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Harnessing Virus Tropism for Dendritic Cells for Vaccine Design

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Abstract

Dendritic cells (DCs) are pivotal stimulators of T cell responses. They provide essential signals (epitope presentation, proinflammatory cytokines, co-stimulation) to T cells and prime adaptive immunity. Therefore, they are paramount to immunization strategies geared to generate T cell immunity. The inflammatory signals DCs respond to, classically occur in the context of acute virus infection. Yet, enlisting viruses for engaging DCs is hampered by their penchant for targeting DCs with sophisticated immune evasive and suppressive ploys. In this review, we discuss our work on devising vectors based on a recombinant polio:rhinovirus chimera for effectively targeting and engaging DCs. We are juxtaposing this approach with commonly used, recently studied dsDNA virus vector platforms.

Introduction

DCs were initially identified after isolation from mouse spleen [1,2]. A role as professional antigen presenting cells emerged after DCs were found to express MHC II and to act as potent stimulators of lymphocytes [3]. While monocytes, macrophages and B cells also are capable of presenting antigens, DCs are estimated to be at least 100-times more efficient at stimulating leukocytes [3]. Therefore, DCs have since been established as the ‘sentinel of the immune system’.

DCs detect invading pathogens through sensors known as Pathogen Recognition Receptors (PRR) and they capture, process and present antigens (both endogenous and exogenous) to T cells. Antigen presentation in combination with cytokine release and co-stimulatory signals

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from DCs educate the generation of T cell responses. Depending on the cytokine release pattern and the co-stimulatory range, DCs can prime Th1-, Th2-, Th17-, cytotoxic CD8 T cell-, or tolerogenic responses such as regulatory T cells (T_{regs}) [4]. Antigen presentation in the absence of appropriate co-stimulation leads to tolerance and immune escape [5]. Because of the central role of DCs in priming of immune responses, a wide range of vaccination strategies have sought to target antigens and proinflammatory stimulation to DCs.

Viral vectors are particularly pertinent for this, because many viruses naturally infect DCs, enabling antigen delivery to DCs, and because viruses naturally provide the range of PRR engagement and proinflammatory stimuli DCs have evolved to respond to. In this review, we discuss fundamental obstacles of effectively targeting DCs with viral vectors and our approach to overcome them.

Viruses target DCs for infection and immune suppression

Given their central role in innate and adaptive antiviral immunity, many human pathogenic viruses have evolved to target host DCs for infection. Ostensibly, infecting DCs offers two advantages to viruses: 1. evade and suppress host antiviral immunity (see below); 2. exploit DC trafficking as a dissemination vehicle [6]. Natural DC targeting is prominent with all viruses commonly harnessed for therapeutic purposes, either as vectors or immunostimulatory agents in cancer immunotherapy. DCs sense viruses via a range of PRRs that detect pathogen signatures revealed during endocytosis or upon appearance of viral genomic material in the host cell interior, unleashing the innate antiviral response. This comprises PRR signaling to innate kinase assemblies TBK1 and IKKα:β; activation of IRF3 and NFκB transcriptional programs; proinflammatory cytokine induction; autocrine and paracrine cytokine signaling; induction of costimulatory molecules.

The innate antiviral response, e.g. in infected DCs, can provide the appropriate costimulatory context for generating T cell immunity. However, human pathogenic viruses have been shown to intercept this process at every conceivable step, ranging from mild immunomodulatory diversion to outright DC killing [7].

Viruses evade or antagonize innate and adaptive immunity

For most members of the human herpesvirus family elaborate immune evasive and suppressive relationships with DCs have been reported, exemplified by cytomegalovirus (CMV) [8] and herpes simplex virus 1 (HSV1) [9]. They evade detection by the host innate antiviral system, e.g. the cytoplasmic vDNA sensor cGAS [10-17] amongst other PRRs [16], and actively intercept signaling through the TBK1/IKKα:β innate kinase assemblies and downstream IRF3/NFκB transcriptional networks [18-21]. Human orthopoxviruses, exemplified by vaccinia virus (VACV), also target DCs [22] and evade host innate sensing [23,24]. This is accompanied by multiple viral strategies to intercept downstream innate antiviral signaling, e.g. blocking of TBK1 [25] and NFκB [26] through actions of the C6 and K1 viral gene products, respectively [26]. Also, the VACV proteins N1 and E3 were shown to inhibit type-I IFN production upon DC infection [27]. Orthopoxviruses express a vast array of viral proteins implicated in host immune evasion and suppression [28]; thus,

