both important variables that influence the outcome of selected delivery of vaccine proteins to DCs, and at the same time, one can probe DC function and mechanisms of action in intact tissues with the targeting approach.

OTHER POTENTIAL RECEPTORS FOR TARGETING PROTEIN VACCINES TO DENDRITIC CELLS

Mannose Receptor/CD206

The MR (CD206) in the steady state is expressed at high levels on certain macrophages and lymphatic and hepatic endothelia (120). Different subsets of DCs also express the MR, primarily interstitial DCs (121) and CD8α^+ splenic DCs (122). The MR recognizes carbohydrates like mannose, fructose, glucose, *N*-acetylglucosamine, and maltose present on the surfaces of bacteria and yeast (120). The function of the MR may explain why mannosylated peptides and proteins are able to stimulate MHC II restricted peptide specific T cells more efficiently than peptides and proteins that are not mannosylated (123).

To specifically target the MR, Ramakrishna et al. (124) generated a monoclonal antibody specific for the human MR (clone B11) and genetically introduced a melanoma antigen, pmel17. Treatment of human DCs with the hybrid antibody resulted in the presentation of pmel17 in the context of HLA class I and class II molecules. Also, the CTLs generated were able to lyse HLA-matched targets. In one initial study to compare the outcome of targeting the MR to DEC-205 in vitro, the MR was less effective in inducing gag-specific CD8$^+$ T-cell responses (118).

In vivo targeting to the MR was also shown using a transgenic mouse model expressing the human MR (hMR Tg mice) (125). The administration of an anti-hMR hybrid antibody fused to OVA induced cellular immunity. The concomitant administration of the anti-hMR-OVA antibody with CpG was able to induce OVA-specific tumor immunity only in hMR Tg mice, while wild type mice remained unprotected.

Importantly, McKenzie et al. (126) could increase the numbers of MR expressing DCs by administering LPS intravenously. When the antibodies were injected 10 minutes later, an increase in the targeting was observed. This illustrates that an adjuvant like LPS might alter the types of DCs that are available to induce vaccine immunity.

Langerin/CD207

Langerin is the lectin that mediates the formation of Birbeck granules, which are the hallmark structures of epidermal LCs (11). Langerin is now known to be expressed on DCs outside the epidermis, particularly the DEC205$^+$ subset of DCs in spleen and lymph nodes (15,127,128), and more recently recognized dermal Langerin$^+$ cells (129–131). A monoclonal antibody has been retrieved, which recognizes the external region of mouse Langerin (15). The heavy and light chains of this L31 mAb have been cloned, and OVA introduced into the heavy chain. Using these anti-CD207-OVA conjugates, Idoyaga et al. have found that Langerin mediates antigen presentation in mice on both MHC I and II products (132).

DC-SIGN/CD209

DC-SIGN/CD209 is expressed in large amounts on monocyte-derived DCs, but only on small numbers of DCs in the T-cell area of lymphoid tissues in the steady state (110,111). In skin sections, DC-SIGN is only expressed on dermal DC, whereas CD1a-positive LCs in the epidermis are negative. Furthermore, DC-SIGN is expressed on DC-like cells present in the mucosal tissues, such as rectum, cervix, and uterus (133,134) as well as lung (135). The efficiency of targeting antigens to human DCs via DC-SIGN was evaluated using humanized anti-DC-SIGN antibody (hD1) chemically cross-linked with KLH (136). This chimeric antibody-protein complex (hD1-KLH) bound to DC-SIGN and was rapidly internalized. The DCs induced proliferation of patient PBMCs at 100-fold lower concentration than KLH-pulsed DCs. In addition, hD1-KLH-targeted DCs induced proliferation of naïve T cells recognizing KLH epitopes in the context of MHC I and II. In another study, Dakappagari et al. (137) used an antibody that cross-reacted with L-SIGN and DC-SIGN fused to a T helper epitope from tetanus toxoid (TT). A T-cell response was induced when the fusion antibody was targeted to DCs.

DECTIN-1 and -2

Both dectin-1 and 2 are expressed on DCs (dermal DCs and CD8α^- DCs), macrophages, neutrophils, and monocytes and are receptors for β-glucan-recognizing β1,3- and β1,6-linked glycans on yeast cell walls (138). The ability of dectin-1 and 2 to present antigen was studied using OVA conjugated to an anti-dectin antibody (139,140). Using adoptive transfer of transgenic OT-I T cells, these authors could show that a low dose of anti-dectin-OVA antibody (1 μg) was able to induce some expansion of OT-I T cells when compared with the protein alone. Also, only the conjugated antigen generated antigen-specific IFN-γ producing cells.

FIRE and CIRE

The F4/80-like-receptor (FIRE) is expressed specifically on CD8$^-$CD4$^+$ and CD8$^-$CD4$^-$ DCs and weakly on monocytes and macrophages (141). C-type lectin receptor (CIRE), on the other hand is expressed by the same DC-subtypes as FIRE but not expressed by monocytes or macrophages (142). When anti-FIRE and anti-CIRE rat monoclonal antibodies were used to immunize mice, anti-rat IgG titers were 100-fold greater than those obtained using nontargeted antibodies (143).

Fc Receptors

FcRs bind immune complexes and mediate both effector and immune activating processes. There is one type of FcR for each class of immunoglobulin: FcαR (IgA), FcεR (IgE), FcγR (IgG), and FcαμR (IgA/IgM). In mice, there are four additional types of FcγRs: FcγRI, FcγRII, FcγRIII, and FcγRIV (144). Antigen presentation is facilitated by immune complexes via FcγR. In humans, the M-DC8$^+$ DC subset present in peripheral blood mononuclear cells (PBMCs) expresses high levels of FcγRIII. When this receptor was targeted by an antibody anti-CD16 (FcγRIII specific) conjugated with a tetanus peptide or a hepatitis C virus peptide, the efficiency of activation of CD4$^+$ T cells was 500 times superior when compared to the free antigen (145).

LOX-1

Scavenger receptors are cell-surface glycoproteins that bind modified lipoproteins and a broad spectrum of structurally unrelated ligands such as modified LDL (Ox- and Ac-LDL) (146), apoptotic cells, and bacteria-derived cell wall components like LPS and lipotechoic acid (147). LOX-1 is a scavenger