Journal of Controlled Release xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Nanoparticulate immunotherapy for cancer

Chintan H. Kapadia [a], Jillian L. Perry [b], Shaomin Tian [c], J. Christopher Luft [a], Joseph M. DeSimone [a,b,d,e,f,*]

[a] Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA
[b] Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599, USA
[c] Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, NC 27599, USA
[d] Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599, USA
[e] Department of Chemical and Biomolecular Engineering, NC State University, Raleigh, NC 27695, USA
[f] Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA

ARTICLE INFO

Article history:
Received 8 June 2015
Received in revised form 25 September 2015
Accepted 28 September 2015
Available online xxxx

Keywords:
Nanoparticles
Cancer immunotherapy
Tumor microenvironment
Vaccine
Immunosuppression

ABSTRACT

Although surgery, radiation therapy, and chemotherapy have significantly improved as treatments for cancer, they can rarely control metastatic disease and cures remain scarce. Promising recent developments suggest that cancer immunotherapy may become a powerful new therapy that clinicians can offer cancer patients. The opportunity to orchestrate the body's own immune system to target, fight, and eradicate cancer cells without destroying healthy cells makes this an extremely attractive treatment modality. Our increased knowledge in anti-tumor immunity and the immunosuppressive tumor microenvironment (TME) has provided many therapeutic strategies to battle cancer. That combined with advancements in the field of particulate delivery systems provide a mechanism to deliver these immunotherapeutics to their specific targeted cells and the TME. In this review we will focus on the current status of immunotherapy and the potential advantages of utilizing nanocarriers within the field.

1. Introduction to tumor immunobiology

1.1. Innate/adaptive immunity

The immune system fights against pathogenic infections via innate and adaptive mechanisms for immediate defense and long-lasting protection. Innate immune cells, such as macrophages, dendritic cells (DCs), natural killer (NK) cells, etc., provide the initial, "first line" of protection by recognizing conserved pathogen-associated molecular patterns (PAMPs) via pattern-recognition receptors (PRRs) [1], including C-type lectin receptors (CLRs), Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and cytosolic DNA sensors [2,3]. Adaptive immunity usually proceeds the innate immune response and requires activation of T and B lymphocytes. This activation requires recognition of specific antigens by T and B cell receptors and, subsequently results into the generation of antigen-specific effector T cells and/or antibody secreting plasma cells. Importantly, adaptive immunity also features production of 'memory' T and B cells that exist in a state of readiness to mount a more rapid attack upon the second encounter of a pathogen. Effective activation of adaptive immunity depends on the sensing of microbes by PRRs expressed on antigen-presenting cells (APCs) in particular DCs [4].

1.2. Cross talk between tumor cells and immune system

Growing evidence has shown that the immune system interacts with tumors throughout tumor development, including initiation, progression, invasion, and metastasis. It is also becoming clear that the complex cross talk between the immune system and cancer cells can both inhibit and enhance tumor growth, which has become a hallmark of cancer [5]. A cancer immunoediting model [6,7] was developed to understand the apparently paradoxical functions of host immunity on cancer, based on the temporal occurrence during tumor progression: an early elimination phase

(elimination of tumor cells by a competent immune system), an equilibrium phase (a balance phase when tumor progression is still controlled by the immune system but sporadic tumor cells that manage to survive immune destruction; immune editing occurs) and an escape phase (when the tumor evades immune surveillance and an immunosuppressive tumor microenvironment is established). Immune editing is believed one of the key aspects why tumors evade surveillance and lie dormant in patients for years through "equilibrium" and "senescence" before re-emerging [8].

