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Review

Smart blood cell and microvesicle-based Trojan horse drug delivery: Merging expertise in blood transfusion and biomedical engineering in the field of nanomedicine

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ABSTRACT

Therapeutic and diagnostic applications of nanomedicine are playing increasingly important roles in human health. Various types of synthetic nanoparticles, including liposomes, micelles, and other nanotherapeutic platforms and conjugates, are being engineered to encapsulate or carry drugs for treating diseases such as cancer, cardiovascular disorders, neurodegeneration, and inflammations. Nanocarriers are designed to increase the half-life of drugs, decrease their toxicity and, ideally, target pathological sites. Developing smart carriers with the capacity to deliver drugs specifically to the microenvironment of diseased cells with minimum systemic toxicity is the goal. Blood cells, and potentially also the liposome-like micro- and nano-vesicles they generate, may be regarded as ideally suited to perform such specific targeting with minimum immunogenic risks. Blood cell membranes are "decorated" with complex physiological receptors capable of targeting and communicating with other cells and tissues and delivering their content to the surrounding pathological microenvironment. Blood cells, such as erythrocytes, have been developed as permeable carriers to release drugs to diseased tissues or act as biofactory allowing enzymatic degradation of a pathological substrate. Interestingly, attempts are also being made to improve the targeting capacity of synthetic nanoparticles by "decorating" their surface with blood cell membrane receptor-like biochemical structures. Research is needed to further explore the benefits that blood cell-derived microvesicles, as a Trojan horse delivery systems, can bring to the arsenal of therapeutic micro- and nanotechnologies. This short review focuses on the therapeutic roles that red blood cells and platelets can play as smart drug-delivery systems, and highlights the benefits that blood transfusion expertise can bring to this exciting and novel biomedical engineering field.

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1. Introduction: merging nanotechnology and blood transfusion expertise

Many therapeutic systemic drugs used to treat cancer, cardiovascular disorders, neurodegenerative diseases, and inflammatory pathologies exert toxicity to healthy cells thereby strongly limiting their usage [1–4]. Side-effects are to some extent associated with insufficient targeting of the drugs to diseased tissues which lead to high-dose therapies affecting normal tissues and causing systemic toxicity. Developing "smart" selective carriers is actively being pursued; these are capable of gradually delivering medications and targeting, as closely as possible, the microenvironment of pathological tissues, with optimal pharmacodynamic and pharmacokinetics profiles [5].

Successful carriers should be designed to encapsulate therapeutically meaningful amounts of drug, to meet suitable half-life requirements in the circulation, to promote safe clearance mechanisms, and, most importantly, to target the intended therapeutic site and avoid or limit deleterious uptake by healthy tissues. Progress in the last decade in biomedical engineering, material science, and nanotechnology has led to the design of novel drug carrier technologies for the efficient encapsulation and controlled release of drugs. Drug-delivery nanostructures include lipid-based carriers like liposomes and various other nanotherapeutic platforms based on polymers (e.g. micelles), inorganic elements (e.g. silica), viruses, and drug conjugates [5]. Liposomal formulations, consisting of lamellar phospholipid bilayers that entrap an aqueous environment containing the drug, were among the first nanomedicines to be developed [6]. Thanks to their phospholipid bilayer, which resembles that of cell membranes, liposomes are biomimetic and biodegradable structures compatible with body fluids. Several liposomal and other nanoparticle formulations are used in clinics particularly to treat various types of cancer [5]. The first priority of liposomal formulations was to reduce the toxicity to healthy tissues encountered when administering the free drug by intravenous infusion [7,8]. To date, over ten different liposomal drugs are on the market [9] and more are in development [5]. Liposomal formulations are not exempt from side-effects, such as complement activation, and they may be cleared too quickly from the blood [10]. Other types of nanomaterials under development may also exert toxicological effects by promoting inflammation or cytotoxicity, illustrating the need for continuous improvements.

2. Surface modifications of nanoparticle carriers to increase circulation time

The capacity of traditional liposomes and other advanced nanoparticles to interact with pathological cells is generally limited by the relative simplicity of their surface compared to biological structures; in addition, complex physiological systems, like blood, in which nanoparticles are intended to achieve a therapeutic effect, may affect their effectiveness as well as pharmacodynamic and pharmacokinetics properties, and toxicity in somewhat unpredictable manners. This strongly limits their capacity for targeting diseased biological structures. Coating liposomes with polyethylene glycol (PEG; PEG-coated-liposomes) is used to prolong the half-life in the blood circulation, improve the passive targeting of cancer cells, and ensure enhanced permeability and retention (known as EPR). However, PEG-liposomes can themselves exert toxic effects, in particular by triggering an anti-PEG immunological response in some patients, as a large proportion may have pre-existing anti-PEG antibodies from previous exposures from food or cosmetics, therefore requiring the design of alternative coating approaches [11–13]. More complex modifications of liposome surfaces by targeting groups is one strategy to improve the efficiency of drug delivery particularly by lengthening residence times in circulation [14].

3. Blood cell-inspired nanoparticles

Recent studies have evaluated the possibility to "inspire" or "decorate" various types of synthetic nanoparticles using biological structures, such as peptides, mimicking blood cell membrane receptors. Some work was initiated to coat drug nanocarriers with whole-cell membranes themselves [15,16], as a strategy to improve tolerance and physiological effectiveness [17,18] as illustrated in Fig. 1. Attempts were also made to model nanocarriers based on red blood cells (RBC), that are used as a physiological and biocompatible benchmark for long-lasting delivery vehicles [19]. RBCs surface proteins have been used to design cues to develop improved delivery systems [20]. Actually, coating