

## Induction of Immunogenic Tumor Cell Death by Attenuated Oncolytic Measles Virus

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### Abstract

Antitumor virotherapy is a developing approach to treat cancer with oncolytic viruses, namely replicative viruses that exclusively or preferentially infect and kill tumor cells. Attenuated strains of Measles Virus (MV) are now being used as oncolytic viruses in clinical trials to treat several types of cancer. The efficacy of oncolytic viruses is mainly due to their capacity to infect and kill tumor cells, but it has also been demonstrated that their capacity to induce immunogenic cell death can activate an antitumor immune response. In this review, we describe the oncolytic capacity of MV and the concept of Immunogenic Cell Death (ICD). We then review how MV induces immunogenic cell death, which can be beneficial for cancer treatment.

**Keywords:** Measles virus; Virotherapy; Oncolytic viruses; Immunogenic cell death

### Introduction

Antitumor virotherapy using replicative oncolytic viruses that exclusively or preferentially infect and kill tumor cells is a field that is growing rapidly, along with progress in molecular biological engineering [1]. These viruses are often derived from attenuated strains that either exhibit a natural tropism against tumor cells or that have been engineered to target tumor cells. Numerous RNA viruses (coxsackievirus, Newcastle Disease Virus (NDV), Vesicular Stomatitis Virus (VSV), Measles Virus (MV), poliovirus, and reovirus) and DNA viruses (adenovirus and vaccinia virus) are now being evaluated in clinical trials against a wide range of malignancies [1]. Adenovirus H101 is now approved in China for the treatment of head and neck cancer, and several other oncolytic viruses, such as HSV, adenovirus, and reovirus have entered phase III clinical trials [1].

### Attenuated MV as an Oncolytic Virus

#### Structure and replication cycle of MV

Among oncolytic viruses, attenuated vaccine strains of MV show an interesting spontaneous tropism for infection and replication in tumor cells, and are now being evaluated for the treatment of several cancers. MV is a Morbillivirus of the Paramyxoviridae family, with an envelope and a negative, non-segmented, single-strand (ss) RNA genome [2]. The World Health Organization (WHO) indexes twenty-four strains of MV, classed into eight clades [3]. The MV RNA genome comprises around 16,000 nucleotides and encodes eight proteins. Two of these are non-structural proteins (V and C), expressed from an alternative RNA transcript encoding the phosphoprotein (P protein). V and C protein are virulence factors, notably implicated in the inhibition of

the innate intracellular immune defense, such as the type I Interferon (IFN) response. P protein, Large protein (L) and Nucleoprotein (N) form the nucleocapsid, which contains the viral ssRNA genome. The matrix (M), fusion (F), and hemagglutinin proteins (H) form the viral envelope with lipids from the infected host cell membrane [2].

The replication cycle starts with the adsorption of MV onto the host cell membrane through the interaction between the H protein and the cell surface molecules, CD150, CD46, and/or Nectin-4 [4]. The F protein mediates the fusion between the viral particle and the host cell membrane, allowing the negative, single-stranded RNA and the associated proteins to penetrate into the cytoplasm. These proteins form a Ribo-Nucleo-Proteic (RNP) complex with the viral polymerase L, which allows replication of the negative ssRNA and transcription of MV genes. The newly assembled viral particles bud from the infected cell plasma membrane, together with the matrix (M) and the envelope glycoproteins (H,F). MV infection is known to induce the formation of syncytia. Indeed, MV-infected cells fuse with neighboring cells, thus forming multinucleated infected cells that increase the efficiency of MV replication.

#### Oncolytic activity of MV

MV uses several receptors to enter cells. The pathogenic wild-type (wt) strains use the signaling lymphocyte activation molecule (SLAMF/CD150), which confers to this virus a natural tropism for T and B lymphocytes and activated monocytes/macrophages [5,6]. This receptor usage explains the reports of spontaneous remission of leukemia and lymphoma in patients who have contracted a wt-MV infection [7-10]. These reports constitute the first proof of concept that MV can be used as a natural oncolytic virus.

Since 2001, the oncolytic activity of attenuated strains of MV has been reported, both in vitro, and in vivo in immunodeficient mice bearing human tumor xenografts. This activity has been demonstrated

against T-cell lymphoma [11,12], myeloma [13], sarcoma [14], pancreatic cancer [15], glioblastoma [16], glioma [17], ovarian carcinoma [18], prostate cancer [19], breast cancer [19-21], melanoma [22], renal cell carcinoma [23], mesothelioma [24,25], medulloblastoma [26,27], hepatoblastoma [28], and lung/colorectal adenocarcinoma [29].

