and cattle offal, as a nutritional supplement. A change in the rendering process resulted in an increase in lipid content of the meat-and-bone meal, allowing the agent causing BSE to survive and become amplified as infected cattle offal was recycled back into the meat-and-bone meal (Wilesmith and Wells, 1991). It now seems highly likely that the new fatal human disease, variant Creutzfeld–Jakob disease (v-CJD), originated from human infection with the agent of BSE, although the route of infection and pathogenesis of v-CJD remain unclear (Schonberger, 1998).

4. New technologies for detection and disease diagnosis

The number of recognized human virus infections has expanded considerably within the last decade through the application of new molecular technologies. Now there are a significant number of viruses that have been described and named solely on the basis of their genome sequences, even though conventional growth in cell culture or serotyping is not yet possible (Table 2). Human papillomaviruses, for example, are now ordistinguished into some 70 different types on the basis of sequence analysis of 2.4 kbp, about one third of the genome DNA. This has allowed individual papillomavirus types to be associated with specific diseases or syndromes, such as cervical cancer or epidermodysplasia verruciformis (Chan et al., 1995).

The discovery of hepatitis C virus by Bradley and co-workers (Choo et al., 1989) involved reverse-transcription and cloning of the virus RNA

Table 2
Recognition by molecular techniques

Virus	Disease
Human papillomavirus (more than 70 types)	Warts, anogenital cancer, laryngeal papillomatosis
Hepatitis C virus	Parenterally transmitted hepatitis, often chronic, leading to carcinoma
Hepatitis E virus	Acute epidemic hepatitis, usually waterborne
Hepatitis G virus	? Parenterally transmitted hepatitis
GB/viruses A, B and C	? Parenterally transmitted hepatitis
Bayou virus	Hantavirus pulmonary syndrome
Human herpesvirus 8	Kaposi's sarcoma

from infected chimpanzee blood and identification by expressing the clone and screening with antisera of infected human patients. Similar techniques were later used to identify the enterically transmitted hepatitis E virus (Reyes et al., 1990). Other human flaviviruses related to hepatitis C virus have been identified by using molecular technologies, but the role of these viruses in causing human hepatitis remains doubtful (Alter et al., 1997).

Once a member of a particular virus family is suspected as the cause of a disease, it may be possible to amplify virus sequences from diseased tissues by using polymerase chain reaction (PCR) with generic viruses. This was carried out, for example, in the case of Bayou virus, which was the cause of a case of fatal hantavirus pulmonary syndrome (HPS) in Louisiana (Morzunov et al., 1995). Bayou virus is related to Sin Nombre virus, first recognized in 1993 as a causative agent of HPS (Nichol et al., 1993), so that identification was possible; once the sequence was obtained, specific diagnostic PCR primers and serologic tests were developed and used to identify two other cases in Texas.

New technologies such as representational difference analysis (RDA), used to identify human herpesvirus 8 (Moore et al., 1996), will undoubtedly reveal more human viruses in the future, expanding the array of emerging viruses against which control measures, such as antiviral drugs, need to be developed.

5. Changes in vector populations

A number of changing ecological factors have been identified as the cause of virus disease emergence. These include human population movements into new arthropod or rodent habitats, as well as increases in the vector population density. For example, lack of effective mosquito control has resulted in a resurgence of dengue virus infections in the Americas and dengue hemorrhagic fever in several parts of the world (Table 3). Deforestation in South America has often been linked to virus diseases acquired from arthropods (e.g. Mayaro virus) or rodents (e.g. South American hemorrhagic fever arenaviruses such as Machupo virus). Newly recognized viruses of this type include arenaviruses Guanarito and Sabiá, carried by rodents in Venezuela and Brazil, respectively and Sin Nombre and related hantaviruses, carried by various species of rodents over a wide area of North and South America. The high mortality associated with human infections with these viruses has attracted the attention of molecular virologists, who are now studying the molecular structure and replication strategies of the viruses and the pathobiology of infection. There are clear opportunities here for antiviral drug design since no specific therapies have been

Table 3
Emerging and reemerging viral hemorrhagic fevers

Virus	Group	Cause
Dengue	Flavivirus	Demographic and societal changes; lack of effective mosquito control
Sin Nombre	Hantavirus	Explosive increase in rodent population; increased human–rodent contact
Guanarito	Arenavirus	Human–rodent contact through deforestation
Sabiá	Arenavirus	Human–rodent contact through deforestation
Ebola	Filovirus	Unknown

developed for HPS. Although ribavirin has been used with some success against human arenavirus infections (McCormick et al., 1986; Enria and Maiztegui, 1994) and some hantavirus infections (Huggins et al., 1991), a more specific antiviral drug is clearly needed.

The reemergence of Ebola virus in Africa in 1995, after 19 years, is not understood since the reservoir for the virus is unknown and the virus appears to be quite stable genetically (Sanchez et al., 1996). Ebola hemorrhagic fever results in very high human mortality, approaching 80% and currently no vaccines or antiviral therapies are available.

6. Conclusion

New virus diseases are being discovered at an alarming rate. They appear to be emerging through virus evolution, changes in human demographics and behavior, the development of new technologies for detection and diagnosis of virus diseases, and changes in contact with vector populations. In addition, some previously recognized virus diseases are reemerging for reasons that are not well understood. Nevertheless, this expanding frontier of virus infections provides great opportunities to develop antiviral strategies for intervention and therapy.

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