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REVIEW

Adenovirus receptors on antigen-presenting cells of the skin

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Abstract

Skin, the largest human organ, is part of the first line of physical and immunological defense against many pathogens. Understanding how skin antigen-presenting cells (APCs) respond to viruses or virus-based vaccines is crucial to develop antiviral pharmaceutics, and efficient and safe vaccines. Here, we discuss the way resident and recruited skin APCs engage adenoviruses and the impact on innate immune responses.

KEYWORDS

adenovirus, antigen-presenting cells, innate immunity, receptors, skin, vaccination

INTRODUCTION

Skin

The skin is the body's first physical barrier against external elements. It is structurally composed of the epidermis, dermis, and hypodermis, each with distinct roles. The epidermis, the outer layer of the skin, can be further divided in four to five layers and contains epithelial cells, melanocytes, keratinocytes, Merkel cells, and resident professional antigen-presenting cells (APCs), including Langerhans cells (LCs). LCs are skin-resident myeloid cells, derived from primitive erythro-myeloid progenitors from the yolk sac and fetal liver. Postnatal self-renewal of LCs is via myeloid precursors that restore the population following an inflammatory response. The dermis is typically thicker and contains fibroblasts, macrophages, and mast cells that are surrounded by fibrous proteins including collagen and elastin, which make up the extracellular matrix. The mechano- and thermoreceptors found in the dermis are involved in the detection of changes in pressure and temperature, respectively, and breaches in homeostasis. In contrast to the epidermis, the dermis is vascularized and contains lymphatic vessels, which allow the emigration of resident APCs to the lymph nodes and recruitment of circulating immune cells to the site of inflammation or infection. Finally, the hypodermis contains fibroblasts, macrophages, and adipocytes, which are a major site of fat storage in the body.

When pathogens create a breach in skin homeostasis, the APCs detect pathogen-, or damage-associated molecular patterns (PAMPs and DAMPs) through pattern recognition receptors (PRRs) on the cell surface, in the cytoplasm, in cytoplasmic vesicles, or even in the nucleus (Lee, 2007). These events induce APCs to release cytokines/chemokines that recruit immune cells via the lymphatic and vascular systems (Hamilos, 1989; Takeuchi & Akira, 2010). Local cytokine secretion also induces neighboring and recruited dendritic cells (DCs), macrophages, LCs, and B lymphocytes to upregulate the expression of major histocompatibility complex (MHC) class II molecules. Eventually, maturing APCs migrate to the secondary lymphoid organs to present antigens to naive $CD4^+$ T lymphocytes (Figure 1). By this mechanism, APCs link the innate immune responses to the establishment of adaptive, antigen-specific memory immunity.

Adenoviridae

Adenoviruses (AdVs) are nonenveloped, icosahedral particles containing a linear double-stranded DNA genome of 34 ± 8 kilobase pairs. Human AdVs (HAdVs), that is, those that have been isolated initially from

