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Curing Cancer with Nanotherapy Continues to be an Elusive Goal

Priyanka Ray

Department of Chemical, Biochemical and Environmental Engineering, University of Maryland, Baltimore County, Baltimore MD, 21250, USA

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***Correspondence:**
*Dr. Priyanka Ray, Department of Chemical, Biochemical and Environmental Engineering, University of Maryland, Baltimore County, Baltimore MD, 21250, USA;
Email: priyanka@umbc.edu.

Nanotechnology has aimed to address limitations of new drug design by "repackaging" FDA approved drugs without compromising their therapeutic benefits while suppressing undesired side effects suffered by patients undergoing chemotherapy. The major hurdles faced by small molecular drugs in treating cancer include hydrophobicity, rapid hepatic and renal clearance, short circulation time, off target toxicity and drug resistance. Most of these factors are addressed using nano formulations comprising lipids or polymers and simultaneously striving to enhance the therapeutic index of chemotherapeutic drugs.

Exploiting the difference between the tumor microenvironment (TME) and healthy tissues, scientists have developed a range of stimuli responsive nanomaterials, capable of specifically targeting cancer cells with minimal collateral damage. In this regard, acidity (pH)[1-3], low oxygen pressure (hypoxia)[4-6], temperature[7], ROS[8] and enzyme[9] gradients have been used as triggers. Drug encapsulation in synthetic or bioderived materials has shown promise as drug delivery agents[10-32]. To enhance drug availability, active targeting strategies employing peptides, aptamers and small molecules have also been employed.

Although nanomaterials are widely researched and appreciated for their advantages over conventional therapeutic methods, there are several limitations to their use. These include targeting properties which are usually achieved by conjugating ligands which bind to over-expressed proteins on cancer cells, but there is a high chance of the nanomaterials leading to off target toxicity when these proteins are produced by healthy cells. Targeting rapidly dividing cells is also a strategy of nanomedicine which may be compromised when there are other growing cells in an acidic environment which do not belong to the tumor tissue, such as are found in the GI tract lining or stomach[33]. In terms of fabrication, reproducibility and scaling up are also challenges thus leading to variations in every batch of nanomaterials produced. Their colloidal stability and shelf life are also factors impeding their translational capacity. Finally, the safety of such materials once injected in the body and their ultimate fate remains controversial[34].

Despite advances made in preclinical trials with nanomaterials, there still looms a large question regarding the immunogenic response of these carriers. Most *in vivo* studies use immunocompromised animals to grow xenograft tumors wherein the therapeutic efficiency is evaluated in the absence of immunological response. Due to the heterogeneity of the tumors, and the existence of "cold" and "hot" tumors both immunostimulation and suppression strategies have been studied in depth (Figure 1).

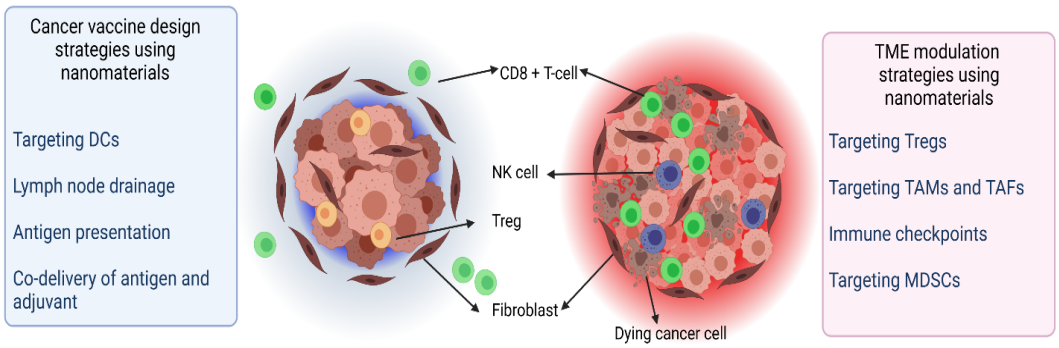

Figure 1. Schematic representation of (left) cold and (right) hot tumors depicting different cell types along with strategies applied while using nanomaterials for cancer immunotherapy (DC: dendritic cell, NK: natural killer cells, TAM: tumor associated macrophage, TAF: tumor associated fibroblasts, MDSC: myeloid-derived suppressor cells (Created using BioRender)

Research models have focused on engineering the tumor immune response and the use of checkpoint inhibitors and immune adjuvants have been beneficial in several cold tumor models which have a poor prognosis due to the presence of immunosuppressive cells that may be nonresponsive to immunotherapy[35]. Their mechanism of action is via binding to Toll like receptors (TLR), thereby enhancing recognition of poorly immunogenic antigens[36]. On the other hand, unwanted interactions with the immune system generate inflammatory or autoimmune disorders which may cause major therapeutic roadblocks. Although these pathways can be bypassed by suitable modification of nanomaterial properties, it does not completely suppress antibody production. Hence. there is a fine balance to maintain while using nanomedicine.

Cancer immunotherapy initially began with the injection of bacteria derived compounds which caused tumor shrinkage[37] and paved the path for tuning and sensitizing the immune system. Ever since, several immunotherapy strategies exploiting neutrophils, macrophages, natural killer (NK) cells, T and B cells have been applied[38-41]. Nanomaterials have been used for immunotherapy to cure cancer due to several attributes which include long circulation times, protection of cargo from enzymatic degradation, delivery of antigens to antigen presenting cells (APCs) and regulation of the TME[42]. Immunotherapy using nanosystems can broadly be classified as immunosuppressive modulation of the TME and cancer nano vaccines. Nanoparticles can alter the TME without creating autoimmunity by selective and specific targeting to deliver therapeutics at the intended site. This is achieved by the enhanced permeability and retention (EPR) effect and using active and passive targeting. Nanocarriers have been used to regulate the TME by using immune checkpoints and mediators as well as targeting Tregs, tumor associated macrophages (TAMs) and fibroblasts (TAFs) and myeloid-derived suppressor cells (MDSCs)[43]. Codelivery of certain cytokines with small molecular inhibitors is a popular strategy in this regard. For cancer vaccine development, commonly employed techniques include the simultaneous delivery of an antigen and an adjuvant, targeting dendritic cells (DCs), lymph node drainage, and antigen presentation. Antigens used for such vaccines can be either tumor-associated antigens (TAA), tumor-specific antigens (TSA), or cancer-testis antigens (CTA). Combinatorial therapy employing traditional methods like radio and chemotherapy along with immunotherapy may also produce promising results in anti-cancer treatment.

As the first line of contact of nanomaterials in the body is with the immune system, of which the protein corona interaction is the most important, the surface properties of nanocarriers play a primordial role in determining their systemic fate. Coupled with insufficient knowledge of the interactions between these materials and ubiquitous biological components and tumor heterogeneity, it is impossible to envision a single system to suit all patients. Hence, there is an urgent need for personalized medicine considering several physiological and clinical factors for the best therapeutic outcome. Several efforts have been underway to address this issue including the use of modeling using CRISPR systems for the investigation of nanoparticle-mediated chemotherapy with TAM polarization[44], evaluation of tumor biopsy including liquid biopsy using circulating tumor DNA[45] and multi omics data analyses to identify the hallmarks and determining the molecular fingerprint of cancer[46].

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