Reproduction of RNA Viruses

The host cell does not have enzymes for polynucleotide strand synthesis on the RNA template . Therefore, RNA viruses must contain information for the synthesis of a specific polymerase, either RNA-dependent RNA polymerase or RNA-dependent DNA polymerase. Virion sometimes has to be equipped with a ready-made such polymerase.

Viral RNA gene expression has a different strategy, according to which viruses can be divided into several classes:

First Class RNA Viruses

The first class of RNA viruses includes picornaviruses (*pico* = small), including poliovirus, the causative agent of poliomyelitis , and arboviruses (arthropode bone = transmitted by arthropods), including the causative agent of tick-borne encephalitis . A virion of this class contains (+) ssRNA . First, a huge protein precursor (a chain of about 2000 amino acid residues) is synthesized on the host ribosomes along this mRNA , which is then cleaved into 7 proteins. Some of them are capsid proteins and one graft is an RNA-dependent RNA polymerase(RNA replicase). This enzyme catalyzes the synthesis of the (-) RNA strand on the virion (+) RNA template and uses it as a template to amplify (+) RNA, ie genomes that are incorporated into new viral particles.

Expression scheme of viral genomes of Pircornaviruses (polio) and Arboviruses (tick-borne encephalitis)

Unlike bacteria, a eukaryotic host cell is able to translate mRNA (even polygenic!) Into a single polypeptide chain. Therefore, the virus uses eukaryotic post-translational proteolysis to make its individual proteins. We encounter a similar mechanism, for example, in the biosynthesis of some peptide hormones (ACTH , endorphins).

Second Class RNA Viruses

The second class includes viruses containing (-) ssRNA in the particle. These include rhabdoviruses (*rhabdos* = stick, stick), such as rabies , influenza viruses, mumps virus and measles virus . This time, virus expression addresses the fact that genomic RNA is a (-) strand, unusable as mRNA, and that the host cell does not have an enzyme that replicates (-) RNA. However, the virion contains an RNA-dependent RNA polymerase(replicase), which first synthesizes five short mRNAs on the viral genomic matrix. These then control the synthesis of 5 proteins on ribosomes (including capsid, coat, and new replicase, which catalyzes the formation of new complete (long) viral (+) RNA and virion (+) RNA). So everything is ready to assemble virions. In this second class of RNA viruses, the problem of how to obtain individual peptides from polygenic information is solved at the transcriptional level. Short mRNAs are synthesized, no protein precursor is formed, which would have to be post-translationally modified as in the reproduction of class I viruses.

Third Class RNA Viruses

The third class is reovirus . It was found in the human respiratory and digestive tracts, although it did not cause obvious respiration and enteric orphans. Its virion contains ten (±) dsRNAs and an RNA-dependent RNA polymerase that uses (-) strands of viral RNA in the host cell as a template for the synthesis of ten mRNAs. Their translation produces 10 viral proteins, including a new replicase. It then replicates to replicate and also produces genomic (±) dsRNA. The individual components are assembled into new virions. Thus, the reovirus genome contains 10 monogenic mRNAs.

Fourth Class RNA Viruses

The fourth class includes retroviruses (eg Rous sarcoma virus - the causative agent of avian sarcoma or HIV - the causative agent of AIDS). The name expresses a special strategy of replication of these viruses, ie the reverse transfer of information from RNA to DNA. The Rous sarcoma virus (RSV) virion contains 2 molecules of (+) ssRNA , RNA-dependent DNA polymerase (reverse transcriptase) and Trp tRNA . These components are enveloped by capsid proteins and a lipid membrane containing the viral glycoprotein.

After the virus enters the cell, the RNA-dependent DNA polymerase in the cytosol transcribes the viral genome into the (-) DNA strand and immediately complements it with (±) dsDNA called provirus . The Trp virion tRNA , which was taken over from the host cell in the previous cycle and associated with a short complementary stretch of viral RNA, serves as a primer in DNA synthesis. The template (virion) RNA is degraded during provirus synthesis.

Retrovirus viral genome expression scheme (leukemia, sarcomas, AIDS)

Retroviral DNA is only transcribed if it is integrated into the host genome. Long terminal repeats (LTR) at both ends of the proviral DNA are used for this purpose. They include sections U3, R and U5. U5 and U3 are different sequences, R is a repeat. There are signal sequences for integration and transcription (enhancers, promoters) in the LTR.

Retrovirus reproduction

(±) RSV dsDNA is first cyclized and then transferred from the cytosol to the nucleus. It integrates (integrates) into a very specific place in the avian genome (it is also able to integrate into the mammalian genome, in various places).