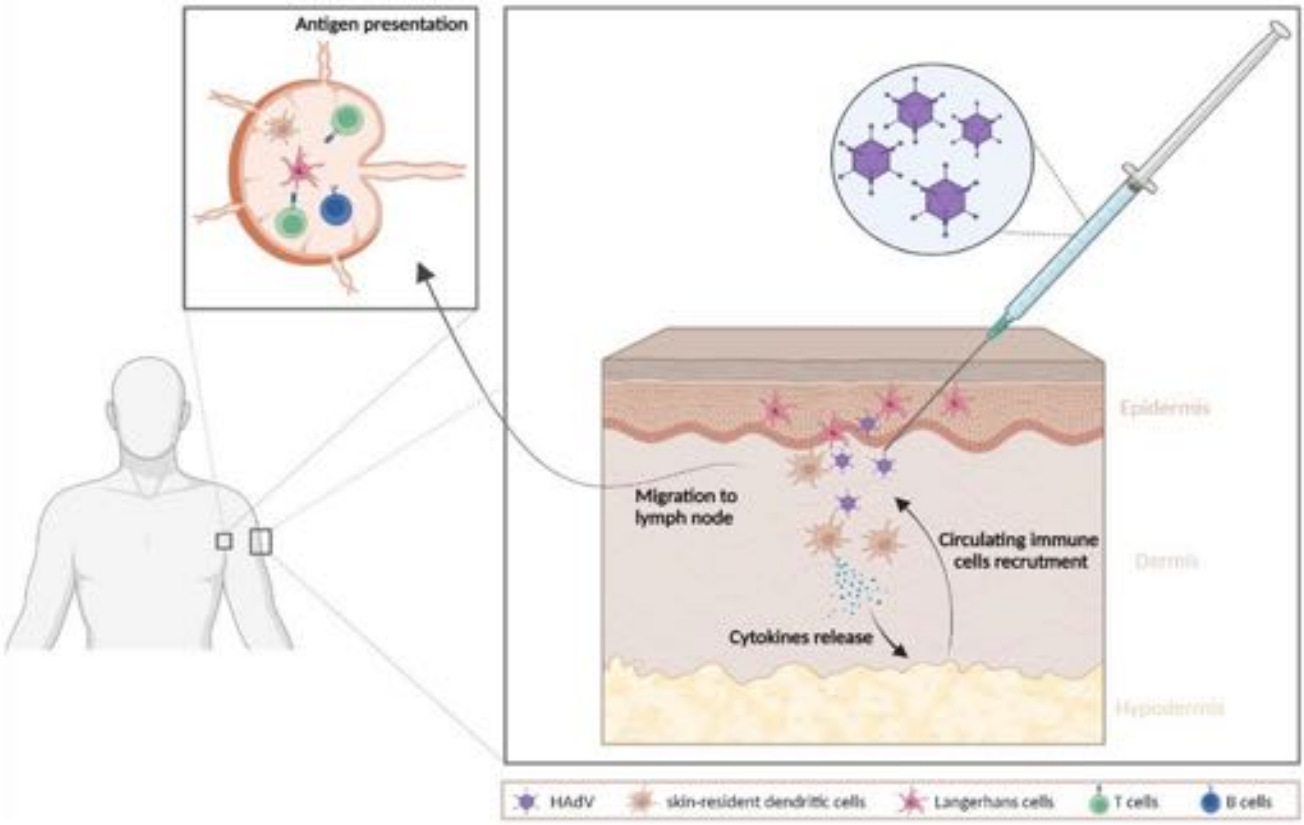

FIGURE 1 Schematic representation of the potential role of skin-resident DCs and LCs in enhancing innate immunity and initiating adaptive immunity during intradermal injection of adenovirus vectors. DC, dendritic cell; LC, Langerhans cell

humans, were initially described almost 70 years ago (Rowe et al., 1953). HAdVs belong to the family *Adenoviridae* and genus *Mastadenoviridae*, and are divided into seven species (A to G), representing more than 110 "types" classified by serological or genetic criteria (Harrach & Benkő, 2021). HAdV-induced disease tends to follow a pattern based on species: species A causing gastrointestinal, respiratory, and urinary infections; species B causing gastrointestinal, respiratory, urinary tract, and occular infections; species C can be responsible for gastrointestinal, respiratory, urinary, and liver infections; species D (which contains the largest number of types) typically causes occular and gastrointestinal infections; species E results in occular and respiratory infections; and finally, species F and G are responsible for gastrointestinal infections. Although HadV infections in humans are generally self-limiting, infections can be fatal in immunocompromised individuals (Lion, 2014).

The external part of the capsid is composed of multiple proteins, including hexon, penton, pIX, and fiber. The most striking morphological difference between AdV types is the length and flexibility of the homotrimeric fibers. The fiber shaft length varies from 6 to 23 beta-repeats (1 repeat = ∼14 aa) (Chroboczek et al., 1995) and the number of hinges can be 0–2 (Schoehn et al., 2008). Both characteristics likely impact tissue/cellular tropism in a handful of ways that are not completely characterized (Lasswitz et al., 2018), including the ability to simultaneously engage multiple receptors, synergize affinity and avidity, and access integrins that can aid internalization. Although rare, some AdV types can have two fibers of different lengths and receptor binding capabilities (Hung-Yueh et al., 1994; Lenman et al., 2015; Nakamura et al., 2003). Thus, the interaction of cell surface proteins with HAdVs is rarely binary and the multiple points of interactions certainly affect uptake (Arnberg et al., 2002b; Burmeister et al., 2004).

In view of the dynamic process cells, and specifically APCs, bind the hundreds of AdV types, we present a description of the high and low affinity interactions that are relevant to cells of the skin.

RECOGNIZED ADV RECEPTORS

Understanding how HAdVs interact with APCs increases our ability to treat HAdV-induced diseases and better exploit AdV-based vaccines and vectors. With respect to human and non-HAdV-based vaccines and vectors, in some cases, it will be advantageous to choose an AdV type that will be poorly taken up by APCs, or generate a

robust innate immune response (Sprangers et al., 2003; Weaver & Barry, 2013; Zhu et al., 2020).

In many instances, specific proteins on the cell surface determine their ability to bind viruses. In the case of AdV–protein interactions, the affinity can be relatively high (nanomolar range), or low (micromolar) and be compensated by increasing avidity.

