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Targeting dendritic cells with nano-particulate PLGA cancer vaccine formulations ☆

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ABSTRACT

Development of safe and effective cancer vaccine formulation is a primary focus in the field of cancer immunotherapy. The recognition of the crucial role of dendritic cells (DCs) in initiating anti-tumor immunity has led to the development of several strategies that target vaccine antigens to DCs as an attempt for developing potent, specific and lasting anti-tumor T cell responses. The main objective of this review is to provide an overview on the application of poly (D,L-lactic-co-glycolic acid) nanoparticles (PLGA-NPs) as cancer vaccine delivery system and highlight their potential in the development of future therapeutic cancer vaccines. PLGA-NPs containing antigens along with immunostimulatory molecules (adjuvants) can not only target antigen actively to DCs, but also provide immune activation and rescue impaired DCs from tumor-induced immuosupression.

Contents

Abbreviations: APCs, antigen presenting cells; BMDC, bone marrow derived dendritic cells; CCR, chemokine receptor; CD40L, CD40 ligand; cDNA, complementary DNA; CFA, complete Freund's adjuvant; CLIP, class II associated in variant chain peptide; CpG, cytosine-phosphate-guanine; CTL, cytotoxic T lymphocyte; DCs, dendritic cells; EBV, Epstein–Barr Virus; ELISPOT, Enzyme-linked immunosorbent spot; ELC, EBV-induced molecule 1 ligand chemokine; ER, endoplasmic reticulum; FDA, Food and Drug administration; Flt3-L, fetal liver tyrosine kinase 3-ligand; GalCer, galactosyl-ceramide; GM-CSF, granulocyte-macrophage colony stimulating factor; HB, hepatitis B; HEV, high endothelial venules; HPV, human papillomavirus; HSP, heat shock protein; ICAM, intercellular adhesion molecule; i.d., intradermal; IFA, incomplete Freund's adjuvant; i.l., intralymphatic; IP-10, inducible protein-10; i.t., intratumoral; IFN-γ, interferon gamma; Ii, invariant chain; IL, interleukin; i.p., intraperitoneal; ISOCOMs, immune-stimulating complexes; LFA, intercellular adhesion molecule lymphocyte function-associated antigen; LPS, lipopolysaccharide; mAbs, monoclonal antibodies; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MPLA, monophosphoryl lipid A; MUC1, mucin-1; NK, natural killer cells; NKT, natural killer T cells; NPs, nanoparticles; NSCLC, non-small cell lung cancer; OVA, ovalbumin; PEG, poly (ethylene glycol); PGE2, prostaglandin E2; PLGA, poly(D,L-lactic-co-glycolic acid); RANTES, regulated on activation normal T cell expressed and secreted; RGD, Arg-Gly-Asp; s.c., subcutaneous; SLC, secondary lymphoid tissue chemokine; TAP, transporter of antigen presentation; Th, T helper; TLR, Toll-like receptor; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; TRP2, Tyrosinase related protein-2; VLPs, virus like particles.

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1. Introduction

Cancer represents one of the leading causes of death, misery and pain worldwide. Cancer patients are usually treated by a combination of surgery, radiotherapy, and/or chemotherapy. The primary tumor might be removed by these standard therapies, but micrometastases of disseminated tumor cells often result in tumor relapse and therapeutic failure. Besides, chemotherapy and radiotherapy are non-specific, destroying healthy tissues along with cancer cells. As a result, cancer patients usually suffer from devastating side effects and very poor quality of life. To overcome these obstacles, there has been a growing focus on immunotherapy as a new avenue for combating this disease [1].

Immunotherapy refers to therapeutic strategies that utilize the immune system to fight cancer. The main focus of such strategies is not only to target and kill tumor cells in a specific manner, but also to alert the immune system, so that the residual tumor cells are kept in check. The expected outcomes are: prevention of the metastatic spread of the disease and the improvement of the quality of life in the affected individuals. Immunotherapeutics are divided into two general forms; active and passive. Passive immunotherapy refers to strategies that complement the immune system, simply by supplying high amounts of effector molecules, such as tumor-specific monoclonal antibodies (mAbs). In spite of their specificity and lower toxicity, compared to standard therapies, mAb-based therapy is very costly, short-lived and dependant on repeated applications [2]. On the other hand, active immunotherapy refers to strategies that activate patient's immune system to target and destroy cancer cells. Active forms of immunotherapy (also known as cancer vaccines) can result in multifaceted polyclonal immune responses, i.e. simultaneous activation of antigen presenting cells (APCs), $CD4^+$ T cells, $CD8^+$ T cells, B cells and innate immune cells, e.g. granulocytes and natural killer (NK) cells. This multi-faceted response of cancer vaccines enables them to target and eliminate a wider range of tumor cell phenotypes compared to passive therapy [3].

