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Review

Drug targeting systems for inflammatory disease: One for all, all for one

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ABSTRACT

In various systemic disorders, structural changes in the microenvironment of diseased tissues enable both passive and active targeting of therapeutic agents to these tissues. This has led to a number of targeting approaches that enhance the accumulation of drugs in the target tissues, making drug targeting an attractive strategy for the treatment of various diseases. Remarkably, the strategic principles that form the basis of drug targeting are often employed for tumor targeting, while chronic inflammatory diseases appear to draw much less attention. To provide the reader with a general overview of the current status of drug targeting to inflammatory diseases, the passive and active targeting strategies that have been used for the treatment of rheumatoid arthritis (RA) and multiple sclerosis (MS) are discussed. The last part of this review addresses the dualism of platform technology-oriented ("one for all") and disease-oriented drug targeting research ("all for one"), both of which are key elements of effective drug targeting research.

Contents

1. Introduction

In the last decades, targeted drug delivery has become an established field in pharmaceutical research. By using a targeting system that assists in directing a drug to the site in the body where it needs to exert its effect, target tissue specificity of the therapeutic agent can be increased while the off target effects can be limited [1,2]. Although a drug targeting strategy can potentially improve the clinical efficacy of therapeutic interventions in many, if not all, diseases, most drug targeting research has been focused on cancer (Fig. 1) [3–5]. The high morbidity and mortality among cancer patients evidently justifies this focus working on tumor-targeted drug delivery systems. At the same time, the large socio-economical

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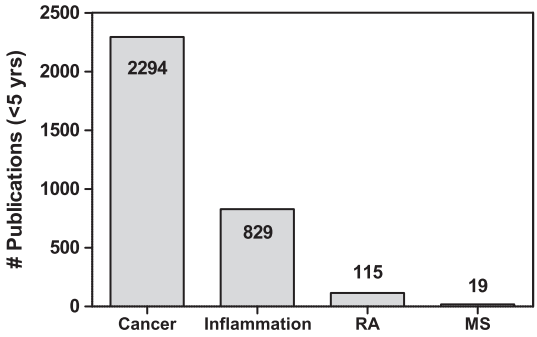

Fig. 1. Number of research publications over the last 5 years related to drug targeting to diseases. Results represent the number of hits of MEDLINE searches (query " drug delivery" or "drug targeting" or "nanomedicine"), specified to malignant diseases (using "cancer"), inflammatory diseases (using "inflamm*"), rheumatoid arthritis (RA, using "rheum*" or "arthritis"), and multiple sclerosis (MS, using "multiple sclerosis" or "encephalomyelitis").

impact of chronic inflammatory disorders, such as rheumatoid arthritis and multiple sclerosis, on both patient and society appears not to be fully appreciated in drug targeting research [6–8].

It is remarkable that there is only limited attention for these diseases, since in principle many strategies employed for targeted drug delivery to tumors would seem applicable for drug targeting to sites of inflammation. In fact, cancer is strongly linked to inflammation and is often designated as a chronic inflammatory disease itself, illustrating the overlap of cancer and inflammation in the context of drug delivery [9–11]. This contribution aims to provide the reader with an update of the current status of the field with respect to drug targeting in inflammatory disorders. In addition, we will give our perspective on how drug targeting can be approached to improve its clinical impact.

2. Drug targeting to inflammatory disease

2.1. Passive drug targeting

A quarter of a century ago, Maeda and coworkers demonstrated for the first time the tumoritropic accumulation of proteins and macromolecules [12]. By coupling poly(styrene-co-maleic acid) to a protein (neocarzinostatin) that has anti-tumor activity, a conjugate (SMANCS) with increased molecular weight was formed which showed an improved *in vivo* half-life compared to the unmodified protein [13]. To relate the efficacy of SMANCS to its target tissue concentration, the plasma clearance and tumor accumulation of neocarzinostatin, SMANCS and several other plasma proteins including albumin, were determined. A clear positive correlation between plasma half-life, molecular size and tumor-specific accumulation was observed, which was attributed to a 'highly enhanced leakiness' of the tumor vasculature for macromolecules [12]. Moreover, upon intratumoral injection of Evans blue-albumin complexes, there was a remarkable reduction of clearance of the complexes in the tumor compared to healthy tissues, indicating a tumor-specific deficit in lymphatic drainage. This phenomenon of enhanced vascular leakiness and impaired lymphatic drainage, now known as the 'enhanced permeability and retention (EPR) effect', has since been used extensively for passive tumor-specific drug delivery, also described as passive targeting, using macromolecular and particulate drug targeting systems [2,14–18].

