Nanomaterials Acting on Natural Killer Cells

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Tumor immunotherapy, which includes immune target inhibition and chimeric antigen receptor cell treatment, is currently evolving quickly. Among them, natural killer (NK) cells are gradually becoming another preferred cell immunotherapy after T cell immunotherapy due to their unique killing effects in innate and adaptive immunity. NK cell therapy has shown encouraging outcomes in clinical studies; however, there are still some problems, including limited efficacy in solid tumors, inadequate NK cell penetration, and expensive treatment expenses. Noteworthy benefits of nanomaterials include their chemical specificity, biocompatibility, and ease of manufacturing; these make them promising instruments for enhancing NK cell anti-tumor immune responses. Nanomaterials can promote NK cell homing and infiltration, participate in NK cell modification and non-invasive cell tracking and imaging modes, and greatly increase the effectiveness of NK cell immunotherapy.

Keywords: NK cell immunotherapy ; nanomaterials ; tumor immunotherapy

1. Types of Nanomaterials

1.1. Metal Nanoparticles

The biomedical area makes extensive use of metal nanoparticles [1], which also play a vital role in controlling host defense and immune cell activation [2][3]. Because of their low toxicity, chemical inertness, and ability to control light, gold nanoparticles are a popular choice for cancer patient detection and treatment [4][5][6][7]. Ahn, for instance, developed an anti-tumor vaccine using Au NPs containing an endogenous EDB autoantigen. Furthermore, studies have shown that Au NPs can stimulate T cell anti-tumor activity and encourage DC cell antigen presentation, which prevents the growth and formation of malignancies [8].

1.2. Liposomes

The existence of liposomes was established in 1965 by Bangham et al. [9]. They discovered that liposomes are spherical, double-layered vesicles that possess both hydrophobic and hydrophilic properties. Furthermore, Chen and colleagues altered liposomes by adding anti-PD-1 and mannose, and they also enclosed anti-angiogenic medications and mTOR inhibitors within liposomes. Studies have demonstrated that this liposome has the ability to not only enhance the volume of mouse colon cancer tumors while concurrently suppressing angiogenesis and glycolysis but also rewire immune cells to enhance the efficacy of conventional anti-PD-1 therapy [10]. Since liposomes do not exhibit anti-tumor properties, they can only be utilized as a drug delivery mechanism in tumor immunotherapy, despite their great encapsulation efficiency and ease of manufacture. However, the emergence of multidisciplinary intersection gives liposomes new capabilities including targeting and immunotherapy, improving their use in clinical tumor treatment.

1.3. Hydrogels

Because hydrogels can load therapeutic medicines efficiently and have strong biocompatibility, tumor immunotherapy frequently uses them in its design. While conventional immunotherapy works well for treating primary tumors, it frequently falls short when it comes to treating metastatic and recurring malignancies. To stop tumor spread and lower tumor recurrence, a new therapeutic strategy must be created immediately. For instance, Chen et al. created novel nanomaterials for tumor immunotherapy using PPP (PLGA-PEG-PLGA) and the ROCKs inhibitor Y27632. Due to the temperature-responsive nature of the two-component combination, the hydrogel state can be preserved during the ensuing treatment procedure. The results showed that when hydrogel entered tumor cells, it caused the cells to split into fragments and released Y27632, which made dendritic cells phagocytize the pieces and present antigens. This, in turn, activated T cells, boosting the immune response against mouse melanoma [11].

2. Application of Nanomaterials Targeting NK Cells

2.1. Nanomaterials for Molecular Imaging of NK Cells

Clinical and contemporary research always employ immunohistochemistry biopsies to provide real-time monitoring of NK cell responses in the body, which complicates the regulation of ACT. Contrast agent-mediated molecular imaging techniques, including immunopositron emission tomography (PET), immunomagnetic resonance imaging (MRI), immunophotoacoustic imaging (PAI), etc., can be used to anticipate the NK cell response and activity in ACT. Thus, developing multimodal imaging nanoparticles for in vivo real-time NK cell response monitoring is crucial for future controllable ACT. Quantitative dynamic footprinting (qDF), total internal reflection fluorescence (TIRF) microscopy, optical live-cell imaging (including multiphoton and confocal imaging), light-sheet microscopy, super-resolution microscopy, and other techniques have also improved in their ability to assess the tracking of NK cells. Many of these techniques rely on directly labeling the surface of NK cells with fluorophores or contrast agents, cell-permeable fluorophores, radioisotopes, or other substances to enable real-time visualization of NK cell immunotherapies in tumors. NK cells have also been labeled for MRI using nanoparticles, such as ultra-small and superparamagnetic iron oxide nanoparticles. It is quite simple to introduce iron oxide nanoparticles to NK cells; either transfection agents or a straightforward incubation electroporation are needed. NK cells tagged with iron oxide exhibit a robust low-intensity signal in T2- and T2*-weighted imaging. The duration of iron oxide labeling can last for up to 4 days, the duration of labeling often depends on the length of time that the NK cells under-going adoptive transferred have survived [12].

