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Combination Of Oncolytic Newcastle Disease Virus (Ndv) and Vaccine Vector Adenovirus (Adv) as a Potential Virotherapy for Cancer: A Systematic Review

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Abstract

Cancer is a disease with high morbidity and mortality, one of the leading causes of death in the world. Nowadays, the foremost clinical cancer therapy in a patient are surgery, chemotherapy and/or radiotherapy. Despite of the great amount of research on cancer and advance technology in medicine, the mortality rate of cancer remain high due to limited therapeutic effects and additional side effects of current therapy. Here we provide an overview on the virotherapy using the combination of Newcastle disease virus (NDV) and the adenovirus (AdV). Both NDV and AdV possess an oncolytic activity and a potential as vector vaccine. However, oncolytic activity of NDV is more potent than adenovirus. In contrast, the AdV potential as a vector of cancer vaccines is better than NDV. Therefore, in this paper, we discuss the development of a virotherapy combination by utilizing oncolytic activity of NDV, and vaccine vector AdV simultaneously for cancer therapy to improve the effectiveness of therapy against cancer.Conclusion: Decreased estrogen level following ovariectomy causes osteoporosis.

Keywords: Newcastle disease virus; Adenovirus; Virotherapy; Cancer

Abbreviations: NDV: Newcastle Disease Virus; AdV: Adeno Virus; VVND: Velogenic Viscerotropic Newcastle Disease; PBMC: Peripheral Mononuclear Cells; HN: Hemaglutinin-Neuraminidase; TRAIL: TNF-Related Apoptotic-Inducing Ligand; JNK: c-Jun N-terminal Kinase; NOS: Nitric Oxide Synthase; dsDNA: Double-Stranded DNA; NK: Natural Killer; CAE: Carcioembryonic Antigen; TLRs: Toll like receptors

Introduction

Cancer is a disease with high morbidity and mortality that leads to death. Until now, cancer is still the leading cause of death in humans. In 2012, approximately 14.1 million cases of cancer have been reported worldwide, and have caused the deaths of 8.2 million people (about 15% of all deaths). It is characterized by uncontrolled cell division, invade surrounding tissue, and metastasize to other organs in the body. The four most commonly reported cancers are lung, breast, colon, and prostate cancer. However, all organs in the human body can be cancer regardless of age, gender, ethnicity, diet, and environment [1]. Generally, cancer is caused by decreased cell death or increased cell proliferation. In other words, any dysregulation of cell cycle or apoptosis will result in uncontrolled cell growth or malignancy [2].

Cancer occurs due to genetic and environmental factors that cause deviations in the growth regulation of stem cell populations. Improving knowledge of the molecular processes underlying cancer development, as well as advances in diagnostic techniques, radiotherapy technology, and chemotherapy, has increased the survival rate of cancer patients. However, recent therapy has not greatly improved the survival of cancer patients who have undergone metastasis. Although modern technology has been developed, cancer is still afflicted millions of people worldwide [3]. This is because, in addition to the limited therapeutic effects, radio and chemotherapy also cause side effects [1]. The ideal cancer therapy is a therapy that selectively kills malignant cells, and does not damage other normal cells in the body. Currently, radiotherapy, chemotherapy, and surgery are the most common modalities in cancer therapy. However, these therapies often cause harmful side effects [4] and often lead to resistance [5].

Therefore, the development of cancer therapy with high effectivity and selectivity for cancer cells with minimum side effects becomes crucial. The idea of using bacteria and viruses

to treat malignancy in humans began in the mid-1800s in which tumor regression was associated with bacterial and viral infections [6]. The development of cell culture technique and virus technology in the early 1950s led researchers to learn more about the potential of viral therapy in human and small animal tumors [7]. The virus is then proven to be useful as an oncolytic agent and immunostimulator. Newcastle disease virus (NDV) that naturally infected poultry, and adenovirus (AdV) that causes human flu, is a potential viral combination as a virotherapy and immunotherapy agent. NDV can directly kill cancer cells (oncolytic activity) and adenovirus can help to stimulate the immune system to recognize cancer cells (immunostimulator activity).

Newcastle Disease Virus (NdV) as an Oncolytic Agent

Newcastle Disease Virus (NDV) is a virus of the order Mononegavirales because it has single strand RNA, negative polarization, unbranded and linear genome [8]. Furthermore, this virus occupies the family of paramyxoviridae due to its pleomorphic envelope, round-shaped with a diameter of 100-500nm, but some are in the form of filaments [9]. This virus causes Newcastle disease that attacks various poultry, especially chickens. Until now, Newcastle disease has been found in various parts of the world including Indonesia, and the cases of velogenic viscerotropic Newcastle disease (VVND) have been reported in Indonesia [10]. In Indonesia, Newcastle disease is endemic as indicated by the finding of this case throughout the year [9].

NDV was firstly reported to possess an oncolytic activity in the mid-1950s [11]. The clinical evaluation of this virus as an anticancer agent over the last few decades shows its safety and effectivity. The effectivity of NDV application is based on high oncolytic activity, and safety of its use is based on replication that selectively attacks tumor cells and does not damage normal cells. Scientists are interested in the use of NDV because it replicates more rapidly in tumor cells than normal cells in humans, and cause oncolytic effects [12]. NDV replicates 10,000 times faster in cells undergoing neoplasmic changes than normal human cells in general [13,14]. There are several molecular pathways that cause the oncolytic effects of NDV, such as apoptosis pathway [1,15]. Induction of apoptosis by NDV includes a series of virus entry processes, replication, de novo protein synthesis and activation of caspases [16]. NDV induces apoptosis through both extrinsic and intrinsic pathways.

