

Viral tumor inhibition

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Clinical and experimental observations of viral tumor inhibition (VTI) are reviewed. A list of viruses with VTI, and diverse terminology used in the field are given. The modalities how these viruses were obtained, principles for their use and different mechanisms of VTI are described. Further studies are needed to improve the therapeutic effect of VTI.

Key words: viruses; tumor inhibition; immunostimulation

Viral tumor inhibition (VTI) after natural infection

First reports on tumor regression after natural viral infection date back to the verge of the 19th century. Thus in 1893 Kovacs drew attention to clinical improvement in leukemic patients after various infections,¹ whereas in 1912 de Pace described the case of a patient with carcinoma of the cervix uteri which regressed after the patient had been vaccinated against rabies, probably with attenuated viable virus.² More recent reports associate previous measles infection with a remission of Hodgkin's disease,³ a regression of Burkitt's lymphoma,⁴ and again a regression of Hodgkin's disease.⁵ Csatory reports on the regression of advanced and metastatic gastric carcinoma associated with an epidemic of fowl plague, or infection with the Newcastle disease virus (NDV).⁶ Pasquinucci

in his report mentions remission of acute lymphoblastic leukemia in children after measles.⁷ Either natural infection or artificial inoculation with varicella virus was often reported to have induced a partial remission of acute leukemia.⁸ Other reports on similar cases have been collected and reviewed by Sinkovics.⁹

Experimental studies of VTI

Published as well as unpublished clinical observations on the viral tumor inhibition rose interest of clinicians as well as experimental oncologists. Growing interest of the latter in this field was noted in the 20's when French investigators studied the growth of viruses in animal tumor models and discovered that some viruses had the potential of inhibiting tumor growth.¹⁰

Renewed interest in this field was apparent in the 50's when the studies centred on the detection of new viruses with tumor growth inhibition potentials gave way to the studies exploring the mechanisms of VTI. A review of the research in this field was presented in the late 50's with a report on 50 different viruses

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tested.¹¹ The viruses were mostly tested *in vivo* in experimental animals, but partly also *in vitro* and in clinical experiments. Many of these experiments proved the existence of VTI, at that time called viral oncolysis.

Viruses with VTI properties were obtained in the following three ways:

- 1) by testing in a number of experimental tumors,
- 2) by adaptation of viruses without initially apparent oncolytic properties to tumors through several passages,
- 3) by isolation of the so-called "passenger viruses" which have contaminated experimental tumors and thus caused a sudden decrease in their growth potential.

In the beginning of experimenting with oncolytic viruses their pathogenic effect on the experimental animals represented a major problem. It also turned out that the most effective viruses were at the same time highly neurotropic. However, further research helped to detect viruses which were practically devoid of any pathogenic effect on the host despite their preserved tumor inhibitory activity. One of such viruses was the neurotropic influenza virus extensively studied in the 70's by Lindenmann and Klein.¹² The results of these studies threw a new light on the immunologic aspect of VTI. The finding that some viruses with VTI properties change the immunogeneity of the infected tumors by inducing new antigens in the cell membranes became widely recognised. Accordingly, a new term viral xenogenization of tumor cells was introduced by Hiroshi Kobayashi, based on the fact that the viral activity renders the tumor tissue alien to the host.¹³

In order to avoid possible virus related danger to the host, in the 70's many investigators began to use the so-called oncolysates, i.e. tumor homogenates infected by virus *in vitro*, which applied particularly to clinical trials.^{14, 15, 16}

Recently, there have been attempts to transfer individual viral genes into the tumor cells with the aim to enhance the immunogeneity of tumor cells, and to avoid adverse effects of viable viruses.¹⁷

With reference to the use of viruses for VTI, the following principles have been established:¹⁸

- 1) Virus should mature by budding through the plasma membrane of the tumor cell;
- 2) The host must be capable of immune response against the budding viral antigens;
- 3) Virus should be fully adapted to a complete tumor cell division cycle;
- 4) Virus should not be oncogenous to the tumor host.