CAR (coxsackievirus and adenovirus receptor)

CAR, encoded by *CXADR*, is a 46-kDa type 1 transmembrane protein whose prototypic role is as a cell adhesion molecule (CAM) (Loustalot et al., 2016). Present on the surface of many mammalian and non-mammalian cells, CAR plays a role in the integrity of many organs, and a particularly critical role during mouse heart development (Lisewski et al., 2008). Indeed, prototypic functions of CAMs help maintain interactions between cells, and between cells and the extracellular matrix (Cavallaro & Dejana, 2011). As the name suggests, CAR is an attachment molecule for coxsackieviruses (subgroup B) and some human and nonhuman (e.g., canine type 2) AdVs, with a notable exception of species B HAdVs (Bergelson et al., 1997; Roelvink et al., 1998; Soudais et al., 2000). Of note, the use of CAR has recently been implicated in species E HAdV uptake (Tsoukas et al., 2022). AdV attachment to high affinity receptors is typically, but not exclusively, mediated by the fiber knob (Louis et al., 1994). The extracellular N-terminal domain (D1) of CAR interacts with the trimeric fiber knob (Bewley et al., 1999; Howitt et al., 2003; Philipson et al., 1968; Seiradake et al., 2009). The interaction of the RGD motifs of the penton base with integrins can increase internalization efficacy in some cell types (Nemerow & Stewart, 1999; Storm et al., 2017; Wickham et al., 1993).

Of note, monocytes, and monocyte-derived, myeloid, and plasmacytoid DCs (moDC, mDC, pDC, repectively) are CAR-negative (Chéneau et al., 2021; Eichholz et al., 2016; Soudais et al., 2000; Tran et al., 2018, 2021). Exceptions to this trend of CAR-negative immune cells are LCs and dermal DCs (Adams et al., 2009). Blocking CAR with a monoclonal antibody had no effect on the percentage of HAdV-C5 infection in circulating immune cells, while it significantly decreased, but did not eliminate, the infection in resident cells isolated from the skin. These data suggest that dermal DCs and LCs take up HAdVs via one or more receptors (Adams et al., 2009). On a side note, CAR – "free" fiber interactions can also aid virus spread: some CAR-binding HAdVs produce excess fiber during propagation. The excess fiber can either bind CAR in the cytoplasm during its trafficking, or the fiber can be released from the cell and disrupt epithelial cell tight junctions allowing HAdVs to access the inner cell layers (Coyne & Bergelson, 2005; Walters et al., 2002). It is unknown if this potentially "pro-viral" phenomenon occurs during AdV infections in the skin.

Cluster of differentiation 46 (CD46)

CD46 is a type I transmembrane protein present on the surface of all nucleated human cells (N.B. mice do not express CD46). It is involved in the regulation of the complement system (Liszewski et al., 1996) and in cross-talk with other PRRs, such as Toll-like receptors (TLRs) (Cardone et al., 2011). In addition to being a receptor for species B HAdVs, CD46 is a receptor for bovine viral diarrhea virus and human herpesvirus 6 (Maurer et al., 2004; Santoro et al., 1999). CD46 contains four complement control protein (CCP) domains, of which CCP1 and CCP2 form the HAdV binding site (Gaggar et al., 2003; Wu et al., 2004). Despite the numerous studies, its role as a receptor for species B HAdVs is still evolving. While some studies describe an interaction with all species B HAdVs (Gaggar et al., 2003) via the fiber knob, others limited this interaction with only some HAdV types, including B3 and 7 (Fleischli et al., 2007; Segerman et al., 2003; Sirena et al., 2004; Wang et al., 2007), -D37 and -D49 (Lemckert et al., 2006; Wu et al., 2004) and possibly -D26 and -D56.

As HAdV–CD46 interactions are reportedly low affinity, the level and location of CD46 on the cell surface likely influence the avidity, which should influence whether cells can take up species B HAdVs (Marttila et al., 2005; Trinh et al., 2012). HAdV-D26, currently used as a vaccine vector due to its low seroprevalence in Europe and North America (Mennechet et al., 2019), interacts with CD46 via hexon (Persson et al., 2021; Hemsath et al., 2022). Of note, CD46 can help deliver species B HAdVs toward vesicular TLR9 in macrophages and DCs (Iacobelli-Martinez & Nemerow, 2007). TLR9 engagement upregulates MHC II expression and the production of pro-inflammatory cytokines.