NDV-induced apoptosis is generally mediated by intrinsic pathway during the late stage of infection, while in the early stage of infection is more likely to be mediated by extrinsic pathway [17]. Activation of intrinsic pathway involves the increased activity of p53 and Bax proteins, as well as decreased expression of the Bcl-2 gene [18] which will activate the Caspase 9. The matrix protein (M protein) of NDV binds to Bax protein and increases apoptosis [19]. Whereas, the extrinsic pathway of apoptosis is induced by NDV-mediated activation of pro-apoptotic cytokines such as IFN-α and TNF-α in peripheral mononuclear cells (PBMC) via its Hemaglutinin-Neuraminidase (HN) proteins [20,21]. The HN protein of NDV also induces expression of TNF-related apoptotic-inducing ligand receptor (TRAIL) [22,23] which further activate caspase 8 [17]. A study has shown that NDV initiates the synthesis of nitric oxide synthase (iNOS), thus increasing apoptosis via the NFκB pathway [24,25].

NDV-infected mouse PC12 pheochromocytoma cell was proved to induce the activation of reticulum endoplasma eIF2a kinase (PERK) resulting in phosphorylation of eIF2a and caspase 12 activations. Endoplasmic reticulum stress may be responsible for the activation of apoptotic pathways in cancer cells infected with NDV [26]. In addition, the induction of the external pathway by NDV also the activation of c-Jun N-terminal kinase (JNK) and p38 pathways, and decreased Akt pathway activity [27]. NDV has an excellent potential as a highly selective virotherapy candidate. This selective effect arises because of the restriction of V protein by host and secretion of virus-induced cytokines (IFN-γ and TNF-α) [28]. The first step of infection by NDV occurs in all types of cells in the body, while the second step (associated with viral replication) occurs only in tumor cells because this stage is terminated very quickly in normal cells [5]. In general, the specificity of NDV to cancer cells occurs because of damage to antiviral pathways and apoptosis in cancer cells [29].

In addition to direct cytopathic effects, NDV anti-cancer activity is associated with the activation of both innate and adaptive immune responses. NDV infection initiates the macrophage-induced synthesis of enzymes that increase anti-tumor activity in both in vitro and in vivo studies [30]. NDV stimulates monocytes that play a role in killing tumor cells via TRAIL induction [31]. The activation of natural killer (NK) cells is also involved in the cytotoxicity mediated by NDV [20]. However, to induce host immune system, the use of cancer vaccines is believed to have far more effective effects than the immunostimulator effects of NDV. The immunotherapeutic approach aims to promote the host antitumor immune response that can destroy tumor cells in both primary and metastatic-affected sites [32]. Genetic therapy-based cancer vaccination technology has been widely developed, with the virus being the most popular vector studied. Adenovirus, in addition to having oncolytic activity, is a very potential and widely used vector on cancer gene therapy and as a vaccine to express foreign antigens [33].

Adenovirus (AdV) as a Vaccine Vector

Adenovirus is a group of viruses from the Adenoviridae family responsible for 5-10% of upper respiratory infections, gastroenteritis, conjunctivitis, and cystitis (CDC, 2015). It has no envelope, icosahedral capsid with a diameter of 70-90 nm and the double-stranded DNA (dsDNA) [34]. Adenovirus has long been used as a vector for gene therapy due to its ability to influence cell biological activity, tolerate large genetic modifications, and encode proteins without integrating into the host cell genome. More specifically, the virus is used as a vector for administration

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of therapeutic targets, either in the form of recombinant DNA or proteins [35].

Several studies using various antigens proved that adenovirus (AdV) is potential as a vector of cancer antigens such as glycoprotein 33 (GP33) from lymphocytic viral choriomeningitis [36], carcioembryonic antigen (CAE) [37], beta-galactosidase antigen [38], GM-CSF antigen (such as T-VEC and Pexa-Vec) [39], E7 antigen from human papillomavirus [40], the gp100 antigen and TRP-2 antigen [41]. It may enhances cellular immunity mediated by T-cell CD8+ cells and IFN-γ-mediated humoral immune specific to cancer cells. The use of AdV as a vaccine vector is relatively safe to use with intradermal methods [42]. Adenovirus administration may stimulates ligand expression of Toll-like receptors (TLRs) and may alter cancer immunosuppressive and proinvasive microenvironment becoming proinflammatory, thus facilitating immunocompetent cells to fight against cancer [39,43,44].

General Perspective

Both NDV and AdV have oncolytic activity and potential as vector vaccine for cancer. However, oncolytic activity of NDV is more potent than adenovirus. In contrast, the AdV potential as a vector of cancer vaccines is better than NDV. Therefore, the development of a virotherapy combination by utilizing oncolytic activity of NDV, and vaccine vector AdV for cancer simultaneously are expected to improve the effectiveness of therapy against cancer. The use of an appropriate combination ratio of these two agents will improve their therapeutic potential for cancer [45,46].

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