The RSV genome contains four genes . The gag gene encodes a large protein precursor (polyprotein) from which several viral proleins are then proteolytically separated. The pol gene carries information for reverse transcriptase synthesis and the env gene for viral envelope glycoprotein production. From a medical point of view, the src gene is interesting , which is not necessary for the reproduction of the virus, but its product causes cell malignancy (fibroblast turns into a sarcoma cell). Therefore, it is included in the group of so-called oncogenes . It encodes a protein kinase that catalyzes the phosphorylation of the tyrosine residue of other proteins. The mechanism by which this enzyme causes a malignant reversal is not fully elucidated.

RSV genome, synthesis of viral mRNAs and proteins

When the RSV genome is expressed , three different mRNAs are synthesized by alternative splicing. Unspliced mRNA becomes genomic, is associated with viral proteins and tRNA. The finished virion "erupts" from the cytoplasmic membrane of the host cell, removing a portion of the membrane without lysing the cell. This makes retroviruses different from DNA viruses. Retroviral DNA replicates with the host genome so that the virus is transferred into daughter cells.

A gene differing only slightly in structure from viral *src was found on the* chromosomes of a healthy chicken . It has been shown to be a normal cellular gene responsible for cell differentiation. It is generally called a proto-oncogene and is referred to as *c-src* , unlike the viral oncogene *v-src* . Dozens of such proto-oncogenes have already been discovered. According to the researchers, the oncogene was transferred to the viral genome secondarily and is transferred from cell to cell by it (transduction). Its expression is then controlled by a viral promoter that is not subject to normal regulation, so the physiological level of its product is not guaranteed. Some viral promoters are very powerful. Viral oncogenes do not have introns, unlike cellular proto-oncogenes.

Retroviral Oncogenes

Retroviral oncogenes can be divided into five groups according to their products:

1. Oncogenes that encode a tyrosine protein kinase (eg, *src*).
2. Oncogenes encoding a protein with growth factor function (eg, the oncogene *sis* encodes a protein almost identical to growth factor PDGF).
3. Oncogenes with information for the synthesis of growth factor receptors (eg *erb-B* oncogene).
4. Oncogenes that control the production of guanylnucleotide-binding proteins, ie G-proteins (eg *Ha-ras* oncogene). Such products are then unable to cleave GTP, which disrupts the regulatory properties of the G-protein and causes cell malignancy.
5. Oncogenes encoding nuclear regulatory proteins (eg, *myb* oncogene).

The diversity of oncogen products suggests that the mechanisms of oncogenesis are different, as these proteins interfere with varying degrees of regulation of cell differentiation and proliferation. *For example, the Erb-B* oncogene produces only the tyrosine kinase portion of the epidermal growth factor membrane EGF. At the normal receptor, the tyrosine kinase is active only after binding of EGF to the receptor. *However, the Erb-B* oncogene product lacks this binding moiety and kinase activity is constitutively unblocked.

Rous sarcoma virus was an example of an so-called acutely transforming virus . Acute leukemia viruses are also included. *In vitro* , cells are transformed with such viruses within 2-3 weeks. In this case, the oncogene is inserted into the viral genome and its transcription is controlled by the viral promoter. There is still a group of slowly transforming viruses (eg chronic leukemia viruses) that induce cell transformation after 4-12 months. The genomes of these viruses do not contain an oncogene. They malignate a cell only when they are integrated in the vicinity of a normal cellular proto-oncogene, which is then driven by a powerful proviral promoter.

Some retroviruses are dangerous without causing a malignant reversal. The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS). The virus is related to the lymphotropic virus, which rarely causes leukemia in humans (HTLV-I). The HIV virus infects and lyses T4 lymphocytes. As a result, the body loses an important component of the immune system. This is because T4 lymphocytes, which are needed to preserve memory for the secondary immune response, are important in the maturation of B-cells into antibody-producing plasma cells and in the maturation of T8 lymphocytes, which are needed to remove infected cells. A person dies of a common infection or malignant tumor.

Thymidinazide formula

Intensive studies of this virus have not yet yielded results that allow effective therapy. Thymidinazide is inserted into the proviral DNA by reverse transcriptase and terminates elongation of the strand, which lacks a free 3'-OH group. The drug slows down the disease.

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- ŠTÍPEK, Stanislav. *Brief biochemistry: storage and expression of genetic information.* 1st edition. Prague: Medprint, 1998. ISBN 80-902036-2-0 .
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