Desmoglein 2 (DSG2)

Given the complexity of species B HAdV–cell interactions, and the recurrent fact that not all the receptors had been identified (Tuve et al., 2006), the Lieber lab continued the search for host proteins involved in their uptake. DSG2 was identified in 2011 as a receptor for a subset of species B types (-3, -7, and -14) responsible for respiratory infections, and HAdV-B11, which is responsible for kidney and urinary tract infections (Wang et al., 2011, 2013). DSG2, an ~100-kDa highly posttranslationally modified member of the cadherin family, is located in cell–cell junctions, particularly in epithelial tissues and the heart (Chitaev & Troyanovsky, 1997). The identification of DSG2 inspired a reclassifi-

TABLE 1 Classification of some species B HAdVs according to their receptor engagement

Type	Receptor(s)	Subgroup
HAdV-B3	Desmoglein 2	II
HAdV-B7	Desmoglein 2	II
HAdV-B11	CD46 and Desmoglein 2	III
HAdV-B14	Desmoglein 2	II
HAdV-B16	CD46	I
HAdV-B21	CD46	I
HAdV-B35	CD46	I
HAdV-B50	Desmoglein 2	I
HAdV-B55	CD46	II

CD, cluster of differentiation; HAdV, human adenovirus.

cation of species B HAdVs according to their receptor engagement (Table 1).

An emerging HAdV type, -B55, has high affinity (nM range) interaction with DSG2 (Feng et al., 2020; Zhang et al., 2021). Indeed, blocking DSG2 decreases HAdV-B55 infection of human cells, and the expression of human DSG2 in transgenic mice induced a significant increase in HAdV-B55 uptake. It is currently unknown whether the low levels (4 nTPM [normalized transcript per millions]) found on dermal DCs and LCs (https://www.proteinatlas.org), are sufficient for HAdV binding or uptake.

Integrins

Integrins are class 1 transmembrane heterodimers (α and β chains) that interact with the extracellular matrix and/or neighboring cells (Doyle et al., 2022). At least 23 different integrin heterodimers have been identified on multiple cell types, and these combinations influence their function and ligand. One of their prototypic roles is adhesion, however integrin engagement and activation also induces signal transduction that influences the cell cycle, cytoskeleton organization, and cell surface proteins (Ginsberg, 2014).

HAdV–integrin interactions are typically low affinity. Prototypic HAdV–integrin interactions occur through an arginine–glycine–aspartic acid motif found in a protruding loop of the penton base. In some cases, binding to a high affinity receptor may be a pre-requirment for efficient uptake (Kremer & Nemerow, 2015). Integrin $\alpha_M\beta_2$ (CD11b/CD18) was reported to be responsible for the binding and uptake of HAdV-C2 by hematopoietic cells (Huang et al., 1996). While integrin $\alpha_V\beta_5$ (CD51) appears to interact with species A and E (Mathias et al., 1998), and may be involved in species B (Summerford et al., 1999) and species C (Lyle & McCormick, 2010) binding, $\alpha_V\beta_1$ and $\alpha_3\beta_1$ integrins (CD49c/CD29) are low affinity coreceptors for species C HAdVs (Li et al., 2001; Salone et al., 2003). $\alpha_V\beta_3$ (CD61) also has a role in interaction with HAdV-D26 (Nestić et al., 2018), as do CD49c/CD29 and $\alpha_V\beta_1$ with HAdV-D37 (Storm et al., 2017). Importantly, the majority of HAdVs interact via α_V integrins (Arnberg et al., 2000) which are expressed by LCs. HAdV-D56 and HAdV-F40, -F41 are the exceptions, as they bind to α7- and α6-containing integrins (Duffy et al., 2018; Rajan et al., 2018), respectively.

Cluster of differentiation 80 and 86 (CD80 and CD86)

CD80 and CD86, also known as B7.1 and B7.2, respectively, are type 1 membrane proteins of the immunoglobulin superfamily (Freeman et al., 1989; Lanier et al., 1995). CD80 and CD86 are costimulatory molecules expressed on the surface of mature dermal DCs and LCs, which, when in contact with $CD28^+$ T cells, induce their activation and survival (Bar-On et al., 2011; Caux et al., 1994; Zheng et al., 2004). CD80 and CD86 appear to be low affinity attachment molecule, via the fiber knob, for some species B HAdVs (Short et al., 2004, 2006).

IMPACT OF POST-TRANSLATIONAL MODIFICATIONS OF CELL-SURFACE PROTEINS

Post-translational modification of cell surface proteins can also play a role in virus binding by generating low affinity (micro- to millimolar), but high avidity, interactions that increase the ability of cells to take up HAdVs.

Sialic acids

Sialic acids (SAs), a collection of ~50 different sugars with a 9-carbon base, are present on all glycosylated proteins on the cell surface. Functionally, SAs modifications can be protectors of proteins, or represent the signal that induces phagocytosis of dead cells.

