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Cell-mediated delivery of synthetic nano- and microparticles

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ABSTRACT

Cell mediated delivery of synthetic nano- and microparticle based drug carriers is a very promising strategy to enhance control over the distribution of drugs and improve targeting. This article will present an overview of work, which has been done to explore cell surface modification strategies for the cellular hitchhiking of synthetic nano- and microparticles. The first part of this article will present and discuss the different types of cells that have been explored for cell mediated drug delivery. The second part of this review will discuss the various chemical strategies that have been elaborated for the conjugation or immobilization of nano- and microparticles on the surface of these cells.

1. Introduction

Small molecule drugs are lacking tissue and organ specificity, suffer from rapid body clearance and are often associated with numerous side effects, especially chemotherapeutic agents, which are usually highly toxic [1]. The use of polymer conjugates or lipid or polymer nanoparticles to encapsulate, transport and release an active substance has allowed to enhance tissue and organ specificity, either in a passive fashion taking advantage of the so-called enhanced permeation and retention (EPR) effect or by exploring active targeting strategies by incorporating ligands that target receptors that are overexpressed at the cancer cell surface [1–3]. While the EPR effect and active targeting strategies allow to modulate the biodistribution to some extent, still only a fraction of all nanocarriers reaches the tumor while the vast majority of drug loaded nanocarriers are cleared by the reticuloendothelial system (RES). Additionally, the clinical translation of the EPR effect from animal models to humans has proven to be challenging [4]. Moreover, whereas the EPR effect may be relatively efficient in some cancer models due to the leaky nature of blood vessels in angiogenic tumors, there is a range of indications to which it does not apply. In several instances, for example, the active substances need to be transported across tight endothelial cell barriers. Finally, targeting circulating or disseminated tumor cells after primary tumor resection is extremely challenging and is unmet with current nanocarrier approaches.

A strategy that potentially allows to overcome many of the challenges listed above and to control biodistribution in a highly specific manner involves the use of cells to mediate the transport of drug loaded nanocarriers [5–7]. Cells have unique properties e.g. to circulate in the blood stream for extended periods of time, to target (cancer) cells or to pass challenging biological barriers. Attaching polymer-drug conjugates or drug-loaded nanocarriers to the cell surface or incorporating them in the cell could provide unique possibilities to enhance the cell or tissue specificity or circulation time of those nanomedicines. While this article will focus exclusively on the decoration of cell surfaces with synthetic nano- and microparticles, cells are also explored as Trojan horses [5]. There are a number of limitations associated with the internalization of drug-loaded particles and polymer conjugates in cell carriers. A first one is the risk of premature degradation of the nanoparticle and its payload inside the cell carrier. A second is the need for the cell carrier to release its cargo at the target site, which adds an additional step to the whole process. Finally, internalization of a cargo is essentially limited to cells with an efficient phagocytic system such as monocytes or macrophages whereas surface functionalization is in principle possible with the entire repertoire of circulating cells, opening doors to long circulating delivery approaches based on red blood cell functionalization or highly specific targeting strategies based on modification of cells from the adaptive immune system such as B and T lymphocytes [8,9] or based on the pathotropism of stem cells [10].

The aim of this article is to provide an overview of the state-of-the art in the use of surface-modified cells to mediate the delivery of synthetic nano- and microparticles. The first part of this article will present and discuss the different types of cells that have been explored for cell mediated drug delivery. The second part of this review will discuss the various chemical strategies that have been elaborated for the conjugation or immobilization of nano- and microparticles on the surface of these cells.

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2. Cells used for cell-mediated drug delivery

This section will give an overview of the different types of cells that have been used as vehicles for the cell surface attachment and transport of synthetic nano- and microparticles.

2.1. Red blood cells

Red blood cells (RBCs) are biconcave disk-shaped cells lacking organelles and a nucleus, measuring approx. 7 μm in diameter. They constitute >99% of the blood and are long-circulating, up to approx. 120 days in humans [11]. They are specialized in oxygen transport, which is mediated by hemoglobin, encapsulated in large amounts inside RBCs. RBCs are highly deformable and flexible to allow them to reach capillary venules. RBCs do not normally extravasate from the circulation into tissues except within the spleen and liver where senescent RBCs are removed from the circulation by the phagocytic system [11]. The plasma membrane of a RBC is slightly negatively charged and comprised of >300 different membrane proteins [12], which offer many opportunities for cell surface modification. RBCs intrinsically play an important role in altering the biodistribution and pharmacokinetics of many drugs, increasing their circulation times [11]. The ability to prolong the circulation time of drugs, together with a high biocompatibility, especially in the case of autologous transfer, are very attractive features in the context of drug delivery. RBCs have been intensively investigated as carriers for the vascular delivery of a variety of surface bound molecules and more recently for the transport of nanoparticulate carriers as will be discussed in the next section [11,13].

2.2. Leukocytes

Leukocytes form the innate and adaptive immune system and respond, for example, against infection, inflammation and tumor growth [14]. Both the innate and adaptive immune system play a crucial role in detecting and killing cancer cells. The unique features of leukocytes, such as their ability to travel to a specific site of disease as well as to transmigrate across endothelial barriers [15] and penetrate into hypoxic tumor regions [16] provide unique opportunities for delivery to areas that are otherwise difficult or impossible to reach by traditional drug delivery approaches. Particularly interesting cells for cell-mediated delivery are monocytes, which are long lived white blood cells deriving from the bone marrow and which can differentiate into tissue-resident macrophages or dendritic cells (DC) [17], as well as B cells, T cells, especially of the $CD4^+$ (helper) and $CD8^+$ (cytotoxic) subtypes and natural killer (NK) cells. The T lymphocytes used in adoptive cell therapy could potentially concomitantly serve as drug carrier. The decorated adoptively transferred lymphocytes are then not only a carrier but also directly exert a therapeutic activity.