Attenuated vaccine strains of MV, such as Schwarz and Edmonston, which are spontaneously oncolytic, use the CD46 molecule as the major cell receptor [30-32]. The membrane cofactor protein, CD46, is an inhibitory complement receptor. Its expression at low density by healthy cells protects normal tissues from accidental injury by activated complement. Interestingly, many tumor types overexpress CD46 to escape complement-dependent cytotoxicity [33,34]. This selective overexpression by many cancer cell types confers on attenuated MV a natural tropism for tumor cells. Above a certain threshold of CD46 expression, the killing and syncytium formation mediated by MV infection increase dramatically [30], whereas healthy tissues with a low density of CD46 remain unharmed [18].

Recently, Nectin-4 (PVRL4) has been identified as a novel receptor for wild-type and attenuated strains [35,36]. This molecule plays a crucial role in the shedding of MV from the respiratory tract of infected individuals for transmission of the disease [37]. In humans, Nectin-4 is mostly expressed in placenta and trachea, and at a lower level in tonsil epithelial cells, oral mucosa, lung macrophages, and neuronal cells of the cerebral cortex [35]. It is also frequently overexpressed in many adenocarcinomas, such as lung, ovarian, colon, and breast tumors [38-40]. Nectin-4 is used by MV for the infection of breast tumor cells [20].

Overexpression of MV receptors is probably not the only factor that determines the ability of MV to replicate and preferentially kill tumor cells. There is now evidence that host translational control of viral replication, and the incapability of some tumor cells to develop a type I interferon innate immune response, affect the oncolytic activity of MV [14,41,42]. All nucleated cells are equipped with intracytoplasmic sensors that are considered as Pathogen Recognition Receptors (PRR) and are able to detect viral infection [43]. In the case of MV, helicases such as the Retinoic acid-Inducible Gene 1 (RIG-I) and the Melanoma Differentiation-Associated protein 5 (MDA5) detect viral RNA and induce the secretion of type I IFN, which protects infected and neighboring cells from viral replication. Indeed, exposure to type I IFN induces the expression of numerous Interferon Sensitive Genes (ISG) that inhibit several stages of viral replication [44]. However, there are often defects of type I interferon response in tumor cells, to avoid the triggering of this response by frequent aberrant RNA transcripts present in these cells [45,46]. It allows the tumor cells to avoid induction of apoptosis or stimulation of antitumor immune response by the type I IFN.

### Clinical trials with oncolytic MV

MV is now being evaluated, in clinical trials being carried out at the Mayo Clinic, for the treatment of several malignancies: ovarian cancer, mesothelioma, multiple myeloma, glioma, and squamous cell carcinoma of the head and neck [1]. A major asset for the clinical use of attenuated MV is its excellent safety profile, proven after the vaccination of millions of children over the past forty years, with no observed reversion to the wt-MV [47]. To date, the results of three clinical trials have been published, for the treatment of cutaneous T-cell lymphoma (CTLC), chemoresistant ovarian cancer, and advanced multiple myeloma, with encouraging results and limited adverse

effects [48-50]. Heinzerling and colleagues carried out the first phase I clinical trial of MV antitumor virotherapy using the Edmonston-Zagreb strain of MV in five patients with CTCL [48]. This clinical study showed that intratumoral injection of MV after systemic treatment with IFN- $\alpha$  (to limit infection of healthy cells) induced local infection and a characteristic cytopathogenic effect of MV on tumor cells, leading to tumor regression in three patients.

MV was also evaluated by intraperitoneal injection for the treatment of patients with taxol- and platinum-refractory ovarian cancers, who were seropositive for measles virus to assure the safety of the trial. In this phase I clinical study, Evanthia Galanis and colleagues used MV-CEA, a modified Edmonston strain that produces the carcinoma embryonic antigen (CEA) as a soluble marker [49]. Indeed, CEA allows the monitoring of MV replication by serum dosage. Escalating doses were given to patients, ranging from  $10^3$  to  $10^9$  TCID<sub>50</sub>, with no observed dose-limiting toxicity. Clinical responses were observed in fourteen of twenty-one patients, notably disease stabilization, with a median duration of 92.5 days. Clinical response was associated with a diminution of the tumor-specific marker, CA-125, in five patients. Median survival time (12.15 months) was increased considerably compared to the expected median survival of the patient population (6 months).

