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Review

Combinatorial prospects of nano-targeted chemoimmunotherapy

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ABSTRACT

Despite the significant increase in our knowledge on cancer initiation and progression, and the development of novel cancer treatments, overall patient survival rates have thus far only marginally improved. However, it can be expected that lasting tumor control will be attainable for an increasing number of cancer patients in the foreseeable future, which is likely to be achieved by combining cancer chemotherapy with anticancer immunotherapy. A plethora of new cancer chemotherapy reagents are expected to become accessible to the clinic in the coming years which can then be used for efficient tumor debulking and aid in antigen exposure to the immune system. Durable remission and the eradication of micrometastases are likely to be achieved with specialized monoclonal antibodies and therapeutic cancer vaccines that modulate the immune system to overcome immunosuppression and kill distant cancer cells. Moreover, the method of drug delivery to tumors, stromal and immune cells is expected to shift largely from conventional 'free' drug molecules to encapsulated in targeted nano-vehicles, therapeutics often referred to or considered part of "nanomedicine". Several biocompatible nano-vehicles, such as metal-nanoparticles, biodegradable-nanoparticles, liposomes or dendrimers are potential candidates for targeted drug delivery but may also serve additional purposes. A dexterous combination of nanomedicine, cancer immunotherapy and chemotherapeutic engineering are likely to become the basis for new hope in the form of targeted cancer therapies that could attack tumors early in their development. One can envision nano-vehicles that would selectively deliver effective doses of chemotherapeutic agents to cancer cells while leaving healthy cells untouched. Furthermore, given that after chemotherapeutic treatment there often remains a limited number of chemo-resistant tumor cells, which go on to drive tumor progression, nano-vehicles could also be engineered to provoke an appropriate immune response to destroy these cells. Here, we discuss the potential of the combinatorial role of cancer chemotherapy, cancer immunotherapy and the prospective of nanotechnology for the targeted delivery of chemoimmunotherapeutic agents.

1. Introduction

Cancer chemotherapy regimens, together with surgery and radiotherapy, are currently the main means of tumor mass debulking. Unfortunately these methods of intervention are often insufficient to cure cancer patients and relapse commonly follows due to clinically undetectable micrometastases. It is tempting to speculate that a combination of cancer chemotherapy, to deplete tumor cells, combined with immunotherapy, to prevent relapses, could increase patients' outcome. In fact, some types of chemotherapies reduce the number of regulatory, immunosuppressive, T cells (Tregs) in the tumor, allowing a more immune-favorable environment to form, thereby clearing a path for an effector and memory T cell response to act in concert to destroy cancer cells [1]. There is evidence that the phenotype and function of the immune infiltrates in tumors markedly affect prognosis of the most common cancer types and patient's outcome may be predicted following cancer chemotherapy by the characteristics of the anti-cancer specific immune responses [2]. Furthermore, considering the advantages and disadvantages of existing cancer therapies, a new approach in which cancer chemotherapy and immunotherapy are rationally combined is conceivably quite more effective than either modality alone. However, drug combinations are also likely to

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increase treatment costs and induce systemic toxicity, an issue that will need to be carefully evaluated during pre-clinical research and clinical trials.

Although a high dose of cytotoxic chemotherapeutics is immunosuppressive, and may lead to lymphopenia, properly dosed and scheduled chemotherapy can rather facilitate, and not inhibit, an immune response against cancer cells [3]. In more recent years it has become apparent that a few specific chemotherapeutic drugs have an attribute, in addition to conventional killing of tumor cells, that is to induce a distinct −immunogenic− form of cell death or by directly having an activating effect on immune cells when provided at low doses [4,5]. Therefore, low doses of immunogenic chemotherapy may synergize with other forms of immunotherapy.

In the emerging field of nanomedicine, nano-sized tools are deployed that generally aim to improve pharmacological therapies, as well as to introduce novel modalities in disease prevention, diagnosis and treatment [6]. Moreover, nanomedicine technology may increase the efficacy, and rationally integrate distinct modalities into one potent anti-cancer treatment. A major segment in this field is the assisted delivery of drugs, commonly with the purpose to decrease bio-distribution of a drug, thereby reducing off-target side effects, whilst increasing drug exposure to target cells only. There is also a significant segment that makes use of inherent physicochemical properties of nanomaterials themselves to achieve desired biological or chemical effects. For instance, photodynamic and photothermal therapy, and nano-agents used for molecular imaging.

In this review, we will describe the immunological state of the tumor microenvironment to illustrate the complex challenges that researchers are confronted with, and how nanotechnology is currently being adopted to improve contemporary and upcoming therapies. Next, we will describe and summarize the immunogenic properties of some commonly used chemotherapies and discuss how current approaches harness, and highlight the future potential, of rationally combined immunotherapy and chemotherapy using nanotechnology.