2. Immune cells and mediators in tumors

Elimination of cancer cells via the immune system is mainly mediated by immune effector cells, such as CD8 + cytotoxic T lymphocytes (CTL), natural killer (NK) cells, and natural killer T (NKT) cells. These

* Corresponding author.
E-mail addresses: desimone@email.unc.edu, vph@email.unc.edu (J.M. DeSimone).

http://dx.doi.org/10.1016/j.jconrel.2015.09.062
0168-3659/

cells have been found within various types of tumors and studies involving cancer patients revealed that the presence of CD3 + or CD8 + tumor-infiltrating lymphocytes (TILs) was associated with increased overall survival [9]. CD8 + CTL is the major anti-tumor player of adaptive immunity. Recognition and elimination of cancer cells by CD8 + T cells require two signals: 1) a signal provided by the engagement of tumor antigenic peptide/class I MHC complex on antigen presenting cells, in particular DCs, with antigen-specific T cell receptor (TCR), and 2) stimulatory signals mediated by interactions between accessory molecules (CD80, CD86, LFA3) on APCs and their cognate receptors on CTLs (e.g., CD2, CD28, LFA1) [10]. Activated CD8 + CTLs kill tumor cells by releasing cytotoxic proteins (perforin, granzymes, and granulysin) or engagement of Fas ligand (FasL) on T cells and Fas on target cells, and subsequent recruitment of the death-induced signaling complex (DISC). NK cells are innate immune effector cells that recognize neoplastic cells via non-antigen-specific surface receptors [11] and trigger targeted attack through release of cytotoxic granules and secretion of cytokines and chemokines to promote subsequent adaptive immune responses [12]. NKT cells (also invariant NKT or iNKT cell), another member of innate immune system, express a semi-invariant TCR that recognizes lipid antigens (e.g. α-GalCer) presented by CD1d (antigen presenting molecules) [13]. Upon activation, NKT cells rapidly produce large amounts of IFN-γ, which can profoundly modulate innate and adaptive arms of the immune system for tumor rejection. NKT cells may also directly mediate tumor lysis via Fas–FasL engagement or release of perforin [14].

In contrast to immune effector cells, CD25 + regulatory T cells (Tregs) and myeloid derived suppressor cells (CD14 + HLA-DR- MDSCs) limit inflammation and immune activation [15] and help to maintain self-tolerance [16] (Fig. 1). Tregs have been found at high frequencies in various neoplastic malignancies such as breast, lung, liver, GI tumors, and melanoma contributing to an immune-suppressive TME [17,18]. Increased recruitment of Tregs is correlated with reduced survival and increased progression in pancreatic and ovarian