multiple other viral gene products (A46, A52, B15, K7) are known to interfere with innate immunity (reviewed in [29]). Adenoviruses evade innate sensing through the E1A oncogene product that blocks the cGAS-STING pathway [30], and inhibit IFN signaling by blocking histone ubiquitination [31], and via Virus-Associated (VA) RNA that inhibits the dsRNA-dependent protein kinase (PKR) [32].

Complimenting their elaborate strategies of evading and suppressing innate antiviral responses in infected DCs, herpesviruses (e.g. CMV [33] and HSV1 [34]), orthopoxviruses, e.g. VACV [35], and adenoviruses [32] encode arrays of immunomodulatory proteins that interfere with virtually every step of antigen processing and presentation [36], including: (i) inhibition of the immunoproteasome/antigen processing [37]; (ii) interference with the functions of the transporter associated with antigen processing (TAP) [38-40] or tapasin [41] in antigen loading; (iii) disruption of MHC I intracellular transport and interference with MHC I surface presentation [42]; (iv) downregulation of MHC I/II expression [43] or sequestration of β2 microglobulin [44]; (v) active MHC I degradation [45]. Moreover, these viruses also suppress the upregulation of costimulatory molecules and production of pro-inflammatory cytokines in DCs, e.g. blocked CD40, CD80, CD86 induction and active suppression of T/B cell activation by CMV [46-48], or absent CD40, CD86, CD83 and CCR7/CXCR4 induction [49] combined with a paucity of pro-inflammatory cytokines (IL-12, TNF-α, IL-6) resulting in poor T cell stimulation by DC infection with HSV1 [50]. Similarly, VACV actively suppresses the induction of maturation markers [22] and proinflammatory cytokine responses, e.g. type-I IFN [51], type-II IFN [52], TNF-α [53] and IL-1β [54] in infected DCs.

In contrast to human pathogenic dsDNA viruses with their sizeable genomes encoding for arrays of complimentary immunomodulatory factors, the extreme genetic austerity of enteroviruses (EV) [55] does not permit elaborate immune evasion and suppression strategies. Yet, even EVs have the capacity to interfere with host innate immune activation and DC function. They accomplish this through simple but effective means of overwhelming their host cells without a need for specialized immunomodulatory proteins.

The flagship EV, poliovirus (PV), infects DCs/antigen-presenting cells *in vivo* [56] and destroys them effectively [57]. EVs target viral translation and replication to a privileged site at the endoplasmic reticulum [58,59], providing relative shelter from PKR-mediated eIF2α (S51) phosphorylation and, possibly, other innate antiviral events [59]. Viral m^7G ('cap')-independent translation via internal ribosomal entry sites (IRESs) provides a highly efficient means for immediate early translation of incoming viral genomic RNA [60,61]. The first viral protein released, via co-translational autocatalytic processing [62], is the viral $2A^{pro}$ protease (Fig. 1). Autocatalytic release of $2A^{pro}$ not only provides the essential cleavage of the P1 and P2 precursors for processing of the viral polyprotein [63], but also is the virus' main agent for subverting the host cell innate antiviral program [64]. A proteolytic program directed by $2A^{pro}$ degrade the central scaffold of the translation initiation apparatus, eukaryotic initiation factor (eIF) 4G [65], and the nuclear pore complex [66], thereby broadly suppressing gene expression in infected host cells. Simultaneously, the 'viral cytotoxic program', dependent on immediate early viral translation of $2A^{pro}$, is antagonized

by detection of vRNA signatures in the host cell interior triggering an early innate host response (Fig. 1).

