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Review Article

Interleukin-12-expressing oncolytic virus: A promising strategy for cancer immunotherapy

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الملخص

الفيروسات القاتلة للأورام السرطانية؛ هي من أنواع العلاجات المبتكرة المضادة للسرطان، التي تستهدف وتدمر الأنسجة السرطانية بانتقائية دون المساس بالخلايا السليمة. اكتسب علاج الأورام بالفيروسات القاتلة المزيد من الاهتمام للمزيد من التطور كنوع جديد من العلاج المناعي بعد موافقة إدارة الغذاء والدواء الأمريكية مؤخرا على فيروس الهربس لعلاج الورم الملانيني المتقدم. ويقوم النهج العملي لتحقيق أقصى قدر من الفاعلية للفيروسات القاتلة للأورام السرطانية على تسليح الفيروسات بالسايتوكاينز المعززة للمناعة، لتكون قادرة على تعزيز القدرة المناعية للهجوم على الخلايا السرطانية بفاعلية. وقد تم تصنيف انترليوكن -١٢ كاسايتوكاينز قوي له أنشطة مضادة للأورام فاعلة، تقوم بتنشيط كلا من الجهاز المناعي الفِطري والتَكَيُفي المضاد للأورام. وأظهرت العديد من الدراسات أن انترليوكن -١٢ ذي خصائص الفيروسات القاتلة للأورام السرطانية، يحسن مؤشر العلاج لعينات الورم قبل السريرية بواسطة تنشيط وتوظيف الخلايا الجذعية، والخلايا السامة الطبيعية القاتلة والخلايا "ت" السامة للخلايا التي بدورها تحسن إزالة الورم. في هذا العرض، نناقش آلية المناعة لعمل الفيروسات القاتلة التي تحوي انترليوكن -١٢.

الكلمات المفتاحية: العلاج المناعي؛ انترليوكن -١٢؛ العلاج بالفيروسات؛ السرطان؛ الفيروس القاتل للورم السرطاني

Abstract

Oncolytic viruses (OVs) are an emerging class of novel anti-cancer therapeutic agents that selectively infect and destroy cancerous tissues without damaging normal cells. With the recent US Food and Drug Administration (FDA) approval of Herpes Virus (T-VEC) for the treatment of advanced melanoma, oncolytic virotherapy has gained more attention for further development as a novel form of immunotherapy. A viable approach to maximize the efficacy of OVs involves arming them with immune-enhancing cytokines that are capable of boosting the host's immune response to effectively attack tumour cells. Interleukin-12 (IL-12) is a powerful cytokine with potent antitumour activities that activates both innate and adaptive anti-tumour responses. Several studies have demonstrated that IL-12-expressing OVs improve the therapeutic index in pre-clinical tumour models by activating and recruiting dendritic cells (DCs), cytotoxic natural killer (NK) cells and cytotoxic T cells, which subsequently improve tumour clearance. In this review, the immunological mechanisms of IL-12–expressing viruses are discussed.

Keywords: Cancer; Immunotherapy; Interleukin-12; Oncolytic virus; Virotherapy

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Introduction

One of the most potent alternative cancer treatments is gene therapy using various agents, such as oncolytic viruses (OVs), which are viruses that can selectively infect, replicate, and generate a greater immune response against cancer and directly kill tumour cells.[1] OVs have been used in clinical trials for the treatment of various cancers, such as pancreatic cancer, ovarian cancer, colorectal cancer and glioma.[2] OVs are designed to target and hijack cancerous cell machinery including: (a) pro-apoptotic targeting where the viruses delay apoptosis of infected cells to promote their replication for the synthesis and assembly of a large number of new viruses before killing the infected cancer cell; (b) transcriptional targeting where an essential viral gene is placed under the regulation of tumour specific promoters; (c) transductional targeting where the ability of the tumour cells to up regulate their tumour-specific receptors is exploited for specific targeting of cancer cells by OVs, and (d) targeting strategies based on the tumour microenvironment where modified microenvironments, such as angiogenesis, hypoxia and activation of certain proteases are exploited.[3] The infected cancer cells eventually produce more infectious particles that infect neighbouring cancer cells; thus, the anti-cancer "infection" spreads.

