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REVIEW

Targeting antigens to dendritic cells in vivo

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Abstract

Dendritic cells (DCs) play a key role in antigen-specific immune regulation. DCs take up and process antigens and present these as peptides through MHC molecules to T cells. Recent pre-clinical and clinical studies have exploited DCs as a means to improve vaccine efficiency. In these studies, monocyte-derived autologous DCs are loaded ex vivo with antigens and re-administered to the patient. These tailor-made vaccines are costly and labor intensive, and therefore less suitable for large-scale immunization programs. As a next step in the development of DC vaccines, it is proposed to load DCs with antigens in vivo. Drug delivery systems harboring antigens have been targeted to DCs via specific surface receptors preferentially expressed by DCs, resulting in priming of humoral and cellular immune responses. The present review focuses on the various antigen delivery systems that are currently in use and the DC surface receptors they target.

Keywords: Adenovirus; Antigen; Cross-presentation; Dendritic cell; Liposome; Targeting

Contents

Abbreviations: CRD, carbohydrate-recognition domain; DC, dendritic cell; FcR, Fc receptor; Gb3, globotriaosylceramide; HSP, heat shock protein; Id, immunoglobulin idiotype; Ig, immunoglobulin; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; MR, mannose receptor

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Introduction

The efficacy of targeting dendritic cells (DCs) in vivo for vaccination purposes depends on a number of factors. First, the efficiency with which the antigen is delivered to the DC will largely depend on the choice of the drug delivery system and on the receptor that is targeted. Second, the efficiency with which a DC processes and presents an antigen will depend on the choice of the drug delivery system, the targeted receptor and the maturation status of the targeted DC. And third, the efficacy of T cell stimulation will mainly depend on the maturation status of the DC at the time it presents an antigen to the T cell. It should be stressed that the optimal maturation states of DCs for antigen uptake and processing differ significantly from the maturation state optimal for presentation to T cells. Therefore, strategies aimed at inducing immunity will require more than just targeting of antigen to antigen presenting cells. DCs will have to mature, and migrate to the lymph nodes to present processed antigen to T cells. This is illustrated by studies in mice, where targeting of antigen to the DC surface receptor DEC-205 leads to tolerance, and co-administration of a DC maturation stimulus is essential to induce immunity (Bonifaz et al., 2002, 2004; Hawiger et al., 2001). These findings are consistent with DC-based vaccination studies in humans, showing that DC maturation is a prerequisite for induction of immunity (de Vries et al., 2003). In this respect, timing of antigen and maturation stimulus delivery is crucial: Administrating the maturation stimulus too late after an antigen reaches the DC might induce tolerance, while antigens targeted to DCs that are already mature are not efficiently cross-presented (Wilson et al., 2006).

Several strategies have been developed to deliver antigen to DC surface receptors. The most direct way is to couple a ligand of a DC-associated receptor or a DC receptor-specific antibody to the antigen of choice. Alternatively, the antigen, or DNA encoding the antigen, can be incorporated into more complex antigen delivery systems, such as liposomes, or viruses, harboring a receptor ligand or receptor-specific antibody. The choice of antigen delivery system determines the antigen route of entry into the cell and the efficiency of presentation via the MHC class I and II pathways.

Targeting antigen to the MHC class I and II pathways

Vaccination strategies aimed at inducing both humoral and cellular responses require antigens to be presented via both the MHC class I and class II pathway. In general, targeting strategies delivering antigen directly into the cytosol, or involving transfection of DC with DNA constructs encoding antigens, are very effective in inducing class I presentation (Fig. 1). By contrast, strategies involving targeting of protein antigen to DC surface receptors will mainly result in presentation of antigen via MHC class II, although to some extent antigens can gain access to the MHC class I loading pathway via a process called cross-presentation. Although endocytosed soluble antigens are less efficiently cross-presented than particulate antigens taken up via phagocytosis (Reis e Sousa and Germain, 1995; Carbone and Bevan, 1990), both have been successfully targeted to DC surface receptors for class I presentation.

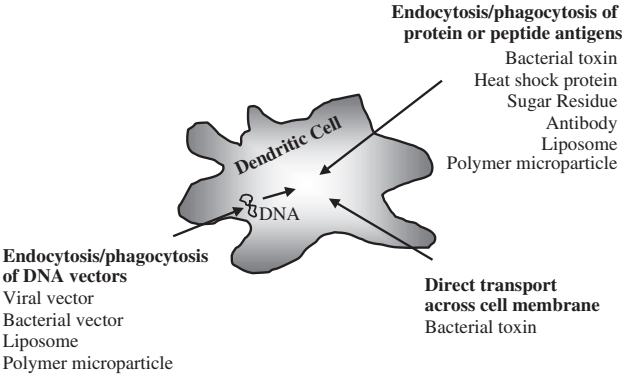

Fig. 1. Antigen delivery systems targeting antigens to DCs for class I presentation. A wide variety of antigen delivery systems is applied for antigen delivery into the cytosol of DCs for induction of class I presentation. Targeting systems carrying DNA encoding protein antigens are internalized via receptor-mediated endocytosis or phagocytosis resulting in expression of the antigens in the cytosol. Other delivery systems carry protein and peptide antigens into the cell via receptor-mediated endocytosis and phagocytosis. These antigens gain access to the MHC class I loading machinery and are cross-presented. In contrast, antigen delivery systems based on a toxin derived from *Bordetella pertussis* deliver protein and peptide antigens directly across the cell membrane into the cytosol without the need for endocytosis or phagocytosis.

Antigen delivery systems

Antigen delivery systems can be subdivided into three main categories: microparticles, live infectious vectors, and receptor ligands. Live infectious vectors and certain microparticles are particularly well suited to deliver DNA to DCs. For delivery of protein and peptide antigens to DCs, both microparticles and receptor ligands are used.

Microparticles

Microparticles include lipid particles, such as liposomes, and polymer particles. Liposomes are phospholipid