Viral vectors and the problem of intrinsic immune evasion and suppression

Given the prevalence of viral immune evasion and suppression strategies targeting DCs, what is the status of devising viral immunization vectors—based on diverse families of viruses—to overcome them? Vectors delivering simian immunodeficiency virus (SIV) signatures based on Rhesus macaque CMV (RhCMV), attenuated through fibroblast adaptation analogous to the TOWNE and AD169 live attenuated CMV strains [67], yielded atypical antigen presentation with unconventional, Class II/MHC-E restricted CD8 T cell responses against non-canonical epitopes [68]. RhCMV vector vaccination achieved outstanding results in Rhesus SIV challenge models [69]. However, clinical studies with human fibroblast-adapted (hybrid TOWNE) CMV strains revealed conventional CD8 T cell responses in humans, suggesting that Rhesus species-specific features are the likely cause for the unconventional T cell response to RhCMV vector immunization [70].

Poxvirus vector platforms include VACV [71], MVA (Modified Vaccinia Ankara) or avipox-based agents such as ALVAC (Canarypox) [72], which are replication-incompetent in mammalian cells. MVA, a result of serial passage of VACV (Ankara) in avian cells [73], carries deletions with some immunomodulatory gene loss [74]. Yet, recent studies with *inactivated* MVA as an intratumor immune stimulatory agent in mouse tumor models yielded better antitumor responses and pro-inflammatory cytokine production than live MVA [75], suggesting that MVA immune evasion/suppression limits the effectiveness of viral adjuvancy. In fact, MVA retains expression of the soluble IL-1β decoy receptor [54] and the viral C6 inhibitor of IRF3/7 phosphorylation [76]. Deletion of these genes from MVA led to enhanced activity as a T cell adjuvant in mice [76,77]. Immunization with an ALVAC-based vector plus recombinant HIV gp120 subunit boost yielded promising early results [78], but failed in a subsequent, pivotal trial (https://niaid.nih.gov/newsevents/experimental-hiv-vaccine-regimen-ineffective-preventing-hiv).

New prototype Adenovirus vectors based on chimpanzee Ad (ChAd) strains, to circumvent the problem of human preexisting anti-Ad neutralizing immunity, demonstrated promising results with the generation of humoral and T cell responses against Ebola [79,80]. Registration trials of this approach are ongoing [81]. ChAd3 is replication-defective with viral E1/E3 gene deletions; E1 and E3 Ad gene products have immune modulatory properties, but even E1/E3-deleted Ad vectors inhibit T cell proliferation due to vector targeting of DCs [82].

Thus, balancing viral replication-dependent epitope expression with virus-mediated immune evasion is likely critical towards developing efficacious viral vector platforms.

We recently designed a recombinant PV viral vector prototype with a peculiar, unexpected potential to engage DCs [83]. This approach has the disadvantage of coding capacity restrictions due to the small (~7.4kB) size of the PV genome, and the inherent genetic instability of (+)ssRNA viruses [84]. However, it has the advantage of robust DC co-

stimulation, in the absence of apparent viral immune suppressive or evasive strategies [83] (Fig. 2). Our strategy is based on the highly attenuated rhino:poliovirus chimera PVSRIPO, the type 1 live attenuated poliovirus (SABIN) vaccine replicating under control of a heterologous human rhinovirus type 2 (HRV2) IRES [85]. PVSRIPO, in non-vector form [86], is being employed as an effective cancer immunotherapy intervention that has safely been used by high-dose intracerebral inoculation in >150 patients with recurrent glioblastoma [87], including children. PVSRIPO has lower basal virulence compared to its type 1 SABIN vaccine precursor due to a—naturally evolved—lower propensity of the HRV2 IRES to recruit host 40S ribosomal subunits [88]. This phenotype is engrained in the structure of the HRV2 IRES stem loop domains V and VI, which harbor the footprint of the eIF4G:4A:4B translation initiation helicase on all EV IRESs [85,89-96].

