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Non-Specific Immunostimulatory Capacity of Newcastle Disease Virus (NDV) and Suppression of Breast Cancer Cells

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ABSTRACT: Newcastle disease virus (NDV) is an enveloped single stranded RNA virus that causes deadly infection to over 250 species of birds, comprising domestic and wild-type, thus resulting in substantial economic loss to poultry industry across the globe. NDV possesses several distinctive properties that make it an outstanding anti-cancer agent. In humans it is reported to have oncolytic and immune-stimulatory effects, precisely replicates in tumour cells while sparing normal cells and causes oncolysis. Although NDV has been extensively studied by researchers there is still need for a vigorous research on its potential use as a new treatment modality to cancer patients through a known process termed viroimmunotherapy. This paper deals with an overview of the research which has been carried out worldwide in the use of immune-stimulatory properties of NDV as an anti-cancer agent.

Keywords: Newcastle Disease Virus, Immune-Stimulation, Anti-Cancer, Cytokines

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INTRODUCTION

Breast cancer remains a major cause of deaths in humans. Regardless of the amazing scientific advancement in the prognosis and treatment of tumour, large numbers of people are still coming down with the disease, owing to resistance to treatment and relapses (Ottolino et al., 2010). Surgery, chemotherapy, hormone therapy and radiotherapy are the current available treatment for breast cancer (Stupp et al., 2005). However one of the many new approaches to treatment of cancer is oncolytic virotherapy (Csatary et al., 1999), which exploits the potential of naturally occurring viruses to selectively replicate in and causes cytotoxicity to tumor cells (Biswas et al., 2012) thus the use of Newcastle disease virus (NDV) to treat cancer patients is an attractive adjunct to conventional therapy (Lordick et al., 2013).

NDV is one of the numerous naturally occurring oncolytic viruses, which selectively infect, replicate in, and kill tumor cells (Fournier et al., 2012). For a long time, the therapeutic efficacy was thought to depend on the direct viral oncolysis, however direct NDV induced cytolysis may not be the only factor that plays a role in anti-tumour efficacy (Sinkovics and Horvath, 2000). The host immune system was considered as a brake that decreases virus delivery and spread, thus researchers paid much attention to enhance virus tumor selectivity and cytotoxicity, but with the discovery of indirect oncolytic mechanism induced by virus such as anti-tumour immunity following viral injection, many research turned their direction toward the arena (Stenzel et al., 2011). Indeed, tumor-specific immune cells persist post-therapy and can search and destroy any tumour cells that escape the oncolytic virus, and thus immune memory may prevent relapse of the disease.

Understanding how the host immune system act together with NDV to accomplish antitumor immunity is essential for effective tumour suppression. NDV has a long history as an immuno-stimulant, inducing a rapid type I interferon (IFN) response in infected cells (Sinkovics and Horvath, 2000). Studying the immune effector molecules produced by NDV infected cancer cells, and the signalling pathways involved in stimulating cytokines and chemokine production in tumour cells, is essential in designing recombinant NDV with enrich immunogenicity that could help in recruit the body's own proinflammatory mechanism for immune mediated clearance of transformed cells (Ababneh et al., 2012).

Therefore, this mini review will summarize researches in the field of Newcastle disease virus immunotherapy and/or its immuno-stimulatory properties in cancer therapy specially breast cancer virotherapy application.

NEWCASTLE DISEASE VIRUS AND THE INNATE IMMUNITY

The pleiotropic immunostimulatory properties of NDV in addition to its noble cell binding and selective proliferation in replicating cells have since been documented (Washburn et al., 2003). Study conducted in vitro, indicated that infection of human immune cells with

NDV, stimulate production and released of cytokines, interferon-alpha (INF-α) and tumour necrosis factor alpha (TNF-α) (Zorn et al., 1994). Likewise, infection of human cancer cells with NDV makes the cells more sensitive to the cytotoxic effects of TNF-α (Phuangsab et al., 2000), although the exact mechanism leading to the stimulation of the human immune system is still under exploration (Omar et al., 2003). One important feature is its capacity to induced large amounts of type 1 IFN response during interaction with human peripheral blood cells, this is associated to the nature of the dsRNA structures, which are produced within the cytoplasm through the viral replication, there by stimulating a robust cellular IFN response (Bian et al., 2006).