Cells use SAs to take up of influenza, rota-, corona-, and polyoma viruses (Delorme et al., 2001; Isa et al., 2006; Schwegmann-Weßels & Herrler, 2006; Springer et al., 1969), as well as some species D HAdVs (types 8, 19, 26, 37, 53, and 64) (Arnberg et al., 2000; Baker et al., 2019). The law of parsimony would suggest that, because SAs are so abundant on cells from so many organisms, using it as an attachment molecule would give some viruses an evolutionary advantage via a large host range.

Of note, HAdV capsid–SA interactions are typically low affinity and charge dependent. For example, the positively-charged HAdV-D37 knob interacts with SAs, while the neutrally charged D19p knob does not (Arnberg et al., 2002a; Burmeister et al., 2004). This principle of charge-dependent HAdV–SA interactions is similar to

that of the above viruses (Delorme et al., 2001; Springer et al., 1969). Of note, the CAV-2 knob has an SA binding site, which may mediate CAV-2 capsid interactions with SAs present on human erythrocytes (Seiradake et al., 2009). HAdV-G52, isolated from a patient with gastroenteritis and the first member of the species G, is also taken up by some cells via SAs interactions (Lenman et al., 2015, 2018). Thus, ubiquitous SAs could provide skin APCs (whose surface SAs changes during differentiation and activation) a means to engage HAdVs (Crespo et al., 2009). ST8 α-*N*-acetyl-neuraminide α-2,8-sialyltransferase 4 (ST8SIA4) is highly expressed LCs, while ST3 β-galactoside α-2,3-sialyltransferase 2 (ST3GAL2) is the most expressed in dermal DCs. Concomitantly, α2,8-sialylated glycoproteins are the most present in LCs, while the SAs in α2,3 linkage are most abundant in DCs.

HSPG (heparan sulfate proteoglycans)

Polysaccharides of the glycosaminoglycan (GAG) family are present on the surface of all cells and the extracellular matrix, have numerous roles including the recruitment of immune cells and the maturation of APCs (Kodaira et al., 2000). GAG are therefore a "natural" adjuvant (Collins & Troeberg, 2019). Consequently, HSPGs are present on LCs (19 nTPM) but expressed more weakly in dermal DCs (3 nTPM) according to single cell RNAseq on the human protein atlas database (HPA) (https://www.proteinatlas.org). HSPG-species B and C HAdV interactions are low affinity, and similar to SAs, likely influence uptake by avidity. Chinese hamster ovary (CHO) cells constitutively expressing HSPGs more efficiently take up HAdV-C2 and -C5 (Dechecchi et al., 2001) and -B3 and -B35 (Tuve et al., 2008). However, HSPG interactions were not necessary for HAdV-C5 to be taken up by hepatocytes in vivo (Zaiss et al., 2015).

Generally, HAdV–HSPG interaction is via the knob domain. However, HAdV-B35 engagement appears to be via an undetermined capsid protein. HSPGs also interact with the short fiber protein of HAdV-F40 and -F41 (their long fiber proteins interact with the CAR) (Rajan et al., 2021). Because skin APCs contain significant levels of HSPGs, they are unlikely involved in interactions with species B, C and F HAdVs. Finally, an HSPG-binding site (KKTK) in the fiber shaft of some HAdV types may be involved in cell engagement (Nicol et al., 2004; Smith et al., 2003).

PATTERN-RECOGNITION RECEPTORS

In the skin, conventional DCs, macrophages, and LCs are among the first APCs impacted during vaccinations (Banchereau & Steinman, 1998). While they possess some of the abovementioned high and low affinity HAdV receptors, they are also equipped with scavenger receptors (SRs) and C-type lectin receptors (CLRs), which are specialized in pathogen uptake. Moreover, TLRs, the quintessential PRRs, can be involved in HAdV internalization in surprising ways.

