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Review

The therapeutic effect of death: Newcastle disease virus and its antitumor potential

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ABSTRACT

Programmed cell death is essential to survival of multicellular organisms. Previously restricted to apoptosis, the concept of programmed cell death is now extended to other mechanisms, as programmed necrosis or necroptosis, autophagic cell death, pyroptosis and parthanatos, among others. Viruses have evolved to manipulate and take control over the programmed cell death response, and the infected cell attempts to neutralize viral infections displaying different stress signals and defensive pathways before taking the critical decision of self-destruction. Learning from viruses and their interplay with the host may help us to better understand the complexity of the self-defense death response that when altered might cause disorders as important as cancer. In addition, as the fields of immunotherapy and oncolytic viruses advance as promising novel cancer therapies, the programmed cell death response reemerges as a key point for the success of both therapeutic approaches. In this review we summarize the research of the multimodal cell death response induced by Newcastle disease viruses (NDV), considered nowadays a promising viral oncolytic therapeutic, and how the manipulation of the host programmed cell death response can enhance the NDV antitumor capacity.

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1. Introduction

Programmed cell death maintains the homeostatic cellular balance under physiological conditions and it is also an essential component of the host defense against pathogens. Lack of regulatory control over the cell death program is one of the key factors behind the pathology of many diseases, including cancer (Igney and Krammer, 2002). In other cases, disease severity might be a direct effect of cell death induction, as it happens in many viral infections (Linkermann et al., 2014). On the other hand, it might be possible to take advantages of the intrinsic ability exerted by some pathogens to manipulate cell death responses. In that sense, the use of viruses in tumor therapy is one example of how to fight a human disorder using a potential pathogen (Bell and McFadden, 2014).

Newcastle disease virus (NDV), an avian paramyxovirus, has been extensively investigated for its use in cancer treatment (Zamarin and Palese, 2012). The inherent anti-tumor capacity of NDV combines two characteristics that delineate what can be defined as the oncolytic paradigm: NDV promotes the induction of tumor cell death accompanied by the elicitation of antitumor immunity.

In this review, we focused our attention on the different cell death responses displayed by NDV-infected cells and the new therapeutic strategies that have emerged to turn this cytopathic effect into an improved antitumor therapeutic response.

2. Newcastle disease virus: biology overview

Newcastle disease virus (NDV) is a highly contagious avian pathogen (Alexander et al., 2012; Ganar et al., 2014). NDV is classified as an avian paramyxovirus-1 (APMV-1) in the *Avulavirus* genus of the family *Paramyxoviridae* (Lamb and Parks, 2007). As other paramyxoviruses, NDV is an enveloped virus whose genome is negative-sense single-stranded RNA. The ssRNA(−) molecule is commonly 15,186 nucleotides long (Czegledi et al., 2006) and contains six open reading frames that encode six structural proteins: the nucleoprotein (NP), the phosphoprotein (P) and the large polymerase protein (L) are, in association with the viral RNA, the components of the ribonucleoprotein complex (RNP). The RNP not only exerts nucleocapside functions but also is the replication unit of the virus. The matrix protein (M) forms an inner protein layer below the inner leaflet of the viral membrane of the virion and participates actively during virus assembly and budding (Shnyrova et al., 2007). The hemagglutinin-neuraminidase (HN) and fusion (F) glycoproteins, in conjunction with a host-derived lipid bilayer constitute the external envelope of the virus and are responsible for viral entry (Villar and Barroso, 2006).

The infection of the host cells starts once the virus HN protein binds to its receptor, sialic acid (Lamb and Jardetzky, 2007). Receptor recognition by HN triggers the activation of the F protein that promotes fusion of the viral and cell membrane and allows the entry of the RNPs into the cytoplasm. Genome replication takes place in the cytoplasm and does not involve any DNA-intermediate stage: the genomic ssRNA(−) is transcribed into (1) messenger RNAs, that will be translated into the different viral proteins, and (2) antigenomic copies, or ssRNA(+), that will be used as template for genomic ssRNA(−) synthesis. Viral proteins and genomic RNPs are then assembled at the cytoplasmic inner leaflet of the host cell membrane and the new progeny of viral particles are released by budding. Last, the neuraminidase activity of the HN protein removes sialic acid residues from the nascent virions preventing their aggregation and facilitating viral spread within the infected tissue.

During the transcription of the P gene, the expression of two additional non-structural proteins, V and W, takes place as result of RNA editing (Steward et al., 1993). The V protein confers to NDV the capacity to evade the interferon response (Park et al., 2003b), interfering with STAT-mediated interferon signals. However, this interplay V-STAT-1 is species restricted and does not apply to mammalian cells. Hence the V protein is considered a major determinant of NDV host range (Park et al., 2003a).

NDV strains have been classified into three pathotypes, velogenic (highly virulent), mesogenic (intermediate virulence) and lentogenic (low-virulence or avirulent), in accordance to the severity of the disease displayed by the avian host (Dortmans et al., 2011). The cleavage site of the F protein is a major determinant of virulence: velogenic and mesogenic strains have a polybasic amino acid motif at the F cleavage site, 112R/G/KR-Q/K-K/R-R↓F117 that can be recognized and cleaved by ubiquitous furin-like proteases hence the F protein could adopt its mature form in the majority of infected cell types (Morrison, 2003). Lentogenic strains, in contrast, have a monobasic amino acid motif, 112GR/K-Q-G-R↓L117, that is cleaved by trypsin-like proteases in the extracellular space and hence their multicycle replication is restricted to specific tissues.

3. Cell death in response to NDV infection

Apoptosis has been identified as a major hallmark of NDV-mediated cytotoxicity in virus-infected cells. Multiple viral proteins have been found to influence cell death, some of which might be strain specific (Table 1). In addition, the susceptibility to undergo apoptosis in response to NDV infection is cell-specific and it is determined by the presence or absence of specific cell death regulatory factors. In that sense and in addition to apoptosis, other cell death pathways have been recently described to participate in the cellular response to NDV infection, especially in cancer cells (Table 2). Interestingly, some of these pathways are exploited by the virus to take control over the programmed cell death.

3.1. Apoptosis

Apoptosis is an evolutionary highly conserved physiological mechanism involved in the specific elimination of aging, harmed, infected or unnecessary cells. With critical implications both in development and in control of homeostasis, deregulation of apoptosis is a major contributor of important disorders as

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