Direct tumour cytotoxicity appears to be only one of the key mechanisms mediating the anti- efficacy of OV.[4] Interestingly, immune-mediated tumour suppression for overall OV efficacy is likely influenced by the initial period of vigorous OV replication and lytic activity, which optimally set the stage for subsequent antitumour immune response.[4,5] Studies have shown that T and NK cell recruitment into tumours associated with increased survival and enhance antitumour efficacy, subsequently, genetically modified viruses coding for immunomodulatory agents, such as cytokines or chemokines, have come into focus. Such engineered viruses can promote an efficient anti-tumour immune response using several mechanisms, including the induction of intrinsic cellular stress pathways that activate innate immunity, expression of stress-induced self-ligands rendering this cell susceptible to natural killer (NK) cell-mediated lysis and the enhanced presentation of tumour-specific antigens to cytotoxic $CD8^+$ T cells.[6] A milestone has been achieved in the usage of cytokine-armed oncolytic viruses when the FDA recently approved talimogene laherparepvec (T-VEC), a herpes simplex virus (HSV) expressing the immunostimulatory cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), in the treatment of patients with metastatic melanoma.[7] A number of OVs that harbour IL-12 have been demonstrated, in which IL-12 significantly enhances the anticancer immune response. Interleukin-12 (IL-12) is a heterodimeric cytokine produced primarily by phagocytic cells and antigen-presenting cells in response to bacteria, bacterial products, and intracellular parasites. The major target cells of IL-12 action include NK and T cells, which induce IFN-gamma (IFN-γ) production, cytotoxic activity, increased proliferation in cooperation with other costimulatory signals, and differentiation of T helper type 1 (Th1) cells.[6] IL-12 is one of the most potent anti-cancer cytokines. Its antitumoural effect is mediated by the activity of T, NK, and NKT cells and by an anti-angiogenic effect. Given its ability to activate both NK and cytotoxic T cells, IL-12 represents the ideal candidate for tumour immunotherapy in humans.

Unfortunately, systemic administration of IL-12 to cancer patients causes excessive clinical toxicity and severe side effects.[8] To avoid such severe side effects, scientists have used novel methods to deliver this cytokine directly to the tumour site, and one of these methods involves the use of OVs. Taking advantage of OV oncotropism, OVs appear to be a promising platform to effectively deliver IL-12 and restrict it is expression within the tumour microenvironment. The present review summarizes the most promising IL-12-expressing OVs as shown in preclinical models and patients.

Adenovirus

Adenoviruses belong to the family of *Adenoviridae*. Their name is derived from the human adenoid tissues from which they were first isolated.[9] Adenoviruses are non-enveloped viruses with a genome of double stranded linear DNA 26–48 kb in size and a capsid of 65–80 nm in diameter.[9] The capsid contains penton, hexon and fibre proteins that are important for the infection of cells by the virus. The virus uses receptor-mediated endocytosis to enter cells.[10] The first vector systems developed for gene delivery and expression were derived from adenoviruses.[11] Subsequently, adenoviruses have emerged as one of the most frequently used viral vectors for gene therapies, including cancer viral therapy.[11] This emergence is related to their ability to affect the metabolic activity of various cells (replicating and non-replicating cells), host large inserted genes, and code for proteins without incorporating into the cell genome of the host.[11]

Various adenovirus mutants, which are capable of killing tumour cells, have been engineered to utilize tumour-associated promoters to regulate the expression of essential viral genes, thus restricting viral replication and spreading to tumour cells.[12] A common strategy in designing oncolytic adenoviruses is to genetically engineer the adenoviral early region 1A (E1A).[13] This process involves a bondage of the CR2 region of adenoviral E1A to the retinoblastoma protein (RB) and other related proteins that regulate the E2F family of transcription factors, which plays a pivotal role in the regulation of cellular proliferation and stimulates the entrance of quiescent cells into the S phase.[13] Given that cancerous cells often exhibit a dysfunctional RB and uncontrolled cell cycle, deletion of the CR2 region allows the mutant adenovirus to replicate selectively in tumour cells.[14,15]

Several adenovirus mutants have been generated to maximize virus selectivity and efficacy, including mutant dl1520 (ONYX-015/CI-1042), mutant dl 922–947 and mutant AdA-24. Mutant dl1520 (ONYX-015/CI-1042) was the first engineered replication-selective virus used in humans and has been demonstrated to be an anti-cancer agent in preclinical studies and clinical trials.[16] Various studies have shown that arming oncolytic adenovirus with immune modulatory cytokines, such as IL-2 and IL-12, induce enhanced antitumour activity. Expression of the genes associated with the pre-cited interleukins induces the production of cytokines that activate the type-1 immune response, thus resulting in the regression of the development