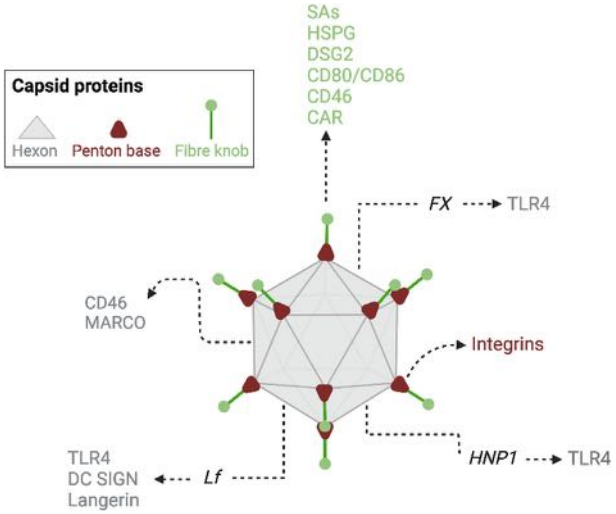

FIGURE 2 Global APCs receptors and coreceptors – HAdVs capsid proteins interactions. Lf, HNP1, and FX are extracellular factors which can mediate certain APCs–HAdVs interactions. HAdV, human adenovirus; APC, antigen-presenting cell; CAR, coxsackievirus and adenovirus receptor; DC SIGN, cluster of differentiation 209; Langerin, cluster of differentiation 207; CD46, cluster of differentiation 46; CD80/86, cluster of differentiation 80 and 86; DSG2, desmoglein 2; FX, factor X; HAdV, human adenovirus; HNP1, human neutrophil protein 1; HSPG, heparin sulfate proteoglycans; Lf, lactoferrin; MARCO, macrophage receptor with collagenous structure; SA, sialic acid; TLR4, toll-like receptor 4

Two HDPs (host defense proteins) are involved in APCs–HAdVs interactions (Figure 2) by binding PRR on APCs and hexon on HAdVs. HDPs are effector molecules of the innate immune system and act via antibiotic-like properties against numerous bacteria and viruses (Brice & Diamond, 2020; Jenssen & Hancock, 2010). Epithelial cells and neutrophils are a rich source of HDPs: ~20% of the cytoplasmic content of neutrophils can be HDPs (Calabro et al., 2011; Moretta et al., 2021). Lactoferrin (Lf), an 80 kDa globular protein present in mucus and most body fluids, and HNP1(human neutrophil protein 1), an α-defensin, have anti-viral activities (Berlutti et al., 2011; Van der Strate et al., 2001).

TLR4

Most of us initiatially think of virus–receptors interactions as binary: a cellular protein and a capsid protein bind, then other interactions may occur to help internalize the capsid. Yet, in the case of HAdVs, soluble host proteins play important roles (Chéneau et al., 2021; Chéneau & Kremer, 2020; Eichholz et al., 2022). Some TLRs are present on the plasma membranes of resident and cir-

culating APCs and recognize an array of DAMPs and PAMPs (Essakalli et al., 2009). TLR4 is the most thoroughly characterized PRR, whose prototypic ligand is lipopolysaccharides from gram-negative bacteria. The initiation of the innate immune response is linked to the signaling cascade that passes through MyD88 and NFkB and leads to the production of pro-inflammatory cytokines (Saikh, 2021).

While a direct interaction between TLRs and HAdVs has not, to the best of our knowledge, been detected, TLR4 is involved in HAdV capsid uptake in APCs via bridges made up of HDPs (Adams et al., 2009; Chéneau et al., 2021; Chéneau & Kremer, 2020; Eichholz et al., 2022). Lf is capable of enhancing the uptake of viruses by initially binding to epithelial cells (Marchetti et al., 2004) or directly to viruses (Swart et al., 1996). Lf was first implicated in species C HAdV uptake by epithelial cells by Arnberg and coworkers (Johansson et al., 2007).

In epithelial cells, α-defensins impair HAdV-C5, -A12, and -B35 infection by stabilizing an intrinsically disordered region of the capsid vertex and thus prevent the disassembly of the metastable HAdV capsid (Flatt et al., 2013; Nguyen et al., 2010; Smith & Nemerow, 2008). However, in APCs, Lf and HNP1 act as bridges between HAdV-C5, -D26, and -B35 and TLR4, and increase uptake by a hexon-based interaction (Chéneau et al., 2021; Eichholz et al., 2022).

Interestingly, in contrast to monocyte-derived DCs, human LCs from the skin, monocyte-derived LCs and dermal DCs do not (or only weakly) express TLR4 on their surface (van der Aar et al., 2007) but Lf still appears to increase HAdV uptake.

Coagulation factor X (FX) is produced by the liver and present in blood. The ability of coagulation factors to bind HAdVs and modify their tropism in mice has been well described (Baker et al., 2013). The anchor point is the hypervariable loops on hexon, which is the most abundant protein present on the HadV capsid (Kalyuzhniy et al., 2008; Waddington et al., 2008). Doronin et al. (2012) also showed that in mice, murine FX binds to some HadV types and acts as a bridge to TLR4 to increase uptake. However, this mechanism could not be reproduced using human FX, HadVs, and human APCs (Eichholz et al., 2015).

MARCO (macrophage receptor with collagenous structure)

MARCO, an SR, is a membrane protein whose prototypic function is recognition of bacteria (Elomaa et al., 1995) and certain enveloped viruses (Fierro et al., 2022; MacLeod et al., 2013; Macleod et al., 2015).

