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The VIZIER project: Preparedness against pathogenic RNA viruses

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Abstract

Life-threatening RNA viruses emerge regularly, and often in an unpredictable manner. Yet, the very few drugs available against known RNA viruses have sometimes required decades of research for development. Can we generate preparedness for outbreaks of the, as yet, unknown viruses? The VIZIER (VIral enZymes InvolvEd in Replication) (http://www.vizier-europe.org/) project has been set-up to develop the scientific foundations for countering this challenge to society. VIZIER studies the most conserved viral enzymes (that of the replication machinery, or replicases) that

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constitute attractive targets for drug-design. The aim of VIZIER is to determine as many replicase crystal structures as possible from a carefully selected list of viruses in order to comprehensively cover the diversity of the RNA virus universe, and generate critical knowledge that could be efficiently utilized to jump-start research on any emerging RNA virus. VIZIER is a multidisciplinary project involving (i) bioinformatics to define functional domains, (ii) viral genomics to increase the number of characterized viral genomes and prepare defined targets, (iii) proteomics to express, purify, and characterize targets, (iv) structural biology to solve their crystal structures, and (v) pre-lead discovery to propose active scaffolds of antiviral molecules.

Keywords: RNA virus; Genomics; Crystal structure; Replicase; Antivirals; Drug-design

1. Introduction

1.1. World epidemic context

Since the discovery of the deadly Ebola virus (filovirus) in 1976 a series of previously unknown pathogenic (emerging) viruses have been discovered, with greater human communication and mobility contributing to awareness and spread, respectively. The World Health Organization (WHO) estimates that the human immunodeficiency virus (HIV), since its discovery in 1983, has killed more than 25 million people and that about 40 million people are today infected with the virus. In 1993, a then unknown lethal hantavirus the Sin Nombre virus, emerged in the Western USA. Shortly thereafter, two unknown paramyxoviruses, both causing lethal diseases, emerged: Nipah virus in Malaysia and Hendra virus in Australia. Before 2002, human coronaviruses were known to cause only mild upper respiratory tract infections. However, the severe acute respiratory syndrome coronavirus (SARS CoV), which appeared in 2002, was highly pathogenic and had a high fatality rate. The avian influenza virus H5N1 strain was first isolated from humans in 1996 in Hong Kong and has caused, since 2003, about 200 casualties. H5N1, as well as other avian influenza viruses, have the potential to develop, either by genetic drift or recombination with other influenza virus strains, into viruses that are highly pathogenic to humans and which have the potential of causing a pandemic. Several viruses have, in recent years, widely expanded their territory, causing the death of an increasing number of people. One such example is the West Nile flavivirus, that was introduced into the USA in 1999, and has since then become endemic in the entire USA and parts of Canada with extensions into Latin America. In the period 2005/2006, the Chikungunya alphavirus resulted in more than 500 000 cases in the islands of the Indian Ocean, probably more than 1.5 million cases in India and is currently sweeping through large parts of southeast Asia, central Africa, and recently Italy. Since the 1970s the number of people infected with the dengue virus (a flavivirus) has been dramatically increasing. In 1975, the WHO surveillance network reported 10 dengue endemic countries and ∼60 000 dengue cases. In 2005, the WHO reported 65 dengue-infested countries, with 1 million reported cases and an estimate of 50 millions actual cases/year.

On the basis of this large, but non-exhaustive list, it is evident that almost all newly emerging, human pathogenic viruses belong to the group of RNA viruses. The RNA-dependent RNA polymerases of RNA viruses have no proofreading capability. As a consequence, these viruses have a very high mutation rate on average about one mutation/virus/replication cycle, allowing fast adaptation to new hosts and environments. Another remarkable observation is that almost all emerging viral infections are zoonotic in nature. The natural hosts for Ebola, HIV, Nipah, Hendra, SARS, H5N1, Sin Nombre, are animals such as bats, monkeys and birds, in which they often have no strong pathogenic effect. An enormous number of yet undiscovered viruses exist in vertebrates. One can state with a high degree of certainty that novel, sometimes highly lethal RNA viruses, will emerge in the future from this large natural genetic pool. Human activities such as deforestation and international travel as well as the results of climate change may facilitate the emergence of such viruses. Other RNA viruses that are known to be pathogenic to man may emerge in regions where they are not yet present, as examplified by the dengue virus in recent years. In addition, changes in the fragile balance of specific ecological niches, may favour emergence of novel pathogenic agents.

1.2. How ready are we to face epidemics?

Fear that H5N1 influenza might develop into an epidemic like that of 1918 fuelled a global effort to be prepared for a future pandemic. A human population of more than 6 billion people must also be prepared for the inevitable emergence of new, highly contagious and lethal viral infections of other origins. The introduction of HIV, the Ebola virus, Sin Nombre virus, Nipah, Hendra, SARS CoV, and many other novel viruses, in the human population was not, and could not have been predicted. Likewise, we are today unable to predict which virus may emerge tomorrow. Preparedness to meet such a threat of an emerging virus includes the ability to rapidly characterize the virus and to be able to take the necessary measures for control. The latter may include vector control, development of vaccines as well as the development of selective antiviral drugs. The former two strategies are most appropriate when a threat has been recognised (i.e. effective in prevention of infection) whilst the latter are essential for quick response to an unknown threat. Today antiviral drugs are only available for the treatment of infections with herpesviruses, the hepatitis B and C viruses, HIV and influenza viruses. In addition Ribavirin has been approved and has shown clinical benefit for the treatment of Lassa virus infections. No specific therapy is available for the treatment of other viral infections. In fact, a crucial statement has to be made here. The drugs that are available against these viruses, have required decades of scientific effort both in the academic and industrial sectors for their development.