Editorial

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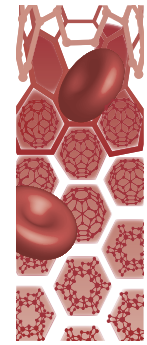

Dendritic cell-targeted theranostic nanomedicine: advanced cancer nanotechnology for diagnosis and therapy

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"A wide range of DC-targeted immunotherapies based on nanotechnology have evolved as safer medications for a variety of diseases and now it has been demonstrated in ongoing clinical trials."

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The development of advanced and efficient tumor immunotherapy is one of the key functional areas in current medicine as a cutting-edge therapeutic approach. Dendritic cells (DCs) are highly effective antigen-presenting cells that display a key role in trapping, processing and presenting antigens to initiate adaptive immunity. These cells play an important role in the development of immune-based nanodiagnostics and nanotherapeutics. A wide range of DC-targeted immunotherapies based on nanotechnology have evolved as safer medications for a variety of diseases and now it has been demonstrated in ongoing clinical trials. The aim of this editorial is to discuss the DC-targeted nano-immunotherapy and its theranostic applications.

Mechanism of DC immune response

In general, DCs are largely present in body parts such as the skin, lungs and the inner linings of the nose and GI tract. In fact, immature DCs are in constant motion to scan invading pathogens in their surrounding environment with the help of pattern recognition receptors that belong to the toll-like receptors group [1,2]. Classically, interstitial antigens are absorbed and processed by DCs in which MHC class II molecules will introduce these processed antigens to $CD4^+$ helper T cells to activate humoral immunity. Nonetheless, when antigens are transmitted to the DCs cytoplasm, the antigens are degraded by cytoplasmic proteasomes with simultaneous upregulation of cell surface receptors, in other words, MHC class I molecules which introduce these degraded antigens to cytotoxic T lymphocytes resulting in the cellular immune response.

Additionally, upregulated DCs, during their course of maturation, travel to lymph nodes through the lymphatic system or systemic circulation and finally to the spleen where they offer processed antigenic peptide to the helper T cells, cytotoxic T cells and B lymphocytes. Thus, the activated helper T cells boost adaptive immunity, cytotoxic T cells kill cancer cell or infected cells, whereas B lymphocytes produce antibodies and memory cells for future immune protection. This cellular immunity is necessary for successful immune cell-dependent tumor therapy [3,4].

Strategy for DC-targeted vaccination

Peptides and proteins can be clinically utilized as antigens to induce antigen-specific immunity. Peptides and proteins are often harmless and well tolerated in their soluble form, although they can produce minimal immune responses due to poor cell-presenting antigen absorption. Furthermore, adverse physiological conditions such as degradation of the enzyme and nonspecific contact with other biogenic materials in the extracellular matrix often interfere with the cycle of the presenting antigen [5].

Biomaterial-based antigen delivery is a promising approach for improving protein and peptide vaccine potency. Antigen-loaded nano-formulations such as liposomes, nanoparticles and polymeric carriers can be used as an anti-tumor vaccine delivery agent because they have the potential to safeguard the antigens against degeneration.

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Antigens enveloped in nanoparticles have also been demonstrated to improve the absorption of DCs antigen and these nanocarriers can release antigens in a sustained manner, resulting in increased cellular and humoral immunity [6–8].

Not only the stimulation of DCs by antigen but also the migration of DCs to draining lymph nodes is crucial for triggering different immune responses through DCs vaccine. Migration development, which is a key measurement for DCs-targeted vaccine to perform their activities, is typically investigated by using a conventional approach called 'FITC painting'. Unfortunately, this procedure cannot be used to realize real-time images of DCs migration, as it involves tissue cutting and staining. In both basic and clinical research, it is essential to establish a noninvasive diagnostic approach for DCs monitoring. Therefore, the unavailability of a highly sensitive and accurate *in vivo* tracing systems of DCs migration needs to be addressed [9,10]. In a recent study, it was determined that iron oxide–zinc oxide core shell nanoparticle could convey carcinoembryonic antigen to the DCs while simultaneously serving as a diagnostic agent [11]. It was also shown that DCs could effectively absorb the nanoparticle–antigen complex within an hour and then be traced *in vitro* by confocal microscopy and *in vivo* by MRI. These results suggested that, in mice immunized with nanoparticular-antigen-complex, DCs can promptly display tumor-specific T-cell activity, inhibit accelerated cancer proliferation and improve survival rate.