Of note, MARCO can also regulate immune responses by blocking TLR activation (Kissick et al., 2014) and is involved in the detection of HadV in mice (Maler et al., 2017; Stichling et al., 2018). Indeed, $MARCO^+$ murine alveolar macrophages were significantly more efficient at taking up some species C HadVs than MARCO-deficient bone marrow-derived macrophages. The presumably low affinity contact between HadV and MARCO takes place via hexon (Maler et al., 2017; Stichling et al., 2018). While no studies seem to have been conducted in human cells or tissues, it is possible that this observation is relevant as MARCO is present on the surface of human monocyte-derived DCs (Matsushita et al., 2010). Of note, MARCO is expressed (47 nTPM) in skin LCs (https://www.proteinatlas.org).

DC SIGN (CD209)

DC SIGN, also known as CD209, is a member of the CLR family and binds mannose groups with high affinity (Gao et al., 2020; Rahimi, 2020). CLRs are involved in tumor recognition, mannose recognition, and antigen presentation. DC SIGN is present on the surface of circulating and tissue-resident DCs. CLRs are also involved in viral responses as it has been described as a receptor for a variety of viruses (Feng et al., 2004; Geijtenbeek et al., 2000; Geijtenbeek & Van Kooyk, 2003; Lozach et al., 2011; Simmons et al., 2003; Tassaneetrithep et al., 2003). Some APCs use DC SIGN to take up HadV-C5 via the above-mentioned Lf bridge (Adams et al., 2009; Günther et al., 2011).

Langerin (CD207)

Similar to DC SIGN, langerin is a CLR that can be used to engage viruses (De Witte et al., 2007; Ng et al., 2015). This transmembrane protein is strongly expressed in LCs and some DCs. Langerin is associated with a unique intracellular structure dubbed "Birbeck granules," which are supposedly involved in antigenic peptide priming on MHC II. Our unpublished results suggest that monocyte-derived LCs, which do not express CAR (unlike the skin-resident LCs), take up HadV-C5 and -D26. However, transient expression of langerin on CHO cells did not induce a significant increase in uptake. These data do not exclude the possibility that langerin is an attachment molecule, or that it is linked to HadV internalization. Whether langerin behaves like DC SIGN and can take up HadVs via a bridging factor is unknown.

CONCLUSION AND PERSPECTIVES

Human and non-HAdVs are among the most widely used viral vectors, particularly in the use as vaccines. A thorough understanding of AdV uptake and induced