Cancer vaccines offer distinct advantages over standard therapies, namely: increased specificity, reduced toxicity and long-term effects via immunologic memory [1]. Continuous efforts in the field of cancer immunotherapy have led to the development of several cancer vaccine strategies that are now extensively studied in multiple clinical trials for various kinds of cancer (reviewed in [4]). Cancer vaccines may be developed as a prophylactic tool to prevent future development of cancer or as a therapeutic approach to boost the elimination of tumor by the immune system. *At the present time*, only two *prophylactic cancer vaccines* have been approved by Food and Drug Administration (FDA); hepatitis B (HB) vaccine and Gardasil™ that prevent the infection with HB virus and human papillomavirus (HPV), respectively [5]. The HB and HPV are believed to be the leading causes of liver cancer [6] and cervical cancer [7], respectively. There is only one *therapeutic cancer vaccine* that has been approved by FDA for human use [8]. This vaccine is called Oncophage® and is used for the treatment of renal cell carcinoma patients. Oncophage® is an autologous heat shock protein (HSP)–peptide complex produced from each patient's own tumor. HSP are intracellular transporters of peptides. Like normal peptides, tumor associated peptides also transported by HSP. Isolation of such HSP/peptide complexes from tumor tissue captures a wide range of important peptides that can help the immune system to recognize cancer [9]. Administered HSP/peptide complexes are taken up by dendritic cells (DCs) through specialized receptor (CD91). Engagement of this receptor further leads to enhanced DC maturation and anti-cancer immune response. HSP/peptide complexes are thus capable of co-delivering both antigenic material and maturation stimulus to same DC population.

In addition to HSP/peptide complexes, there are four other main categories of cancer vaccines under development. *First* category includes cell-based vaccination strategies. This category includes various cell types (tumor cells or DCs) that have been *ex vivo* activated, or genetically modified to express immunostimulatory cytokines, chemokines or growth factors e.g. IL-2, IL-6, IL-7, TNF-α, IFN-γ and GM-CSF [10–12]. Alternatively, DCs could be also engineered so that they are devoid potent immunosuppressive cytokines, e.g., IL-10 [13]. While these strategies show promise, the techniques used are laborious, time consuming and very expensive to carry out in large clinical trials. Second category employs the use of antigenic preparations, e.g. synthetic peptides, purified antigens, and tumor cell lysates [14–16]. While these alternate approaches bypass many of the production difficulties associated with cellular vaccines, they are poorly immunogenic and often result in less efficient vaccines. Third category is plasmid and viral vectors encoding tumor antigens [17,18]. Most of these are powerful activators of immune responses; however, safety concerns have hindered their human application. In addition, repeated administration of most virus vector systems often results in the generation of anti-vector antibodies, which neutralize the effect of subsequent treatments [14,19]. Fourth category of cancer vaccines includes non-living nano/micro-sized vaccine delivery systems (also called particulate delivery systems), which are the focus of current review paper. These systems comprise three main components; first, an antigen against which the immune responses are induced. Second, an adjuvant that acts as danger signals to alert the immune system and activate early as well as long-lasting immune responses. The third component is the delivery system that delivers vaccine antigens and adjuvants to DCs in a targeted and prolonged manner [20].

This review will describe the rationale behind the choice of DCs as the target for delivering vaccine components. We will explore the unique features of these cells (DCs) that enable them to be the most professional APCs. Different mechanisms by which the DCs can uptake, process and present vaccine antigens are also described. Next, we will highlight the crucial role of Toll-like receptor (TLR) ligands as potent immunostimulatory adjuvants in cancer vaccine formulations. A special emphasis will be put on monophosphoryl lipid A (MPLA), one of the most promising candidates of TLR ligand's family. The rational and expected outcomes of simultaneous delivery of antigen and adjuvant to DCs using particulate vaccine delivery systems will be explored and an overview on the application of lipid and polymer based nano-particulate delivery systems for the development of therapeutic vaccines will be provided. More attention will be paid to research on the use of PLGA-NPs as efficient vaccine delivery systems for DC targeting and the generation of robust immune responses in cancer immunotherapy.

2. DCs are the most professional APCs

APCs are a group of cells that can process antigens of both endogenous and exogenous origin [21]. Endogenous antigens (such as