In recent research from Yang *et al*. a DC-targeted nano-formulation that triggers the proliferation of tumor allied antigens was evaluated [12]. The formulation was based on chimeric crossed-linked polymersomes derived from the self-assembly of a triblock copolymer, encapsulated with low-dose doxorubicin and a photosensitizer, in other words, pyropheophobide-a, to accelerate immunogenic cell death and to facilitate photodynamic therapy respectively. The *in vivo* results proved that following a single intravenous injection of nano-formulation, maturation of DCs in tumor lymph nodes and accumulation of cytotoxic T cells in tumor tissue were promoted. As a result, primary and distant MC38-colon adenocarcinoma cells growth was inhibited.

In other research works, antigen-caged upconversion nanoparticles (UCNPs) were used to tag and trigger DCs that could be accurately traced after injection into rats and stimulated antigenic specific immune activity. It was found that the model antigen ovalbumin, can be adhered on to the exterior of dual polymer-coated UCNPs through electrostatic interaction, producing a nanoparticle–antigen composite that was effectively captured by DCs and induced DCs maturation and release of cytokines [13]. Furthermore, extremely responsive *in vivo* upconversion luminescence detection of DCs that were tagged with nanoparticles was efficiently performed, the researchers witnessed the presence of DCs at tumor-draining lymph nodes after *in vivo* injection [14]. Also, a competent antigen-driven specific response including boosted T-cell proliferation, interferon-gamma development and cytotoxic T lymphocyte conveyed responses, was initiated by a nanoparticulate pulsed DCs vaccine. This is favorable for effective DCs-targeted immunotherapy against tumors. Additionally, bio-friendly nature and near-infrared triggered UCNPs will be ideal candidates for tumor diagnosis and therapy [15].

Safety margin of DC-targeted cancer immunotherapy in clinical trials

The nontoxicity of DC-targeted immunotherapies has been well established in several Phase I and Phase II clinical trials. The available Phase III trials, in which DC vaccines were compared with placebo, corroborated their safety profile. DC vaccination, is therefore, considered safe in patients with cancer and is expected to improve their quality of life. More research is, however, necessary to enrich these clinical results and to take advantage of the full potential of immunotherapies based on DCs [16–19].

Most recently, in a Phase I clinical trial (IRB # 03-04-053) of DC vaccine for subjects with a brain tumor, it was reported that this vaccine is safe in patients with malignant brain tumors and prolonged the survival of a number of patients. Furthermore, in the ongoing follow-up Phase II study (NCT01204684) to establish the most active vaccine components, DCs isolated from the subject's own blood will be treated with isolated tumor cell lysate of tumor tissue that is taken from the same subject during surgery [20]. This pulsing combination of antigen-presenting DCs with the tumor lysate will be performed in an attempt to trigger the subject's own immunity to detect and destroy their intracranial brain tumor.

Conclusion

On the whole, we conclude that DC-targeted cancer immunotherapy will be a safe and promising strategy for the diagnosis and treatment of many malignancies. Biomaterial-based nanocarriers, loaded with cancer-specific antigens and diagnostic principles, can further improve the pharmacokinetic profiles of the loaded antigen and in turn, facilitate *in vivo* tracking of the carriers. For the last 20 years, with a wide range of DC subsets, culture

procedures and treatment strategies, several clinical trials have been conducted. The safety and efficacy of DCs vaccination to elicit anti-tumor responses were well established. DCs vaccination has been proven for safety and feasibility in multiple clinical trials. In the future, we believe that DCs vaccination will have greater acceptability for clinical use based on its low toxicity profile and tumor-specific immune responses [2,16,20].

Financial & competing interests disclosure

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