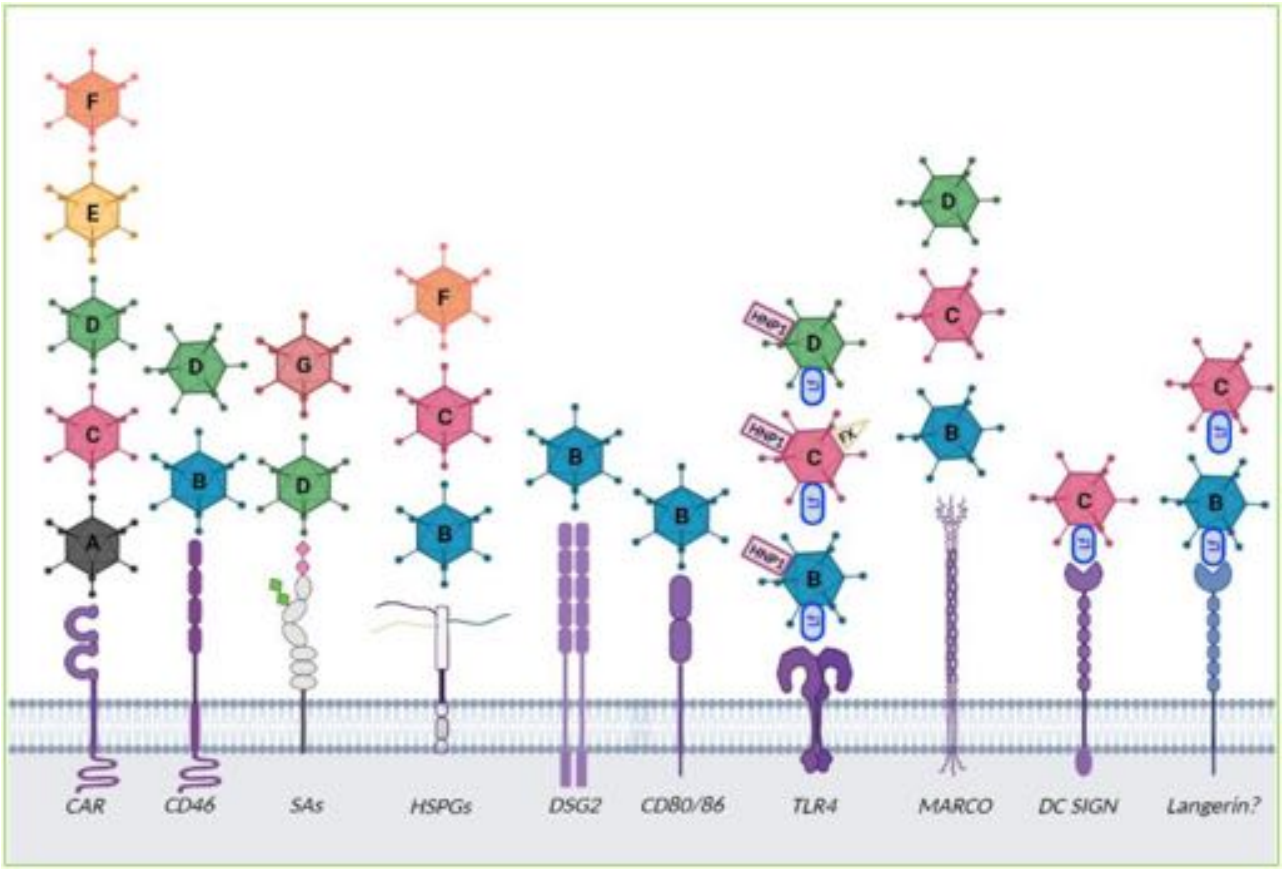

FIGURE 3 Cellular proteins used by APCs for direct or indirect binding to HAdVs. Lf, HNP1, and FX are extracellular factors that can bridge HAdVs and cell surface proteins. The orientation of the virus particles indicates if fiber or hexon capsid protein is used in the interaction. The low affinity of HAdVs for the sialic acids and heparan sulfates that adorn the proteins suggests an interaction with several at the same time to increase the stability of the interaction. (DC SIGN: cluster of differentiation 209; Langerin: cluster of differentiation 207). APC, antigen-presenting cell; CAR, coxsackievirus and adenovirus receptor; CD46, cluster of differentiation 46; CD80/86, cluster of differentiation 80 and 86; DC, dendritic cell; DSG2, desmoglein 2; FX, factor X; HAdV, human adenovirus; HNP1, human neutrophil protein 1; HSPG, heparin sulfate proteoglycans; Lf, lactoferrin; MARCO, macrophage receptor with collagenous structure; SA, sialic acid; TLR4, toll-like receptor 4

immunity is *sine qua non* if we want to continue to develop AdVs as vaccines. Human and non-HAdVs interact, directly and indirectly, with a wide range of cell surface proteins (Figure 2). As with many viruses, highly conserved cellular proteins are often implicated in virus engagement. Each AdV type has its quirks, which is both intruiging and expected. Even single amino acid changes can modify the charge of a domain and induce or prevent electrostatic interactions with proteins, SAs, or HSPG.

Uptake and immunogenicity are also important when one contemplates using AdV-based vectors for long-term gene transfer. While attending a "gene therapy" conference, we will be bombarded with a refrain similar to – adenovirus vectors are highly immunogenic. The refrain has been repeated so often that too few are left standing to point out that this blanket statement is "pathologically" wrong. Yes, some AdV types induce strong immune responses – but not all and not in all tissues. Two striking examples are HAdV-B35 and CAV-2. Finding an individual with HAdV-B35 neutralizing antibodies is exceedingly difficult compared to the likely prevalence of this HAdV type. What about CAV-2 vectors? Transgene expression of a foreign protein with ΔE1 CAV-2 vectors can last for at least 5 months in rodents, and at least 12 months when using a helper-dependent vector (del Rio et al., 2019; Li et al., 2016; Soudais et al., 2004).

In this review, we give a summary of what is known about HAdV receptors on APCs, focusing on skin DCs and LCs, which are the first immune cells present at the subcutaneous injection site of Adv-based vaccines. Understanding how AdVs induce APC activation and innate immune response allows insight into why some AdV types are, and are not, immunogenic (Figure 3).

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AUTHOR CONTRIBUTIONS

Eric J. Kremer conceptualized the review, Elina Gerber-Tichet Dienst wrote the first draft, and both authors contributed to revisions and have agreed on the submitted version.

CONFLICT OF INTEREST

The funders played no role in study design and analysis, the decision to publish, or preparation of the manuscript. We declare that we have no competing interests.

DATA AVAILABILITY STATEMENT

All data are freely available and/or are included in the review.

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