More recently, a third phase I clinical trial was performed in two MV-seronegative patients with relapsing, drug-resistant, metastatic multiple myeloma [50]. These patients were given, by intravenous injection, a high dose ( $10^{11}$  TCID<sub>50</sub> infectious units) of Edmonston MV recombinant for the sodium/iodide symporter (NIS), which allows viral replication to be followed in vivo by radioiodine Single-Photon Emission Computed Tomography (SPECT)-Computed Tomography (CT) imaging. Both patients responded to the treatment, with one experiencing a complete response during six months that is still on-going at the time of this publication.

## Immunogenic Cell Death (ICD)

### Discovery of ICD

Until the mid-1990s, it was thought that the major factor that conditions the induction of an immune response was the discrimination between “self” and “non-self”. The presence of Pathogen-Associated Molecular Patterns (PAMPs) was necessary for the induction of an efficient immune response [51]. PAMPs are conserved molecular motifs specific to pathogens that are notably able to activate Antigen-Presenting Cells (APC) such as Dendritic Cells (DC), via PRR such as Toll-Like Receptors (TLR) [52]. When exposed to PAMPs, DC that capture antigens in peripheral tissues migrate to secondary lymphoid organs and initiate an adaptive immune response. PAMPs can also be detected during pathogen infection by intracytoplasmic PRR, which are expressed by all nucleated cells. This detection activates a cellular innate immune defense known as the type I IFN response that leads to secretion of type I IFN. These molecules act by autocrine and paracrine modes to block pathogen replication and eventually induce apoptosis.

The self/non-self-model fails, however, to explain why some microorganisms, such as commensal bacteria, are well tolerated, and why some self-constituents can trigger an immune response without the presence of pathogen, such as in the case of autograft. To take into account these phenomena, Polly Matzinger proposed the “danger theory”, which postulates that the immune system does not concern so

much with self and non-self, but rather detects situations that present danger [53]. Indeed, while apoptosis was considered to be nonimmunogenic, this theory implies that in certain conditions of stress, such as injury by pathogen, cell death can be accompanied by the release of cellular danger signals that are able to activate the immune system. These danger signals released during ICD activate APC, notably DC that, after capturing antigens, migrate to secondary lymphoid organs and initiate an adaptive immune response. Danger signals were later renamed Damage-Associated Molecular Patterns (DAMPs), as opposed to PAMPs [54]. The integration of both types of signals, DAMPs and PAMPs, induces and orients the immune response.

### Inducers and types of ICD

Numerous inducers of ICD have now been described. Pathogens such as viruses can induce ICD [55]. Some chemotherapeutic drugs used for the treatment of cancer, such as doxorubicine, have also been shown to induce ICD [56]. In addition, some physical stimuli can induce ICD, such as ionizing radiation used in radiotherapy [57], ultraviolet-C irradiation [58], high hydrostatic pressure [59], hyperthermia [60,61], and freeze/thaw cycles [62].

Different types of ICD have now been described [63]. Indeed, ICD can result from apoptosis accompanied by an endoplasmic reticulum (ER) stress and autophagy [64,65]. This form of apoptosis is characterized by preservation of cell membrane integrity with the formation of blebs, and by the release of DAMPs, such as high-mobility group box 1 (HMGB1) protein and adenosine triphosphate (ATP), and the exposition of calreticulin on the surface of apoptotic cells. ICD can also result from pyroptosis, characterized by activation of the inflammasome that leads to the activation of caspase-1, able, notably, to transform pro-IL-1 $\beta$  into IL-1 $\beta$  [66]. Furthermore, pyroptosis is associated with the formation of cell-membrane pores that results in cell lysis. Pyroptosis is especially used by immune cells, such as neutrophils and leads to a rapid induction of inflammation in response to some pathogens. Necroptosis is an active necrosis program that can be induced notably by the presence of Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) produced in response to a pathogen. TNF- $\alpha$  can trigger its receptor TNFR1 which lead to activation of receptor-interacting protein kinase 1 and 3 (RIPK1 and RIPK3). This signaling pathway will lead to necroptosis. This form of ICD is accompanied by the passive release of DAMPs such as HMGB1 and long genomic DNA, due to the loss of cell membrane integrity [67,68]. Finally, ICD can also result from passive necrosis induced by pathogen infection, toxin exposure, or physical trauma, and accompanied by the passive release of DAMPs such as HMGB1 and Heat Shock Proteins (HSP), and the exposure of F-actin [68,69]. Much work is still needed to understand the regulation of these different cell-death pathways and, importantly, their outcomes regarding the initiation and orientation of the immune response.

