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Surface chemistry dependent immunostimulative potential of porous silicon nanoplatforms

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ABSTRACT

Nanoparticles (NPs) have been suggested for immunotherapy applications in order to optimize the delivery of immuno-stimulative or -suppressive molecules. However, low attention towards the impact of the NPs' physicochemical properties has presented a major hurdle for developing efficient immunotherapeutic agents. Here, the effects of porous silicon (PSi) NPs with different surface chemistries were evaluated on human monocyte-derived dendritic cells (MDDCs) and lymphocytes in order to highlight the importance of the NPs selection in immuno-stimulative or -suppressive treatment. Although all the PSi NPs showed high biocompatibility, only thermally oxidized PSi (TOPSi) and thermally hydrocarbonized PSi (THCPSi) NPs were able to induce very high rate of immunoactivation by enhancing the expression of surface co-stimulatory markers of the MDDCs (CD80, CD83, CD86, and HLA-DR), inducing T-cell proliferation, and also the secretion of interleukins (IL-1β, IL-4, IL-6, IL-10, IL-12, IFN-γ, and TNF-α). These results indicated a balanced increase in the secretion of Th1, Th2, and Treg cytokines. Moreover, undecylenic acid functionalized THCPSi, as well as poly(methyl vinyl ether-alt-maleic acid) conjugated to (3-aminopropyl)triethoxysilane functionalized thermally carbonized PSi and polyethyleneimine conjugated undecylenic acid functionalized THCPSi NPs showed moderate immunoactivation due to the mild increase in the above-mentioned markers. By contrast, thermally carbonized PSi (TCPSi) and (3-aminopropyl)triethoxysilane functionalized TCPSi NPs did not induce any immunological responses, suggesting that their application could be in the delivery of immunosuppressive molecules. Overall, our findings suggest all the NPs containing more nitrogen or oxygen on the outermost backbone layer have lower immunostimulatory effect than NPs with higher C–H structures on the surface.

1. Introduction

Immunotherapy is one of the most promising approaches for the treatment of many diseases in which the immune system is involved [1,2]. Many studies have already developed effective and safe immunotherapeutic molecules via cell-mediated and humoral (antibody-mediated response) immunity induction [3,4]. The method underlying the immunoactivation response involves either applying an external stimulus for the immune system to act more forcefully or exposing the immune cells to man-made or naturally-derived antigens so that the immune system can recognize it as a foreign entity, and consequently, suppress all the cells expressing the antigen in the body [5–7]. To get a proper immune response, antigen presenting cells (APCs; e.g. dendritic cells, DCs) should maturate, and then, present the antigen to T cells in order to induce immunological responses, including the proliferation of B cells for antibody production or cytotoxic T-lymphocytes for direct attack against the immunogenic cells [8].

The organized interaction between the T cells and DCs during antigen presentation is known as an immunological synapse [9]. Three main activation signals are required by APCs to stimulate

