

VIRUSES FOR CANCER THERAPY: NEW PERSPECTIVES AND OPPORTUNITIES

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The history and current state-of-the-art of the research and development in the field of oncolytic viruses are described. The information about types and mechanisms of actions of these viruses is presented together with situation of clinical trials in different countries.

Key words: cancer virotherapy, oncolytic viruses, gene therapy of cancer, therapeutic viruses, viral cancer therapy

Micromachines, micro-robots or microorganisms capable to selectively and effectively lyse cancer cells have been a subject of dreams of generations of oncologists for decades because the first cases of recoveries of cancer patients as a result of microbial infections were described since the beginning of 20 century. Because of poorly predicted effectiveness of this approach, the intensive development of this type of treatment started about 20 years ago only. However, in 2005-2007 two different recombinant adenovirus-based anticancer drugs - Oncorine and Gendicine - were officially approved for cancer treatment in China. The reasons of selective lysis of cancer cells by viruses had been substantially clarified during the last ten years, and now we know the following:

1. The oncolytic viruses selectively infect cancer cells because these cells use metabolic ways which differ from those normal cells use;
2. The oncolytic viruses do not attack normal cells and attack specifically cancer cells because these viruses have special mutations in their genomes or intentionally inserted genes which make them specific to cancer cells and specifically kill them;
3. The infection of cancer cells by viruses induces tumor-specific immunity.

The modern oncolytic viruses may be divided into three different categories: wild or natural animal virus strains which usually do not infect healthy human cells but are cytotoxic for cancer

cells; attenuated human viruses which are specifically selected to kill cancer cells; and non-pathogenic human viruses with significant by size genome in which special cancerolytic genes are inserted and in which special attenuating mutations are introduced.

The oncolytic viruses are being developed now in the USA, Japan, China, Germany, Finland and some other countries. During the two last decades, more than 50 different clinical trials of oncolytic viruses were conducted in the USA alone. And in 2015 the US Food and Drug Administration officially, for the first time in the history, approved wide Phase 3 clinical trials of attenuated recombinant strain of herpesvirus (Imlygic) for treatment of melanoma and also wide clinical trials of recombinant vaccinia virus (Pexa-Vec) for liver cancer treatment. The limited, Phase 2, clinical trials were also approved for some attenuated or non-pathogenic for humans strains of the following virus families: Paramyxoviridae, Picornaviridae, Reoviridae and Adenoviridae. About 100 Phase 1-3 clinical trials is being performed at the Mayo Clinic and other leading cancer treatment centers in the USA and in other countries.

In Russia in 2007, the quite promising Phase 1 clinical trials of the recombinant oncolytic type 5 adenovirus strain were performed at the Russian Federal Oncological Research Center named after N.N.Blokhin. Nevertheless, researchers were unlucky in obtaining funding for Phase 2 clinical trials because of financial crisis in 2008. But because of the megagrant funding during 2010-2012, the development of the oncolytic viruses in Russia started in Moscow in the Engelhardt Institute of Molecular Biology of RAS, and in Novosibirsk: at the State Research Center of Virology and Biotechnology Vector, Novosibirsk State University and the Institute of Chemical Biology and Fundamental Medicine of SB RAS. And the first Phase I clinical trials will soon start in Russia with 2 or 3 different oncolytic virus preparates.