For instance, Dong Hyun Kim et al. created magnetic nanocomposites (HAPF) that can be used to identify NK cells using protamine, hyaluronic acid, and superparamagnetic nano iron oxide—materials that the FDA has approved for clinical use. Effective adhesion of the produced HAPF to NK cells (HAPF-NK) is observed. Applying an external magnetic field stimulates natural killer cells (NK cells) and encourages the production and release of lysosomes. Magnetically activated HAPF-NK cells also allow MR imaging to guide NK cells through intraductal arterial (IA) infusion for the treatment of hepatocellular carcinoma (HCC) solid tumors. Tumor development was decreased following therapy with magnetically activated NK cells injected by IA, suggesting an increased therapeutic efficacy of image-guided local delivery of magnetically activated HAPF-NK cells.

2.2. Nanomaterials Enhance the Anti-Tumor Activity of NK Cells

The primary variables influencing the immunological activity of natural killer (NK) cells are the negative regulatory factors released by tumor cells, including TGF-β and IFN-γ. By reducing the expression of NK cell surface-activating receptors, they suppress activation signaling and NK cell cytotoxicity as well as the anti-tumor immune response. Therefore, inhibiting TGF-β signal transduction is a good place to start if we wish to increase the anti-tumor activity of NK cells. Liu et al., for instance, created nanoemulsions with selenocysteine and a TGF-β inhibitor. Research revealed that the nanoemulsion up-regulated the expression of the NKG2DL receptor and dramatically blocked TGF-β/TGF-βR1/Smad2/3 signaling, thereby successfully increasing the anti-tumor activity of NK cells [13]. Furthermore, low response rate, medication resistance, and patient heterogeneity are issues that nanomaterials can solve for traditional therapy to increase efficacy [14]. For instance, selenium-based nanoparticles can boost the anticancer activity of natural killer cells (NK cells) while simultaneously eliciting a non-specific immune response, hence increasing the overall immunotherapy efficacy [15][16]. Consequently, adding nanomaterials can greatly enhance the therapeutic benefit of NK cell treatment while also lowering its clinical adverse effects. Research on how cancer patients are treated is very important.

2.3. Immune Modification of NK Cells by Nanomaterials

As the first effectors to identify and track tumor cells, NK cells are increasingly giving way to CAR-NK as the next wave of cutting-edge immunotherapy tools. Simultaneously, the advancement of CAR-NK immunotherapy has facilitated the delivery of nanomaterial-based chimeric antigen receptor genes. Through the use of their own permeability, retention effect, and aggregation energy, chitosan nanoparticles loaded with IL-21 and NKG2D genes have been shown in studies to more successfully activate NK cells in vitro and exhibit superior anti-tumor effects [17][18][19]. Therefore, by altering NK cells with pertinent cytokines, nanomaterials can dramatically suppress the proliferation of tumor cells.

Furthermore, the nanomaterial-modified synthetic natural killer cells have the ability to kill tumor cells directly. For instance, it was discovered that a new nanomaterial made of NK cells transfected with the human ferritin heavy chain (hFTH1) gene and embedded in gold nanoparticles could direct NK cells into TME and give excellent transfected NK cell imaging [20]. Consequently, by exploiting the immunological modification of NK cells, biocompatible multifunctional nanomaterials can enable the real-time monitoring of NK cells in patients [21].

2.4. Nanomaterials Enhance NK Cell Homing and Infiltration

The homing behavior of NK cells is mainly dependent on the signal transduction between the homing receptor on the surface and the ligand, while the infiltration of NK cells is influenced by the interaction with TME [22][23]. Studies have found that once NK cells infiltrate tumor cells and homing receptors bind to ligands, immune cell activation signals will be transmitted and secrete perforin, granzyme, and apoptosis-inducing factors [24] to play the anti-tumor immune role of NK cells. In order to prevent the growth of tumors, it is therefore essential to employ nanomaterials to improve NK cell homing and infiltration. For instance, conjugating iron oxide nanoparticles to primary NK cells dramatically improved their homing abilities and increased granzyme and perforin production [25]. Furthermore, recent research has shown that external magnetic guidance also influences the homing and infiltration of NK cells. Wu et al., for instance, subcutaneously implanted polydopamine-coated magnetic iron oxide nanoparticles into mice. The outcomes demonstrated that the magnetic particles might enhance NK cell homing and infiltration while simultaneously activating NK cells to attack tumor cells directly, exhibiting more potent anti-tumor activity [26]. Tumor invasion and metastasis can be controlled by NK cells' homing behavior. Because they affect NK cell homing, nanomaterials thus have a bigger impact on the clinical therapy of malignancies.

2.5. NK Cell-Associated RNAi Loaded on Nanomaterials

RNA effectors, such as siRNA, miRNA, and shRNA, have the ability to silence particular immune cell genes, altering the function of their genomes and boosting anticancer activity [27]. These RNA effectors can be better delivered by using nanomaterials, which can also serve as a great nano-delivery mechanism. For instance, *CD47* and *PD-1* expression might be markedly reduced by cationic liposomes loaded with epithelial cell adhesion molecules including siCD47 and siPD-1. Furthermore, the liposome has the ability to speed up the transmission of anti-tumor immune response signals and enhance NK cell proliferation in addition to potently inhibiting tumor growth and lung metastasis. In a lung metastasis model, systemic treatment of LPP-P4-Ep may dramatically suppress the formation of solid tumors in subcutaneous mice and diminish lung metastasis in mice by effectively silencing *CD47* and *PD-L1* compared to single-gene silencing in vivo. Target delivery of LPP-P4-Ep enhanced the release of many cytokines, including IFN-γ and IL-6, and enhanced anti-tumor T cell and NK cell responses both in vivo and in vitro [28].

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