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Oncolytic viruses: the next major breakthrough in cancer treatment

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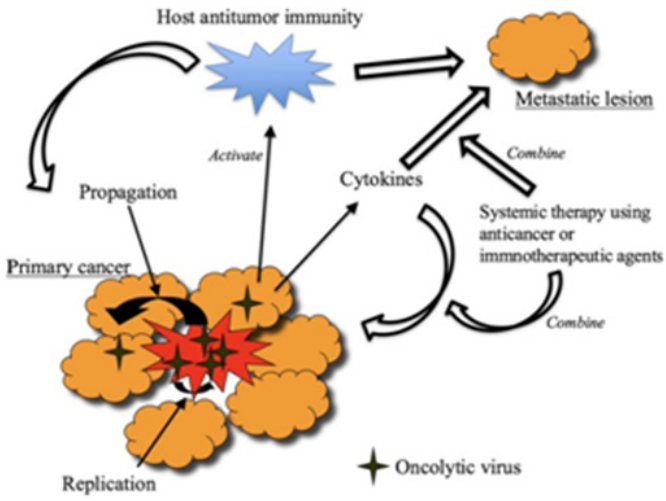
Abbreviations: OVs, Oncolytic Viruses; FDA, Food and Drug Administration; OV, Oncolytic Viruses; T-VEC, Talimogene Laherparepvec; HSV-1, Herpes Simplex Type 1 Virus; DRR, Durable Response Rate; OS, Overall Survival

Mini review

Oncolytic viruses (OVs) are emerging as a promising new class of therapeutic agents in the treatment of cancer. Using a "killer to kill a killer"[1] that's the strategy behind using viruses to kill cancer cells. The first evidence of the ability of oncolytic viruses to kill cancer cells has been documented a century ago but it's only recently that clinical trials demonstrated the effectiveness of OVs in humans with recent US Food and Drug Administration (FDA) approval of an oncolytic virus in advanced melanoma.[2] Oncolytic viruses open a new era in cancer treatment. This short article provides a comprehensive overview of Oncolytic viruses, their use as cancer therapeutic agents and discusses the future and the challenges in the development of oncolytic viruses as a new therapeutic approach in cancer treatment.

Oncolytic viruses: at the origins

Oncolytic viruses (OV) are viruses that can selectively infect, replicate and kill cancer cells while not affecting normal tissue.[3] Although the mechanisms of action are not fully elucidated oncolytic viruses are thought to mediate antitumour activity through two distinct modes of action: selective replication within cancer cells resulting in a direct lysis of tumour cells and an induction of systemic antitumour immunity. Although oncolytic viruses can enter cancer cells as well as normal cells, cancer cells are defective at killing the virus. One reason is that the protection mechanisms against viral infections are impaired in most of the cancer cells.[4]



Mechanisms of action of oncolytic virus therapy[4]

Local replication of oncolytic virus induces specific antitumor immunity in the course of its oncolytic activities that act on remote lesions. A combination with immune checkpoint inhibitors or chemotherapy may enhance the efficacy of oncolytic virus therapy. Arming oncolytic viruses with immunostimulatory gene(s) or cancer therapeutic genes may also be beneficial.

The concept of using virus as antitumour agents emerged over a century ago. In 1904 a tumour regression has been observed for a woman diagnosed with uterine cancer and after being given the rabies vaccine. Between 1950 and 1980, many patients were treated with a wide range of wild type or attenuated viruses (West Nile fever, adenoviruses, hepatitis, measles) with no success. Controlling and maintaining the replication of the oncolytic virus in cancer cells was the main challenge. Attempts to develop cancer cell-specific viruses gave birth to a variety of native and genetically engineered viruses used as oncolytic agents.

Oncolytic viruses: Promising results

Today there are numerous oncolytic viruses under clinical development. We will focus on two Oncolytic viruses with proven efficacy in clinical trials: T-VEC (IMLYGIC™, Amgen) and Reolysin® (Oncolytics Biotech).

Genetically engineered oncolytic viruses

Talimogene laherparepvec (T-VEC), a genetically engineered herpes simplex type 1 virus (HSV-1) developed by Amgen emerged as a serious candidate for cancer treatment. Selective genetic deletions have been made to reduce the overall pathogenesis of the original HSV-1 virus. The GM-GSF gene has also been inserted in the viral genome to improve the induction of the antitumour immunity. In preclinical studies T-VEC demonstrated to be effective against several

tumor cell lines. In clinical phase T-VEC treatment improved durable response rate (DRR) and overall survival (OS) in patients with advanced melanoma. T-VEC (IMLYGIC™) was the first oncolytic viral therapy approved in the USA by the FDA in the treatment of melanoma in 2015, a major breakthrough for the field.

Naturally occurring oncolytic viruses

Many studies have also been conducted on naturally occurring oncolytic viruses like the reovirus. Reovirus is a double-stranded RNA virus that preferentially replicate in tumour cell line but not in normal cells. The virus ability to replicate selectively in cancer cells is due to cancer cells mutations on a growth pathway known as the Ras signaling pathway. Many clinical trials investigated the potential use of an oncolytic reovirus developed by Oncolytics Biotech, Reolysin®, for the treatment of melanoma, head and neck cancer or lung squamous cell carcinoma. In 2015, the FDA granted Reolysin® an orphan drug designation for malignant glioma, ovarian cancer and pancreatic cancer.

Future approaches

Oncolytic virus therapy is probably the next major breakthrough in cancer treatment after the immune checkpoint inhibitors revolution. There are a large number of other promising oncolytic viruses in clinical development including measles virus, Newcastle virus, Vaccinia virus, Coxsackievirus, and Poliovirus. Other viruses (Seneca Valley Virus, Parvovirus and retroviruses) are in early stages and need to be validated.

Although Oncolytic virus immunotherapy is a promising approach, the development of that therapeutic agents requires careful attention. Oncolytic viruses are a promising approach and we can anticipate in the future development of that new class of antitumour therapy. Recent approaches try to combine Oncolytic viruses with other treatments like immunecheckpoints inhibitors to enhance the efficacy of the viruses. Promising results were obtained with Reolysin in combination with anti PD-1 antibody in melanoma.[5] We can also imagine combining different viruses with different antitumour functions according to the type and stage of cancer. Oncolytic viruses have a bright future and reveal to be a serious option for cancer patients.

Acknowledgments

None.

Conflicts of interest

None.

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