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Review

The potential of nanoparticle vaccines as a treatment for cancer

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ABSTRACT

A complex and multifaceted relationship exists between cancer and the immune system. Advances in our understanding of this relationship have resulted in significant clinical attention in the possibilities of cancer immunotherapy. Harnessing the immune system's potent and selective destructive capability is a major focus of attempts to treat cancer. Despite significant progress in the field, cancer therapy still remains significantly deficient, with cancer being one of the largest contributors to morbidity and mortality in the developed world. It is evident that the design of new treatment regimes is required to exploit cancer immunotherapy. Herein we review the potential for nanotechnology to overcome the challenges that have limited the more widespread implementation of immunotherapy to cancer treatment.

1. Introduction

The ability of the immune system to detect and inhibit neoplastic growth, a concept termed immunosurveillance, was first proposed in the early 1900's (Dunn et al., 2004). In the 1950's it was observed that some nascent tumours were eliminated by the immune system before they became clinically significant. It was also observed that there was an increased incidence of some tumours in immunosuppressed hosts (Dunn et al., 2004). There is now an appreciation that all cancer cells must acquire, or inherently possess, mechanisms by which they can escape destruction by the immune system in order to survive. These mechanisms include editing of antigenic expression by downregulation of major histocompatibility complex (MHC) molecules, shedding of immunogenic antigens, expression and/or secretion of immunomodulatory factors as well as recruitment of immune regulatory cells (Schreiber et al., 2011). Although the details of these mechanisms are yet to be fully understood, it is clear that the anti-neoplastic capability of the immune system holds significant potential for cancer therapy.

The central aim of immunotherapy is to tip the balance of power back in favour of the immune system, thereby facilitating it's immunosurveillance role and tumour regression. This can theoretically be achieved in multiple ways, including adoptive T cell transfer, and the administration of immune checkpoint inhibitory factors. Adoptive T cell transfer centres around isolation and expansion of antigen-specific T cells *in vitro,* with or without transgenic manipulation, followed by reinfusion back into the patient (Fesnak et al., 2016). The limitation of adoptive T cell transfer, in addition to it being an expensive and laborious process, is the occurrence of immune-related adverse events (irAEs). These include autoimmune consequences due to targeting of self-antigens by the high affinity engineered T cells (Hinrichs and Rosenberg, 2014). Alternatively, immune checkpoint inhibition aims to inhibit key 'break pedals' of T cell activation, thereby enhancing immune activation in an attempt to overcome tumour associated immune suppression (Page et al., 2014). Monoclonal antibodies targeting CTLA-4 and PD1 (ipilimumab and nivolumab respectively), receptors that provide inhibitory signals for T cells, have shown promise in clinical trials. Ipilimumab has received FDA approval for the treatment of melanoma, and is being considered for the treatment of other tumours including small-cell lung cancer and Hodgkin's lymphoma (Antonia et al., 2016; Shin and Ribas, 2015). Although immune checkpoint inhibitors have shown some exciting results, they have also been reported to elicit irAEs, ranging from mild gastrointestinal upset to fulminant hepatotoxicity and hypophysitis (Spain et al., 2016). Paradoxically, after the immune system has been stimulated by these treatments, it is then suppressed with various immune modulating medications in an

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attempt to control irAEs, creating a delicate balancing act and highlighting a significant limitation to their application (Spain et al., 2016).

Cancer vaccination is an alternative approach to cancer immunotherapy and aims to stimulate naïve and/or anergic tumour specific T cells via the administration of tumour associated antigen (TAA) (van der Burg et al., 2016). Prophylactic vaccines aim to prevent the onset of cancer, typically by vaccinating against known oncogenic pathogens, as is the case with the human papilloma virus vaccine that acts as a preventative for cervical cancer (Herrero et al., 2015). Conversely, therapeutic vaccines aim to treat cancer as opposed to prevent its onset, and are typically given in the context of an established tumour. The traditional paradigm of therapeutic cancer vaccination is that by administering TAA in the presence of an appropriate adjuvant, the resulting immune response is capable of reversing T cell anergy and/or ignorance. This allows the effector arm of the immune system to eradicate tumours. Encouraging results with this approach have been reported particularly in the realm of treating early and pre-malignant lesions and preventing reoccurrence after remission. One of the most notable cancer vaccine successes pertains to Provenge (sipuleucel-T), which has FDA approval for the treatment of metastatic castrate resistant prostate cancer, and has shown an increase in three year survival by 38% in clinical trials (Kantoff et al., 2010). Interestingly, this approach differs from the traditional vaccination paradigm in that dendritic cells (DCs) are isolated from patients, followed by incubation with TAA and GM-CSF *in vitro* before re-infusion (Fig. 1a).