INTERFERON-INDUCTION BY NDV FOR TUMOR SELECTIVITY

NDV express a different pattern of replication in normal cells upon comparison with tumour cells. Its weak replication in normal cells can be associated with a well-organised antiviral response within the infected cells. In contrast, its efficient replication in tumour cells has some connection with a weak antiviral response of the cancer cells (Ramp et al., 2012). Many NDV strains have better replication ability in transformed cells than in non-transformed cells (Schirrmacher et al., 1999). This may be the reasons for classifying the virus as essentially harmless in humans and for the importance of its use as tumour therapeutics, surprisingly NDV has strong ability to persuade type I interferon response (Fournier et al., 2003). Replication of viral RNA in infected cells instigates the initiation of an innate antiviral response that recruit the transcription of RNA responsive genes, this response encompasses gene regulation by the interferon regulatory factor (IRF) family of transcription factor (Taniguchi and Takaoka, 2002). NDV stimulate the production of interferon induced genes like antiviral enzyme protein kinase R (PKR), RNaseL, with antiviral activity (Haller and Weber, 2007), RNaseL was lately reported to show generation of a small self-RNA, thus increasing the augmentation of innate antiviral immunity (Malathi et al., 2010).

To further explain the mechanism of the differences in susceptibility of normal and tumour cells to viral infection, the pathways for the interferon-induced antiviral enzymes was examined, and the results showed many defect in the antiviral interferon defence response of the tumor cells, no response to UV-inactivated NDV, however normal cells responded significantly with high degree of antiviral enzymes (Fiola et al., 2006, Umansky et al., 1996). This indicate that, early and strong induction of an antiviral response in normal cells may explain the reasons for the break of the NDV replication cycle after making of the positive stranded RNA, perhaps this result could be the reason for the progressive replication cycle of the virus leading to high expression of the viral protein in tumour cells (Fiola et al., 2006).

NDV ACTIVATION OF MACROPHAGES

Non-specific immune stimulating potential of Newcastle disease virus (NDV) and its various anti-tumour activity received much attention recently (Umansky et al., 1996), activation of macrophages to tumoricidal state is a multistep process resulting in production of cytotoxic factors, which eventually destroy neoplastic cells (Fidler and Schroit, 2012). A research was carried out to examine the capability of NDV to trigger anti-tumor activity in murine macrophages, discovered that macrophages were activated following infection with different NDV strains, Several macrophage enzymes become up regulated and anti-tumour effector molecules such as nitric oxide (NO) and tumor necrosis factor (TNF-α) were also established in the supernatants (Pecora et al., 2002). (Table 1). The NDV activated macrophages displayed cytotoxic anti-tumour activity in vitro and were active against cancer cell lines such as mammary carcinoma, lungs and mastocytoma (Schirrmacher et al., 2000). Antitumor activity by NDV activated macrophages could be transferred in vivo. This result demonstrated that NDV can strongly and fectively activate macrophages to perform anti-tumour activity in vitro and in vivo (Kianizadeh et al., 2002) (Fig.1).

NDV interact with cells of the innate immunity on the surface of infected tumour cells where it causes the expression of TRAIL on monocytes and NK-cells, it causes the synthesis of nitric oxide (NO) and tumor necrosis factor (TNF-α) on macrophage.

Study by Washburn et al. (2003) indicated that tumoricidal activity of NDV stimulated macrophages is mediated by TRAIL with high expression of mRNA for TRAIL, 14 hours after NDV macrophage activation of anti-tumour cytotoxic activity that kills the TRAIL-R2 receptor expressing tumour line was observed. This cytotoxic activity may be stop by soluble TRAIL-Fc but not by recombinant TNF-α Fc-binding protein (Washburn et al., 2003). Induction of NO production in NDV activated macrophages is associated with activation of nuclear factor-kB (NF-kB). These reactions are part of an activation method comprising of stimulation of ADA and inhibition of 5`-nucleotidase, suggesting that signalling requirements of NF-kB activation and NO generation are similar in NDV-activated macrophages (Umansky et al., 1996).