There are 3 known sites of productive poliovirus propagation in humans: an unknown population of cells within the enteric tract epithelium [97], spinal cord anterior horn motor neurons [98,99], and $CD11c^+$ DCs/macrophages [56]. PVSRIPO's phenotype in the enteric tract is unknown. The finding that PVSRIPO's growth potential in primary explant human renal epithelial cells is lower than type 1 poliovirus (SABIN) [88] suggests a similar scenario for enteric epithelial cells. PVSRIPO has profound neuron-specific incompetence [88], due to a ribonucleoprotein complex forming at the foreign HRV2 IRES in neuronal cells that intercepts eIF4G binding/40S subunit recruitment [100,101]. Similarly, in contrast to wild type PV or the SABIN vaccines [57], PVSRIPO infection is non-cytopathogenic in DCs [102]. Rather, viral translation is sluggish and transitory, and $2A^{pro}$ mediated cleavages of host proteins, e.g. eIF4G, do not occur [83,102]. Yet, low-level viral propagation in infected DCs is surprisingly durable, with lingering replication ongoing for several days [83]. Sublethal PVSRIPO vector infection of DCs produces a constant source of vector-encoded antigen expressed in DCs that is presented via the classical pathway [83].

We hypothesize that PVSRIPO's intrinsically lowered capacity for recruiting host cell translation machinery tips the balance in favor of the host innate antiviral response (Fig. 1). This is the reason for a potent, sustained innate inflammatory response with type-I/III IFN-dominant inflammation in PVSRIPO-infected DCs, accompanied by upregulation of co-stimulatory molecules CD40, CD80, CD86 and CCR7 [83,102] (Fig. 2). Due to HRV2 IRES recombination, delaying immediate early translation and autocatalytic release of $2A^{pro}$, PVSRIPO lacks any capacity to intercept or suppress innate antiviral immunity in infected DCs, [103]. We have devised a sophisticated strategy to derive genetically stable vector prototypes through recombination with foreign inserts in the viral 5' untranslated region [83].

Conclusions

The main attraction of viral vectors devised for immunization purposes is their capacity to provide the natural, evolved costimulatory signals needed to generate effective T cell immunity. This valid objective has to contend with the elaborate, pernicious strategies of viruses to evade and suppress host innate and adaptive immunity, in large part achieved by targeting DCs directly. In this review, we discuss our strategy of harnessing recombinant PV

for vector use, based on a peculiar host relationship in human DCs providing for a proinflammatory pattern with ideal costimulatory properties (Fig. 2).

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Highlights

- Dendritic cells are central protagonists in viral vector immunization approaches
- Many viruses naturally target dendritic cells for immune suppression
- Viral vector-mediated immune suppression intercepts innate and adaptive immunity
- Recombinant poliovirus unfolds peculiar non-cytopathogenic relations with dendritic cells
- These result in profound dendritic cell engagement for co-stimulation of T cell immunity

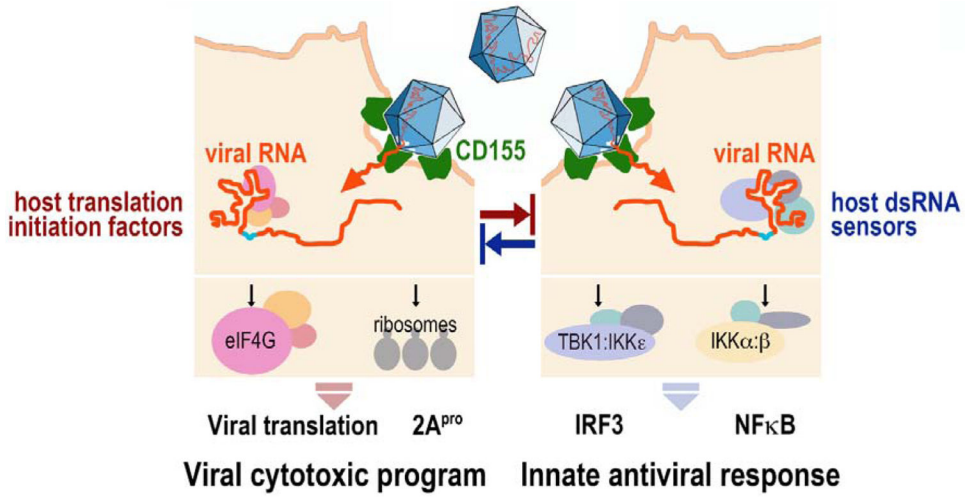

Figure 1.