### DAMPs and ICD

Several DAMPs have now been identified, and they exert various roles. Firstly, cells that undergo ICD expose, on their membrane, "eat-me" signals for phagocytosis by APC. During ICD induced by ER stress and autophagy, calreticulin, which is normally located in the ER membranes, is rapidly exposed at the plasma membrane of apoptotic cells and can be recognized by scavenger receptors on APC [70,71]. During necrosis, F-actin is exposed to the extracellular environment and may also act as an "eat-me" signal for phagocytosis mediated by

DNGR1, also known as Clec9a in humans, a receptor found on DC that is specialized in cross-presentation [69]. Secondly, cells that undergo ICD can release some DAMPs that are implicated in the attraction and activation of immune cells. Among these, the first-described DAMPs that are released during ICD, and that induce DC maturation, were from the HSP family, notably HSP70, HSP90, and gp96 [72]. Later, HMGB1, which is a nuclear protein that binds DNA, was reported as a major DAMP released during ICD that triggers activation of APC by several receptors, such as RAGE, TLR2, TLR4, TLR9, and TIM3 [73,74]. During ICD, ATP is another major DAMP that is released by dying cells and that attracts immune cells by triggering P2Y2 receptors [75] or P2X7 receptors [76]. Furthermore, ATP release during ICD has been shown to play a role in the induction of the antitumor immune response induced by some chemotherapeutic agents [77]. IL-1 $\beta$  is often considered as a DAMP released during pyroptosis following the activation of the inflammasome and caspase-1 [66]. IL-1 $\beta$  plays an important role in the inflammatory response.

## Oncolytic Measles Viruses and The Induction Of Tumor ICD

### Evidence of ICD induction by MV from clinical trials

The induction of immunogenic cell death by oncolytic viruses is probably an important parameter for their efficiency in antitumor virotherapy treatment [1,78,79]. As an example, it has been shown in a phase II clinical trial testing intratumoral injections of a modified oncolytic herpes simplex 1 virus in melanoma patients that tumors distant from the injection sites can regress, notably some visceral metastases [80]. In another phase II trial, injections of the oncolytic JX-594 vaccinia virus into treatment-refractory advanced hepatocellular carcinoma tumors also induced the regression of distant metastases [81]. The authors further showed that such treatment causes neutrophil infiltration into the injected tumor, an antibody response against tumor cells, and evidence of a cytotoxic T-cell response.

In the first phase I clinical trial using oncolytic MV, a positive effect on the antitumor response was reported [48]. In this trial, the Edmonston-Zagreb strain was used to treat five patients with cutaneous T-cell lymphoma. This study showed that intratumoral injections of MV after systemic treatment with IFN- $\alpha$  induced tumor regression in three patients. Interestingly, some regressions of distant lesions where MV was not injected were observed, suggesting that the treatment triggered the activation of an antitumor immune response. Furthermore, in a model of human lymphoma xenografts in immunodeficient mice, the injection of MV has been shown to induce tumor infiltration by activated neutrophils [82]. Altogether, these reports indicate that intratumoral MV injections can stimulate an antitumor immune response.

### Interaction of MV infected tumor cells and dendritic cells

Our laboratory and others have been interested in characterizing, in vitro, how MV-infected tumor cells stimulate APC such as DC to induce their capacities to stimulate an adaptive antitumor immune response [22,25,83,84]. We first showed that MV infection of mesothelioma tumor cells induced ICD, in contrast with ultraviolet-B (UV-B) irradiation of tumor cells that undergo a nonimmunogenic cell death [25]. Indeed, MV-infected tumor cells induce the

maturation of monocyte-derived DC, notably by the release of DAMPs such as HSP (HSP70, gp96), whereas apoptotic UV-B-irradiated tumor cells did not stimulate DC. We further showed that DC internalized materials from MV-infected tumor cells, notably tumor antigens such as mesothelin, and induced from naive lymphocytes a T-cell response directed against this tumor antigen. Altogether, these results not only show that MV kills tumor cells, but also that MV induces the release of tumor antigens allowing DC to cross-prime a specific CD8<sup>+</sup> T-cell response.

In 2011, Donnelly et al. confirmed that MV-infected tumor cells undergo ICD that is able to induce maturation of DC [22]. Furthermore, they identified the immunogenic factors released during ICD. They also showed that DC co-cultured with MV-infected melanoma tumor cells induces cytotoxic T-cell responses against tumor cells. They identified numerous DAMPs and cytokines released by MV-infected tumor cells that make the cell death immunogenic. They showed that MV-infected cells release HMGB1 and numerous inflammatory cytokines, such as type I IFN (IFN- $\alpha$  and IFN- $\beta$ ), IL-6, IL-8, RANTES, and IL-28.