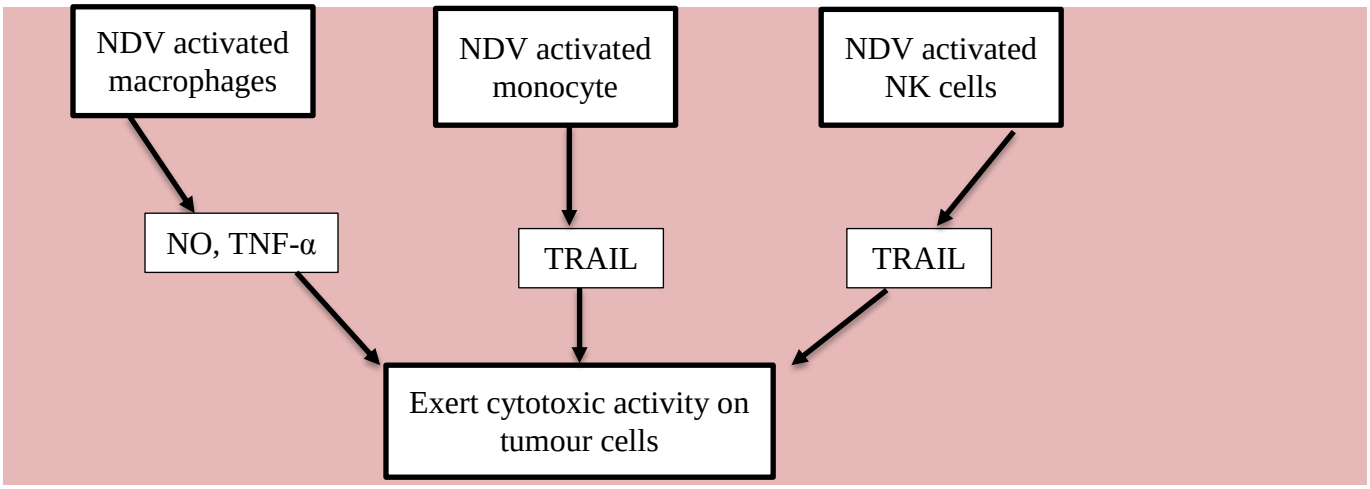

Fig. 1. NDV activation of innate immunity for cytotoxic activity on tumor cells.

NDV ACTIVATION OF NATURAL KILLER CELLS (NK-CELLS)

Infection with NDV have been described previously to cause increase cytotoxic activity of NK-cell fraction in peripheral blood lymphocyte, correlating with virus induced INF-α production (Finan et al., 2010; Zorn et al., 1994). The mechanisms of NK activation by NDV are largely unresolved (Jarahian et al., 2009), in a study to investigate whether NDV infection of tumour targets results in the direct activation of NK cells through the induction of NK- activating ligands. The established human carcinoma cell lines PANC-1, HeLa, and A549 and the recently isolated melanoma cell line Ma-Mel-8a were infected with lytic and nonlytic NDV strain, where it was demonstrated that NK cells exercise significantly improved cytolytic activity in vitro in contrast to many tumour cell lines infected with NDV (Schirrmacher, 2005). Both the nonlytic NDV strain and the lytic strain instigate direct NK-triggering effect. Moreover, it has shown that the incubation of NK cells with inactivated NDV particles was able to enhance the cytotoxic activity of the NK cells against uninfected targets (Fournier and schirrmacher, 2013) In addition to the previously reported IFN-α/β mediated induction of the death receptor ligand TRAIL on NK cells, the direct activation of NK cells by NDV may thus contribute to the known oncolytic properties of certain NDV strains in vivo (Schirrmacher, 2005). It has also been shown that NDV infected tumour cells induced NK cells to secrete increased amount of IFN-α and TNF-α can contribute to the antitumor cytotoxicity of NDV activated macrophages (Schirrmacher et al., 2000). These results suggest that direct activation of NK cells contributes to the antitumor effects of NDV.