However, the EPR effect has not been observed exclusively in tumors. In fact, in 1971, 15 years before the landmark study of Matsumara and Maeda, Kushner and Somerville described a similar relationship between the molecular size of proteins and their localization in arthritic joints of patients with rheumatoid arthritis (RA) and other arthritic diseases [19]. Although the precise mechanism remained unclear, one of the suggested mechanisms was an inflammation-induced 6- to 40-fold increase of blood–joint barrier permeability for high molecular weight molecules [20]. Consequently, a complication frequently observed in patients with RA is hypoalbuminemia, which may be attributed to an increased albumin extravasation and metabolism within the inflamed joint [21,22]. Similarly, an increase in blood–brain barrier (BBB) permeability for serum proteins, such as fibrinogen, has directly been correlated to areas of (active) demyelinization (i.e. plaques) in multiple sclerosis (MS) [23–25]. While the lymphatic drainage in inflamed tissues, when compared to tumors, appears to be still functioning [26], the significantly increased vascular permeability in the target tissues allows for the successful application of passively targeted drug delivery strategies in models of inflammatory diseases such as RA and MS [27–31].

It is important to emphasize that the size and the pharmacokinetic profile of the drug carrier are key characteristics of passively targeted drug delivery systems [32,33]. A lower size limit of ~50 kDa and an upper size limit in the range of ~200 nm enhance targeting of the carrier-associated drug by means of the EPR effect while preventing glomerular filtration [34,35]. The long circulation time of these carriers increases the statistical probability for sufficient target accumulation of the drug to take place. Indeed, significantly higher drug concentrations may be obtained in the target tissue by employing such passively targeted drug delivery systems, but the term 'targeted' may appear somewhat deceptive in this context [36,37]. Macromolecules and nanoparticulate carrier systems that are too large to be cleared renally from the body are taken up by phagocytic cells of the reticuloendothelial system (RES), mainly in liver and spleen [38]. As a result, by far the largest part of the injected dose is 'targeted' to these organs, while on average only a much smaller fraction (less than 10%) of the injected dose will end up in the tissue where the drug needs to exert its effect. Nevertheless, the therapeutic consequences of passive targeting (of macrophages) are likely more complex than the mere target tissue accumulation: there is, for example, evidence that the anti-tumor effect of liposomal glucocorticoids may be related to a decrease in white blood cells, rather than the accumulation in the target tissue [39].

2.2. Active drug targeting

While local drug concentrations in the diseased tissue can be increased by employing a passive targeting strategy, directing the drug delivery system to a specific cell type by means of a targeting ligand (i.e. active targeting) may help to further improve the efficacy of the targeted drug. Generally, such strategies do not increase the overall concentration in the target tissue, but rather change the distribution within the tissue. A notable exception in this case is targeting within the blood stream for which extravasation is not required and therefore not the rate-limiting step. In chronic inflammatory diseases such as RA and MS, a shortage of oxygen and nutrients induces the formation of new blood vessels, a process known as angiogenesis, which contributes to the pathogenesis and development of these diseases [40–45]. By interfering with the angiogenic process in preclinical models of RA and MS, it has been shown that the disease intensity can be alleviated [46–49]. Both vascular endothelial cells and monocyte-derived cells, including macrophages, are closely involved in the angiogenic process in chronic inflammatory diseases, which makes them attractive targets for an active drug targeting approach [50–54]. As a result of the pro-inflammatory microenvironment, membrane receptors that are involved in angiogenesis signaling are upregulated, marking the cells expressing them 'inflammation-specific', and designating them as possible targets for drug delivery [55].