Plasmacytoid DC (pDC) is another type of DC specialized in antiviral immune response. Accumulating evidence suggests that it would be beneficial for cancer patients to stimulate this subset of DC within tumors, as these cells are able to induce an immune response by type I IFN production and antigen presentation, and can exert direct tumoricidal activity [85,86]. Conflicting reports have been published regarding the capacity of attenuated MV strains to stimulate IFN- $\alpha$  production by pDC [87,88]. Duhon et al. reported that attenuated strains of MV induce IFN- $\alpha$  secretion by pDC, whereas Schlender et al. reported that they do not induce this secretion, but on the contrary inhibit it. We explained this discrepancy recently by investigating the activation of pDC in response to MV or MV-infected tumor cells [84]. We showed that pDC exposed to MV without IL-3, a survival factor that is required for in vitro culture of pDC, do not produce IFN- $\alpha$  as reported by Schlender et al. [88], whereas pDC exposed to MV in the presence of IL-3 do produce IFN- $\alpha$  as reported by Duhon et al. [87]. We also observed that pDC exposed to MV-infected tumor cells produce huge amounts of IFN- $\alpha$  due to the triggering of TLR7 in the endosome by MV single-stranded RNA. Finally, we showed that, like monocyte-derived DC, pDC exposed to MV-infected tumor cells are able to internalize and cross-present tumor antigens such as NYESO-1 to CD8<sup>+</sup> T lymphocytes to induce an antitumor immune response. In contrast, pDC exposed to UV-irradiated tumor cells keep an immature phenotype and are unable to cross-present the tumor antigen. Altogether, these studies show that MV infection of tumor cells induces an ICD that is able to activate tumor antigen cross-presentation function of both myeloid and plasmacytoid DC.

### The type of ICD induced by MV

The type of ICD induced by MV infection of tumor cells is not well characterized. It is not yet described whether ICD is associated with ER stress and autophagy, pyroptosis, and/or necroptosis. It is now clear that HMGB1 is released from tumor cells following MV infection [22] (and unpublished personal data). These results suggest that it could be ICD accompanied by ER stress and autophagy or necroptosis. Infection by attenuated MV strains has recently been shown to induce autophagy in several waves [89,90]. The interaction of MV with CD46 receptors induces an early wave of autophagy followed by a second wave dependent on MV replication, and finally a third wave upon syncytium formation [90]. However, it is not clear from this study if

autophagy participates in the induction of apoptosis, since the author states that this sustained autophagy flux is exploited by MV to limit the death of infected cells and to improve viral particle formation. More work is needed to better define which ICD pathways are induced by MV after the infection of tumor cells.

MV is known to trigger the antiviral type I IFN response in nucleated cells [14,91,92]. However, MV has evolved virulence factors, such as the V protein that inhibits type I IFN signaling at the level of STAT1 and STAT2 downstream of the type I IFN receptor, IFNAR [93,94]. The V protein also inhibits MDA5 signaling [95]. Another viral factor, the C protein of MV, blocks type I IFN signaling [96]. In attenuated MV such as Edmonston and Schwarz strains, the V protein carries a mutation that reduces its capacity to inhibit type I IFN signaling [97]. Thus, attenuated strains of MV do not completely inhibit the type I IFN response. Type I IFN produced by infected tumor cells or by pDC exposed to infected cells, can exert a diversity of beneficial effects on the antitumor immune response. IFN- $\alpha$  not only induces an antitumor cytotoxic activity of pDC by an autocrine loop, but can also act directly on tumor cells to induce apoptosis [98]. Type I IFN also play a role in NK activation and are required in a mouse model of NK-cell-dependent tumor rejection [99]. Type I IFN is also known to activate DC and their capacity to induce a cytotoxic T-cell response [100,101]. Thus, the triggering of type I IFN production by MV in infected tumor cells probably participates in the immunogenicity of cell death.

### Conclusion

MV is a promising oncolytic virus that is currently being evaluated in phase I/II clinical trials. Its capacity to induce ICD, which probably participates in its oncolytic activity, is now proven. However, more studies are needed to better understand which ICD pathway is induced in tumor cells after infection. Apoptosis induced by oncolytic viruses is very specific to the virus type [1] and may be different from one tumor cell line to another, since these cells accumulate defects in antiviral innate response and apoptosis pathways. Finally, all the studies on MV-induced ICD suggest that it would be of interest to monitor the antitumor immune response after treatment of cancer patients by oncolytic MV to determine its importance in the efficacy of treatment.

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