2. Nanomedicine

Recent developments in the field of nanomedicine have highlighted major advantages of nano-vehicles (NVs) in anti-cancer drug delivery with the aim to reduce systemic wide chemotherapy distribution and reducing adverse effects whilst increasing treatment efficacy [7]. These vehicles, with sizes ranging from the nano to the micro scale, are versatile and highly adaptable. A manifold of NV types are currently in research, such as NVs that react to a magnetic field, certain pH levels or temperatures, or convert light to heat and radical oxygen species. A distinct class of NVs is used for transport and delivery of therapeutic compounds of which several types are currently being developed, such as dendrimers, metallic nanoparticles, liposomes (LPs) and nanoparticles (NPs). From these, both LPs and NPs are of particular interest, as they have been proven to be biocompatible, to efficiently transport and deliver antigens to antigen presenting cells (APCs), but also to protect the antigens from degradation and to gradually release the antigens, thereby prolonging half-life. It has been demonstrated that LPs are suitable carriers of antigens for efficient delivery to APCs for a variety of pathogens [8]. Among its many advantages, LPs are absent of toxicity, low immunogenic, do not induce hypersensitivity or form granuloma at the site of administration, are simple to make and are inexpensive. LPs that are taken-up via endocytosis by APCs, such as immature dendritic cells (DCs), result in a highly concentrated amount of intracellular (cytoplasmic) antigen, which favor cross-presentation via major histocompatibility complex (MHC; HLA region in humans) class I, pivotal to mount an effector T cell response [9,10].

Unlike LPs, the advantages of NPs, such as the poly(lactic-co-glycolic acid; PLGA) particles, are the excellent stability benefiting long-term storage, and the exceptional biodegradability and biocompatibility. The catabolic remnants of the PLGA particle in the body are lactic and glycolic acid, both natural and non-toxic metabolites and PLGA particles have been used for decades in various therapeutic applications in the clinic. PLGA-NPs are FDA approved and like LPs its physicochemical properties can be manipulated for controlled time- and location-specific release of drugs. Particularly the size and type of coating determine the blood circulation time with particle size being the main determining factor. Particles <20–30 nm in size are eliminated by renal excretion while particles >300 nm are removed by opsonization (surface modulation) and are scavenged by circulating phagocytes and macrophages or are filtered by the liver and spleen [11,12]. The NP optimum circulation time size range is 70–300 nm and may be further enhanced with a surface polyethylene glycol (PEG) coating. PEGylation of NPs is reported to extend half-life, reduce immunogenicity and not to form any additional toxic metabolites [13,14]. Conversely, PEGylation has also been reported to decrease bioavailability, enhance serum protein binding and elicit immune responses [15]. From a chemical perspective, PEGylation provides a highly flexible platform that allows the attachment of chemical residues or useful molecules to target PLGA NPs to specific cells [16].

2.1. Active and passive tumor targeting

In the context of anti-cancer drug delivery, NVs can target the tumor in a passive or active manner. Passive targeting is a process of accumulation of NVs in solid tumors that occur due to the enhanced permeation and retention (EPR) effect, which is caused by leaky blood vessels in tumors, originated from unregulated secretion of angiogenic factors, and decreased lymphatic drainage [17]. The aberrant vasculature decreases the efficient exchange of molecules into the bloodstream thereby allowing the accumulation and retention of NVs. The retention time is long enough to facilitate the NV uptake by cancer cells via pinocytosis or to be exploited by the NVs that use the retention time for self-disintegration and the release of its contents in the tumor cell and its surroundings [18]. In case of absence of the EPR effect, NV extravasation into the tumor bed is unlikely and therefore access to cancer cells is challenging, although some strategies may be employed to circumvent such obstacle [19,20].

Interestingly, although the EPR effect does not always exist or found to be pronounced enough in cancer patients, in some cases it is possible to induce or augment the EPR effect, e.g. increase systolic blood pressure via slow angiotensin II infusion or the administration of topical nitroglycerin that is converted to nitric oxide in the tumor microenvironment [21,22].

Active or targeted delivery may enhance drug delivery by covalent coupling of ligands on the NP surface (e.g. PEG residues) that increase the affinity of NVs to specific cells and may enhance retention and specific uptake [23]. Notwithstanding, the EPR effect is still indispensable to expose the target cells to the targeted NVs in the first place. Examples of targeting moieties that could be used are specific ligands or monoclonal antibodies targeting receptors, integrins and selectins found overexpressed in cancer cells. These targeting moieties are best directed to specific or overexpressed receptors with endocytic capability, such as the folate receptor or the gonadotropin-releasing hormone receptor, which are often found overexpressed in tumors [24–26]. A graphical overview depicting the main differences between passive and active tumor targeting is given in Fig. 1.

To illustrate that active targeting may indeed enhance target cell