Enterovirus 5' m^7G-cap independent translation via its IRES drives viral translation and a cytotoxic program unleashed by immediate early release of $2A^{pro}$. Simultaneously, vRNA signatures are detected by host cell dsRNA sensors that initiate the host innate antiviral response. The outcome of the infection is determined by the balance of viral, IRES-mediated translation vs. host sensing of incoming vRNA templates.

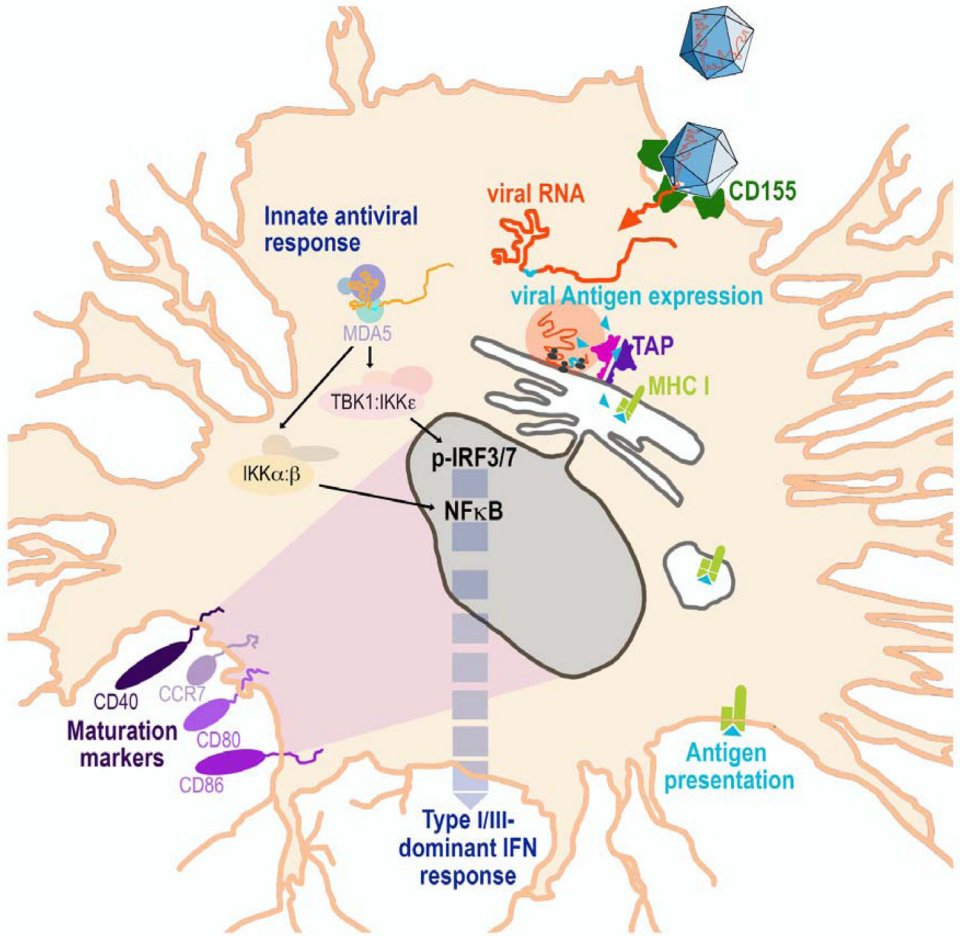

Figure 2.

Illustration of PVSRIPO's peculiar host relationship with DCs (see [83] for context). Polioviruses naturally target DCs/macrophages via CD155. PVSRIPO-based vectors express encoded antigens internally, for presentation via the classical pathway. Marginal, ongoing viral propagation provides a steady supply of antigen, but subdued viral translation is insufficient to damage the host. Potent, sustained type-I/III IFN-dominant inflammation induces maturation markers and profuse cytokine release.