DENDRITIC CELLS (DCS) PULSED WITH NDV ONCOLYSATES

Research has shown that dendritic cell is associated with innate recognition of danger signals and induction of immune response, which is a critical link between innate and adaptive immune responses (Mogensen, 2009). Their ability of picking up, processing and presentation of antigen to naive memory T-cells could be through in vitro or in vivo, all the characteristics exhibited by DCs make them unique candidates for immunotherapy aiming at inducing effective T cell-mediated anti-tumor immunity (Finkelman et al., 1996), large amount of DCs can be generated from PBMC derived monocytes, the activation, maturation and protection of DCs is said to be driven by dsRNA (Cella et al., 1999). The systematic data presented in this review provide new understanding into the strategy and mechanism of function of NDV-induced DC, the virus serves as a potent mediator to Th1 response, favouring the induction of DC maturation, the release of pro-inflammatory cytokines and the enhancement of antigen cross-presentation (Fournier and schirrmacher, 2013), all these stages are crucial for the priming and activation of a CD8+ T cell-mediated tumor-protective immune response (Fournier et al., 2009).

Table 1. Indicates of some related researches on effect of NDV induced immune cells derived products and their tumoricidal roles

Immune cells	Cytokines released	Tumoricidal role	Reference
Macrophages	IL, NO, TNF-α.	Cytostatic	(40)
Monocytes	TRAIL, IFN-α	Cytotoxic/ Apoptosis	(38)
Natural killer cells (NK-Cells)	TRAIL	Cytotoxic	(28)
Peripheral blood mononuclear cells (PBMC)	TRAIL, TNF-α	Cytotoxic	
Dendritic cells (DC)	TRAIL, CD40, CD36	Cytotoxic	(33)

Dendritic cells activated with NDV oncolysates were reported to be effective in stimulating autologous T-cells from cancer patients (Haas et al., 1998). This research shows that DCs from breast cancer patients were pulsed with lysate from MCF-7 cancer cell line or from NDV treated MCF-7 cells and compared for stimulatory capacity in an ELISPOT technique response of the autologous bone marrow-derived memory T-cells (Bai et al., 2002). DC pulsed with viral oncolysates showed increased expression of co-stimulatory molecules in comparison with culture of T-cells and DCs pulsed with non-infected tumour lysates and induced significantly higher ELISPOT memory T-cell responses (Schierer et al., 2012). Supernatants from co-cultures of MTC and TuN-L pulsed DC contained increased titers of IFN-alpha and IL-15. NDV infection of tumour cells resulted in a number of differences in protein expression including a heat-shock protein which became phosphorylated (Singh et al., 2012). The results suggest that a DC preparation pulsed with viral oncolysates includes danger signals (e.g. dsRNA, cytokines, HSP molecules) and is superior for MTC stimulation to a DC preparation pulsed with lysate from non-infected tumor cells (Bai et al., 2002). These studies highlighted the importance of the immunostimulatory component of NDV therapy and demonstrated the potential of both naturally and recombinant NDV expressing a tumor-associated antigen to be used as a therapeutic cancer vaccine vector.

DISCUSSION

It is generally believed that oncolytic NDV therapy follows in two stages, an initial stage in which the virus mediates direct oncolysis of tumor cells, leading to the second stage in which it induced immune response carrying on to facilitate tumour damage after the viral vector has been cleared.

Newcastle disease virus is a promising clinical candidate as it shows sign of inducing anti-tumoural immunity, and this is surely a step forward to success for this agent. Different forms of NDV such as live once, heat attenuated and UV inactivated has been tested and proved to be effective in killing tumour cells (Umansky et al., 1996), in all these cases NDV provoked the production of weak tumour antigens, destruction of tumour immune tolerance and production of immune response against the tumour antigen (Bai et al., 2002) The increase in TRAIL expression in NDV activated peripheral blood mononuclear cells (PBMC), DCs, and NK-cells indicated that TNF induced apoptosis could be the central mechanism in oncolytic NDV induced apoptosis, however the exact mechanism by which NDV induced cytokines suppresses the tumor cells has not been completely elucidated, thus finding the sequence of immunological/ cytokines reactions that mediate the NDV induced oncolysis will significantly help in constructing genetically engineered NDV strain with enhance oncolytic activity which could be more safer to the breast cancer or cancer patients in general.

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