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Retroviruses: from infectious agent to therapeutic assistant

Viruses are infectious particles that use the machinery and metabolism of a host cell to replicate. While they do display similarities to accepted forms of life, viruses are not considered as much. The family of retroviruses is particularly known for its most notorious representative, i. e. the human immunodeficiency virus (HIV), which leads to AIDS and for which no cure or effective vaccine is currently available. However, retroviruses are not only of interest for researchers looking for effective cures for viral infections, their characteristic properties also make them promising laboratory and gene therapy tools. Since the first human application of retroviruses for the treatment of a young girl in 1990, numerous gene therapy studies have been carried out; around one fifth uses retroviruses as vectors for the efficient introduction of DNA sequences into mammalian cells.

Outside the cell, viruses occur as virions, physical entities that consist of an outer lipid membrane, proteins that are required for infection, and a protein envelope enclosing the viral nucleic acid (either DNA or RNA, depending on the type of virus). Intracellularly, viruses are genetic material that contains the information for the replication and reproduction of the virions. Viruses can only replicate by infecting a suitable host cell and using the host's replication machinery and metabolism.

AIDS viruses before and after their secretion through the plasma membrane of the infected cell.

© Prof. Dr. Hanswalter Zentgraf, German Cancer Research Center

The typical infection cycle of retroviruses starts with the attachment and fusion of the viral particle and the host cell membrane. A hole forms in the cell membrane and the genetic contents of the virus are released into the host cell. Retroviruses have single-stranded RNA, which is transcribed into double-stranded DNA by the enzyme reverse transcriptase. This is the reverse of the usual pattern of producing RNA from DNA. The name retrovirus – short for reverse transcriptase oncovirus – originates from the ability of the viruses to transcribe RNA reversely. Discovered in retroviruses in 1970, the enzyme reverse transcriptase has since become an important tool in the field of molecular biology.

After transcription, the retroviral DNA is transported to the nucleus of the host cell where it is integrated into the host genome. The host cell then treats the viral DNA as part of its own DNA, making the proteins that are required to assemble new virus copies; viral proteins are packed into new viral particles, virions, which then "bud" from the host cell.

In contrast to such exogenous retroviruses, viral DNA can also be incorporated into the host genome as a provirus and be passed on to daughter cells without leading to disease. A special variant of retroviruses are endogenous retroviruses whose DNA is integrated into germline cells and passed on to subsequent generations. Endogenous retroviruses make up around 8% of the human genome, which clearly shows that retroviral integration in germline cells has happened quite frequently during evolution (1).

Viral gene delivery service

Retroviruses specialise in entering certain cells and integrating their genetic material into the host genome. Scientists use this feature in gene therapy to introduce genetic material, which has been packaged into viral particles, into a host genome. The process of introducing foreign DNA into another cell via a viral vector is called transduction. However, the risk associated with gene therapy is that the foreign DNA is inserted into the wrong spot, where it would interfere with the function of intact host genes. This might lead to the reactivation of intact growth genes, which in turn would lead to uncontrolled cell growth and hence to the generation of tumours. Viral vectors are widely used in haematopoietic stem cell gene therapy, where the inability to control the destination site of a working gene has in the past led to numerous patients developing leukaemia when the gene ends up next to a cancer gene that it can switch on.

The first approved gene therapy case took place in 1990 to treat a patient suffering from severe combined immunodeficiency (SCID) caused by a defective adenosine deaminase gene. Doctors introduced a functional version of the gene into the patient's haematopoietic cells via retroviruses and the corrected cells were reinjected into the patient whose condition subsequently

improved. Since then, 17 clinical studies for testing the efficacy of gene therapy using retroviruses have been carried out in Germany (2), and in November 2012, the first gene therapy was granted marketing authorisation by the European Commission: "Glybera" was approved for the treatment of lipoprotein lipase deficiency (LPLD); the enzyme lipoprotein lipase (LPL) is essential for breaking down fats. Glybera does not involve retroviral vectors; instead, an active copy of an LDL gene is delivered in an adenovirus-derived shell.

HIV – still undefeated

Model of an HIV virion
© Boehringer Ingelheim

The threat posed by retroviruses as the causes of widespread infectious diseases becomes particularly evident with the appearance of the HI virus, a viral infection that eventually leads to the immunodeficiency disease AIDS if left untreated. The virus uses immune cells of the host for replication, i. e. T-helper cells which support other immune cells in fighting off intruders. Despite worldwide research efforts, there is currently no cure or effective HIV vaccine. The high genetic variability of the HI viruses makes it virtually impossible for the immune system and researchers to systematically attack the pathogen in the human body. This is due to the high error rate of the enzyme reverse transcriptase, which leads to constant modification of the viral genome and hence also of the virus.

Despite the fact that AIDS cannot be cured, enormous progress over past years has led to considerable improvements in the treatment of the disease. Aggressive treatment regimes are used to suppress HIV replication and progression of the disease, including HAART, highly active anti-retroviral therapy, which combines three or more drugs of different substance classes. This regimen has been proven to reduce viral replication, thereby reducing HIV-related symptoms and at least partially restoring immune system function. Examples of AIDS drugs are: tipranavir, which is marketed by Boehringer Ingelheim under the trade name APTIVUS® and nevirapine, which the company markets as IRAMUNE®. Nevirapine was the first non-nucleoside reverse transcriptase inhibitor (NNRTI) to receive marketing authorisation and is now the most common anti-retroviral drug worldwide. The drug has also proven suitable for the treatment of HIV-infected breastfeeding women as a way of reducing mother-to-child transmission. Tipranavir is a second-generation protease inhibitor predominantly used for patients who have already become resistant to one or several protease inhibitors.

Harmless member of a dangerous family

Foamy viruses, which belong to the spumavirus genus, differ considerably from other retrovirus genera. Spumavirus infection does not cause disease. Their molecular biology and replication cycle makes these viruses ideal vectors for gene therapy. Researchers from Prof. Martin Löchelt's group at the German Cancer Research Center in Heidelberg explore foamy viruses for their suitability for the treatment of specific human cancers. In cooperation with the Robert Koch Institute in Berlin, the researchers are also focussing on the development of foamy viruses as HIV vaccine vectors. The idea is to integrate typical HIV epitopes into foamy viruses, which would then trigger the formation of antibodies and protect the vaccinated person against HIV. This would help circumvent the problem of having to use attenuated (i.e. pathogens with reduced virulence, but still viable) viruses, which in the case of HIV are not safe for human application. Initial tests involving foamy viruses as HIV vaccine vectors have been initiated, but developing an efficient vaccine will still take a long time.

Publications:

1) Lander E, et al.: Initial sequencing and analysis of the human genome. Nature 2001, 409:860-921
2) FMPHost. (o. J.). GTCT. Abgerufen Januar 2014, von https://a873679.fmphost.com/fmi/webd/GTCT

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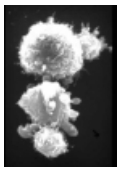
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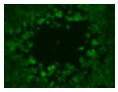
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