The above principles, which partly restrict the applicability of VTI, have been based on the experiences with viruses which have a specific mechanism of activity. A comprehensive overview of the scope of VTI application and its perspectives has been presented by Sinkovics.¹⁹

Viruses with VTI potential

VTI inducing viruses can be found in almost all families of viruses (Table 1); some of them are pathogenic for humans, and others for animals. Most viruses with VTI potential, discovered till 1973, were neurotropic.²⁰

The analysis of quotation frequency of individual viruses with VTI, including viral oncolysates, shows which viruses have been studied most thoroughly, and which might be regarded as most promising for clinical application. Thus, after 1960, among the most frequently quoted have been retroviruses, NDV, influenza and vaccinia virus, which come far before all others. Among other frequently investigated viruses are also adenoviruses, virus of lymphocytic choriomeningitis, as well as viruses of vesicular stomatitis, measles, mumps, herpes simplex, and bovine enterovirus type 1. As a family, paramyxoviruses play by far the most important role both in studies and in natural viral infections associated with VTI. Paramyxoviruses are followed by the group of retroviruses which are mainly responsible for opportunistic infections in experimental animals and tissue cultures.

Mechanism of VTI

In the beginning, investigators of VTI believed that the effect of viruses on tumor cells was

Table 1. Classification of viruses with VTI by viral families.

Virus family	Nucl. acid type	Virus
Poxviridae	DNA	vaccinia, neurovaccinia, ectromelia
Adenoviridae	DNA	different types of adenoviruses, cow mamillitis
Herpesviridae	DNA	herpes simplex, varicella-zoster
Papovaviridae	DNA	polioma
Retroviridae	RNA	mouse leukemia and sarcoma (Gross, Friend, Moloney, Rauscher)
Paramyxoviridae	RNA	NDV, Sendai, mumps, measles
Ortomyxoviridae	RNA	influenza
Picornaviridae	RNA	coxsackie, Mengo, hepatitis A, encephalomyocarditis
Arenaviridae	RNA	lymphocytic choriomeningitis, Junin, Pichinde, Tacaribe
Rhabdoviridae	RNA	vesicular stomatitis
Bunyaviridae	RNA	Bunyamwera
Togaviridae	RNA	West Nile, dengue, Kyasanur forest disease, St. Louis, Ilheus, Sindbis.

mainly attributable to lytic infection. Therefore, viruses exhibiting VTI properties were called oncolytic viruses.¹¹ However, it soon became apparent that the immune response of the host should be regarded as an important factor in this process. It has been proved that a change in the antigen structure of the tumor cell membranes occurs due to viral infection.^{21, 22, 23} Such antigens can be seen particularly in the viruses which leave cells by budding. Thus, tumor cells acquire antigens extrinsic to the organism, which trigger humoral and cellular immune response. Some authors call this viral effect immune cytolysis.²⁴ The appearance of virus-specific antigens on tumor cells was extensively investigated in retroviruses²⁵⁻²⁸

On the other hand, many authors describe a direct effect of viruses on the immune system. Thus, Byrne and co-workers report a significantly decreased NK cell activity in malignant melanome bearing animals,²⁹ the infection with vaccinia virus induced the NK cell activity to reach the level seen in animals without tumor. Molomut and co-workers point out the importance of interferon induction by means of Pichinde virus which on the other side stimulates the activity of NK cells.¹⁸ Virus also prolongs the virus- and tumor – specific response of cytotoxic leukocytes. Vaccinia virus infection

was associated with the appearance of activated macrophages which exerted cytostatic and cytotoxic effect on malignant melanoma cells,³⁰ as well as with an increased sensitivity of human tumor cells to homologous complement.³¹

Apart from its activity on the immune system, viruses may also exert other effects. Steeg et al. have found that the transfection of adenovirus 2 Ela into tumor cells influences the expression of gene responsible for metastasising, thus inhibiting the metastatic process of the tumor.³² Fearon and co-workers also reported on transfection of the gene coding hemagglutinin antigen of influenza virus into the undifferentiated cells of murine colon cancer.³³ Thus, a strongly immunogenic tumor was obtained, which did not grow in the singeneic mouse but rather protected the animal against transplantation of unaltered tumor cells. Toolan and co-workers noted a decreased incidence of dimethylbenzanthracene induced tumors in new-born animals which were inoculated with parvo virus H1.³⁴ As a possible explanation of this phenomenon, Guetta et al developed the theory that carcinogens activated viral proliferation thus causing VTI with tumor cell lysis.³⁵

The reported cases of VTI mechanisms have been selected only to illustrate the large spec-

trum of possible mechanisms and their variability from one virus to another.

Conclusion

In spite of extensive research on VTI there are only few encouraging results for its application in tumor therapy in men. To improve the latter, much work is still needed to clarify the mechanisms of VTI and factors influencing the effect of VTI.

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