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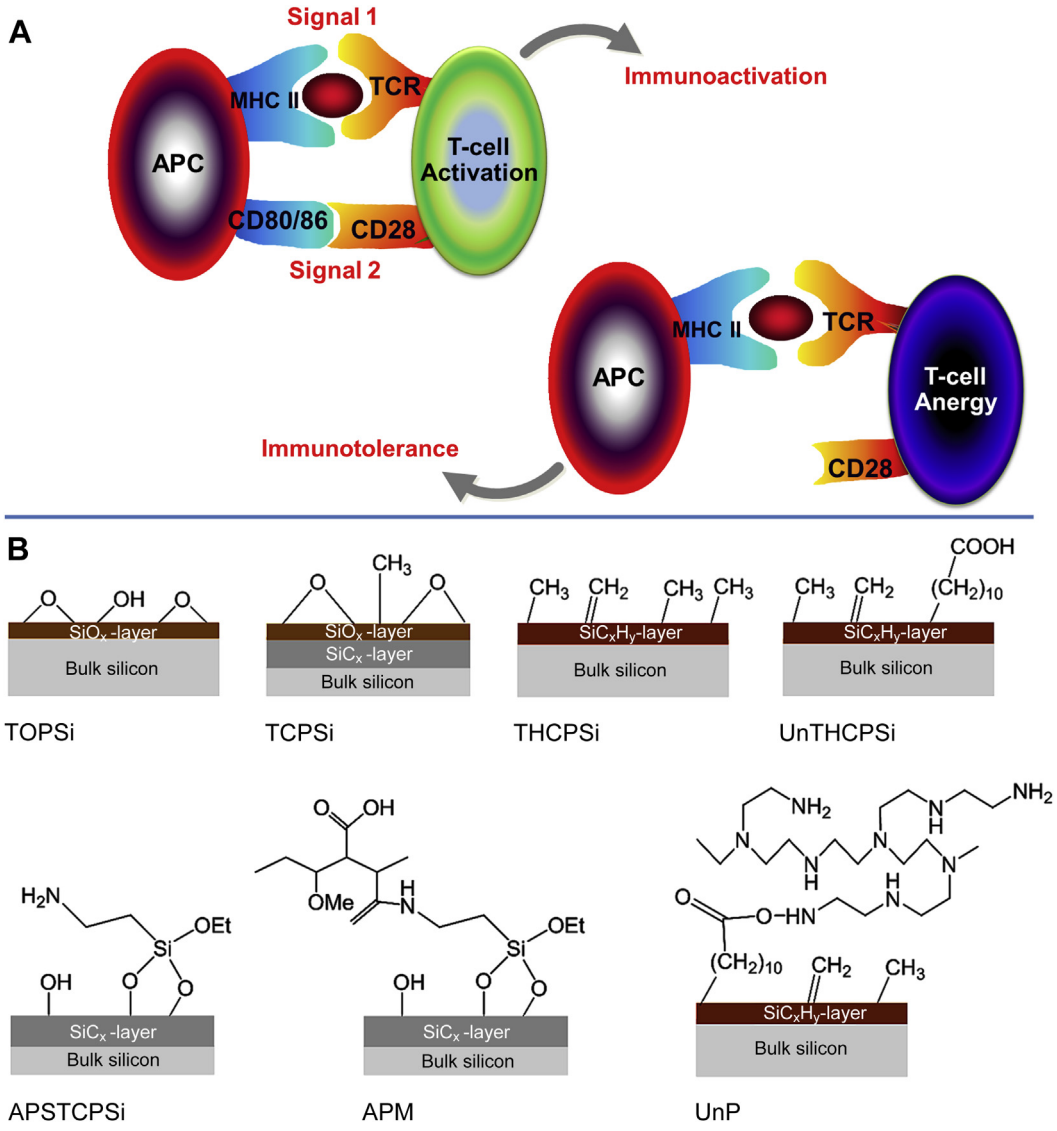
resting T cells [10]. The first signal is antigen-specific provided through the presentation of antigens to T cell receptors (TCR) via MHC (major histocompatibility complex)-II molecules on the surface membrane of DCs. The second co-stimulatory signal is antigen nonspecific and becomes activated through the binding of CD28 receptors on the surface of T cells to cognate ligands (CD80/CD86) of DCs (Scheme 1A) [10,11]. In many cases, the main reason for deficient immunotherapy is that despite the recognition of antigens, the T cells cannot be activated enough owing to the lack of the second signal (CD80/CD86), resulting in defects in immunosurveillance mechanisms of the body because of an anergy response [12–14]. Parallel to the mentioned signals, the third signal in which cytokines and chemokines are involved will shift the response towards the development of either Th1/Th17 for effector responses against infectious agents, Th2 for allergic diseases or Treg for regulatory responses [15].

To circumvent the above-mentioned shortcomings, nano-based immunotherapeutics with the intrinsic ability of co-stimulatory ligand activation can be applied for the delivery of antigen or other immunostimulating molecules, or even inducing nonspecific immunotherapy without targeting a certain cell or antigen [16,17]. Currently, the combination of both approaches enables to boost the immune system and the efficacy of immunotherapy [18–19].

Several factors such as size, charge, and concentration have been reported to have a strong impact on the immunological responses of various NPs [20–22], allowing the rational design of NP-based immuno-stimulative or -suppressive therapeutics that guide the immunesystem towards desired responses. Nonetheless, the lack of knowledge about the potential of the nanoporous silicon (PSi) materials in immunotherapy as well as promising applications of these particles in many aspects of medicine [23–26], bring an essential need to investigate the immunological consequences of these NPs and the possible factors affecting on it.

In this study, we hypothesize that the failures or efficient responses of nano-based immunotherapeutic formulations may, at



Scheme 1. Illustration of DCs and T-cells interactions (A) and the structure of PSi NPs with different surface chemistries (B). T cell activation requires the interaction of the TCR on the surface of T cells with MHC-II on the surface of DCs presenting an antigen. T cell activation also requires a co-stimulatory signal involving the interaction of CD28 on the T cell with CD80 or CD86 on the antigen-presenting cell. The presentation of antigens without the presence of the co-stimulatory molecules leads to T-cell anergy and immunotolerance. It is hypothesized that NPs with various surface chemistries may activate or suppress the immune system via interleukin secretion induction or modulating the co-stimulatory signal expression.