Despite success in animal models and evidence that vaccination with TAAs can stimulate tumour specific T cell expansion in humans, this does not always correlate with tumour elimination. There have been a number of anti-cancer vaccines tested in clinical trials in humans where their results to date have been disappointing (Kissick and Sanda, 2015). In a comparison of 23 phase II/III clinical trials assessing the efficacy of 17 different anti-cancer vaccines, 18 trials did not demonstrate improved patient survival (Ogi and Aruga, 2013). It is evident

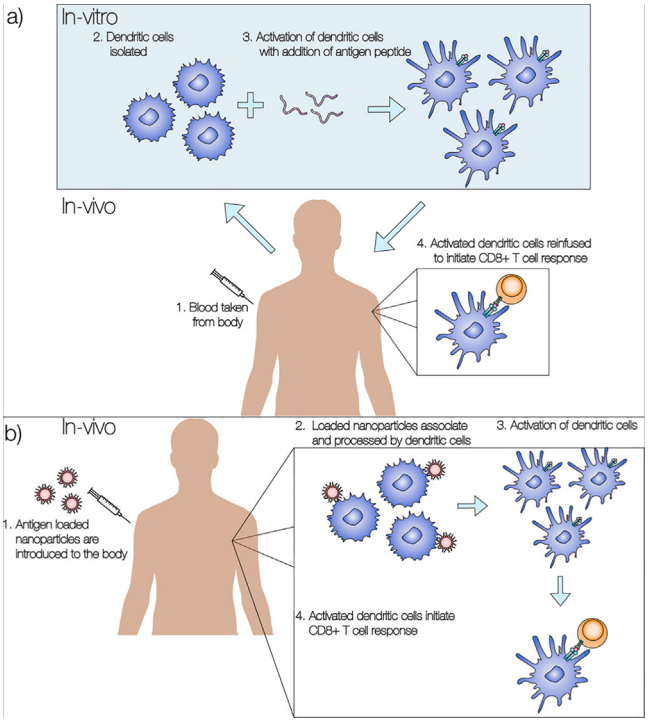

Fig. 1. Antigen delivery to dendritic cells is critical for an effective immune response. (a) In current clinical therapies such as Provenge, DCs are isolated with from the patient, incubated with antigen and then reinfused into the patient. This overcomes the degradation of antigen *in vivo* and ensures efficient activation of DCs. (b) Nanoparticles have the potential to deliver antigen directly to DCs *in vivo*, bypassing the costly step of isolating and reinfusing DCs into the patient.

that conventional vaccination strategies ie. injection of antigen with adjuvant, is inefficient in inducing an immune response robust enough to overcome tumour associated immune tolerance. Thus new strategies are required to enable cancer vaccination to become a widely implemented immunotherapy.

The poor success rate of cancer vaccinations are most likely a result of ineffective presentation of the TAAs. The success of Provenge is considered to stem from the use of DCs in the treatment regime. DCs (Merad et al., 2013) play an integral role in the host anti-tumour immune response by providing the context in which TAAs are presented to tumour specific T cells (McDonnell et al., 2010). These professional antigen presenting cells (APCs) capture and present exogenous and endogenous antigens to $CD8^+$ and $CD4^+$ T cells *via* MHC I and MHC II respectively. Maturation of $CD8^+$ T cells into cytotoxic T lymphocytes (CTLs) is central to the effector arm of the anti-tumour immune response, and difficulties in stimulating robust effector CTL responses is widely recognised as one of the primary factors limiting cancer vaccine efficacy. Initiation of a CTL response requires the capture, processing and presentation of antigen by DCs. For antigen that is captured from outside the cell, its presentation by MHC I involves an intracellular trafficking pathway termed “cross-presentation”. Cross presentation is an important pathway in the anti-tumour immune response. DCs encounter TAA and *via* cross presentation stimulate CTL specific for tumour cells (Joffre et al., 2012). In the mouse XC-chemokine receptor 1 (XCR1) expressing DCs (termed cDC1) are particularly efficient at cross-presentation and inducing CTL immunity (Merad et al., 2013). In humans effective cross-presentation can be achieved by numerous DC subsets depending on their activation status, origin and the type of antigen involved (Durand and Segura, 2015). The canonical pathway of cross-presentation involves exogenous antigen being released from the endosome into the cytosol, proteolysis by the proteasome, transport *via* transporter associated with antigen processing (TAP) into the endoplasmic reticulum (ER) and loading into MHC I (Grotzke et al., 2017). Peptide antigen that gains access to the cytosol also has the potential to be transported by TAP into the ER where it will be loaded into MHC I molecules. The importance of how antigen gains access to the cytosol becomes evident when considering methods for enhancing anti-tumour CTL responses *via* cross presentation.

In addition to presenting antigen, DCs enable T cell activation by delivering co-stimulatory signals *via* surface-expressed molecules such as CD80 and CD86 (Lenschow et al., 1996). Immunogenic adjuvants are used in vaccine design to stimulate enhanced DC co-stimulatory molecule display. Many different adjuvants, from aluminium hydroxide to bacterial cell wall components, have significant effects on the immune response and thus vaccine efficacy in cancer settings (Banday et al., 2015). Current research focuses on the design of novel adjuvants that can selectively target specific pathogen recognition receptors (PRRs), of which Toll-like receptors (TLRs) are the most well characterised (Takeda et al., 2003). TLR-7/8 agonists have potential with regard to tumour therapy, particularly due to their ability to stimulate a CTL response (Foged et al., 2012; Kobold et al., 2014). Indeed the only FDA approved TLR agonists indicated for cancer therapy (imiguimod and resiquimod) are targeted to TLR-7 (Holldack, 2014). In a comparison of adjuvants that target TLR-2 or TLR-3, TLR-3 activation is favoured for cancer vaccination due to its ability to enhance co-stimulation and cross-presentation without inducing tumour associated inflammation, cytokinemia or toxic disease (Seya et al., 2015). Taken together, the role of DCs in stimulating and shaping the immune response exemplifies the power of DCs in enhancing cancer vaccination efficacy.

2. The potential of nanoparticles

Nanoparticles (NPs) have significant potential as a vaccine delivery system with several benefits to their use in cancer vaccination and/or immunotherapy. A number of excellent reviews have been written highlighting a comprehensive list of nanoparticle formulations (Irvine