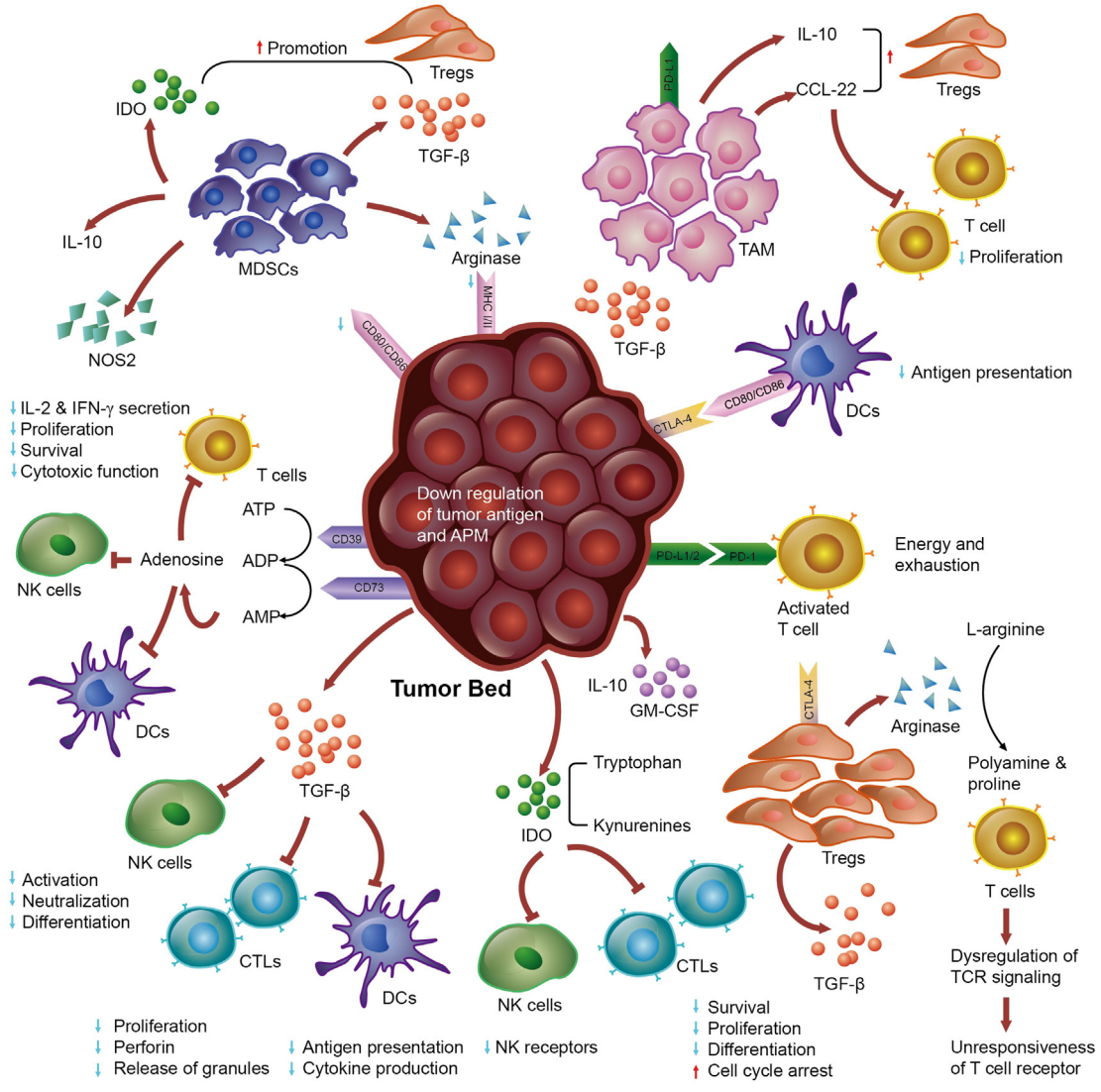

Fig. 1. Immunosuppressive regulators in tumor microenvironment. Tumors escape immune surveillance by various mechanisms that operate in parallel with anti-tumor immunity. Anti-tumor immunity can be suppressed by various cell types including tumor cells, stromal cells and immune cells such as MDSCs, Tregs and TAMs. These immunosuppressive cells secrete numerous soluble mediators such as arginase, prostaglandin E2, TGF-β, IDO, adenosine and NOS2. Arginase and IDO limit T-cell functions by depleting arginine and consuming tryptophan. TGF-β, IDO and IL-10 suppress the activity of T cells and natural killer cells as well as cause the expansion of Tregs. TGF-β can also suppress or alter activation, maturation and differentiation of DCs, CD4 + and CD8 + T cells. Moreover, due to changes in epigenetic machinery of tumor cells, expression of MHC-I/II molecules, proteins associated with APM and costimulatory molecules (CD80/CD86) is down-regulated which prevents successful antigen presentation and tumor detection. Moreover, tumor cells also express surface molecules such as PD-L1/PD-L2 that engage PD-1 receptor on the surface of activated T cell which cause the anergy and exhaustion of T cells. CTLA-4 receptor on tumor binds to co-stimulatory molecules on APCs and prevents antigen presentation. Collectively, tumors escape immune surveillance via inhibitory mechanisms utilized by all of these cell types.

Please cite this article as: C.H. Kapadia, et al., Nanoparticulate immunotherapy for cancer, J. Control. Release (2015), http://dx.doi.org/10.1016/j.jconrel.2015.09.062