The primary mission of monocytes is to replenish the pool of tissue-resident immune cells [18]. Furthermore, they are also involved in the innate immune response against bacterial, fungal, parasitic and viral infection [19]. In humans, 3 classes of monocytes coexist in the peripheral blood circulation, which are characterized by their relative expression of CD14 and CD16 surface markers. The largest subpopulation, consisting of approx. 80 to 90% of all monocytes, is the $CD14^+CD16^-$ subset, which shows the highest phagocytic activity and also produces IL-10. In contrast, the others subpopulations are expressing CD16 and express CD14 at high or low level. These are divided in two classes (i) the $CD14^+CD16^+$ subset, which is entirely responsible for the production of TNF-α and IL-1 and which also has a phagocytic activity and (ii) the $CD14^{dim}CD16^+$ subset, whose actual function is not well understood. Monocytes of this last subset express low level of the CD14 markers. They are poorly phagocytic and do not express cytokines such as TNF-α and IL-1 [20].

Tissue differentiated macrophages are present in a broad spectrum of pathological conditions including cancers and several inflammatory diseases [18]. Monocytes and macrophages along with DCs, neutrophils and mast cells are 'professional' phagocytic cells, which express specialized membrane receptors and are able to detect apoptotic/necrotic cells, opsonized pathogens or cell debris [18]. The phagocytic competence of macrophages and monocytes represents a major challenge in attaching and immobilizing a cargo on their surface for delivery purposes [21]. The few successful examples of stable and long-lasting surface functionalization required the use of very large synthetic particles, which have a disk-like shape, thus avoiding internalization (see Doshi et al. [22]). These examples will be discussed in more detail in the following section.

B and T lymphocytes are part of the adaptive immune system and immunological memory. B lymphocytes originate from the bone marrow and are the central player of the humoral immunity [23]. Upon antigen exposure, mature naïve B cells, which trafficked to secondary lymphoid organs, differentiate via a series of fast evolutionary selection steps to antibody-secreting B cells also called plasma cells [24]. These plasma cells can subsequently reenter the blood circulation via the lymphatic system to reach distant sites of infection/inflammation. T lymphocytes derive from the thymus and are classified in two important subsets, which mediate the adaptive cellular response through (i) activation of other immune cells ($CD4^+$ Helper T cells) or (ii) via killing target/infected cells ($CD8^+$ Cytotoxic T cells) [25]. Lymphocyte trafficking depends on their activation status. While blood-borne naïve T cells, similarly to naïve B cells, possess surface markers that enable them to home to secondary lymphoid organs, antigen-experienced lymphocytes migrate towards sites of inflammation [26]. This duality in homing properties, i.e. secondary lymphoid organs vs inflamed tissues is very attractive for cell-mediated drug delivery, especially in the context of cancer therapy, in which these distinct trafficking patterns allow targeting either the primary tumor or disseminated tumor cells in the lymph nodes. T lymphocytes are activated by DCs in the lymph nodes via interaction with the MHC class II complexes. The migration and accumulation of lymphocytes into diseased tissues is general to all subsets of circulating leukocytes [27]. It is triggered by an adhesion cascade, consisting of a series of interactions between endothelial recruiting molecules called selectins and activation of lymphocyte chemoattractant receptors. This activation induces the expression of integrins on the lymphocytes, which mediate firm binding to intercellular and vascular endothelial adhesion molecules. Finally, lymphocytes diapedese through the endothelial barrier to reach their target area [25].

$CD8^+$ T cells elicit their cytotoxic effect essentially by secreting perforin together with a variety of granzymes or via activation of the tumor-necrosis factor receptor Fas of target cells and to a lesser extent via production of cytokines such as tumor-necrosis factor (TNF) and interferon-γ (IFN-γ) that have cytotoxic action when secreted nearby target cells [28]. $CD4^+$ T cells mediate the immune response via the release of cytokines of two different classes, T helper 1 (Th1) type and T helper 2 (Th2) type, which activate different cells of the innate and adaptive immune system [29].

Natural killer (NK) cells represent about 10–20% of all peripheral blood mononuclear cells [30]. Human NK cells are subdivided into 5 categories depending on the relative expression of the surface markers CD56 (an adhesion molecule) and CD16 (a low affinity Fc receptor) [31]. NK cells are not only localized in peripheral blood but are also present in lymph nodes, spleen and bone marrow where they exert different functions based on their phenotype [30]. NK cells are mainly involved in innate immunity [32] but also influence and shape adaptive immune responses [31]. Their role in immunoregulation is also important and predominantly mediated through secretion of cytokines of the Th1 type [32]. NK cells are activated by a variety of stimuli, in particular by contact with DCs, MHC-I-negative cells, IgG of the immune complexes or via direct activation by tumor-associated markers present on tumor cells or pathogen-derived products as well as a myriad of interleukins and type I interferons [30]. NK cells represent the first line of defense against tumor and infected cells, recognizing stressed cells with low