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'Smartening' anticancer therapeutic nanosystems using biomolecules

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To be effective, anticancer agents must induce cell killing in a selective manner, something that is proving difficult to achieve. Drug delivery systems could help to solve problems associated with the lack of selectivity of classical chemotherapeutic agents. However, to realize this, such systems must overcome multiple physiological barriers. For instance, they must evade surveillance by the immune system, attach selectively to target cells, and gain access to their interior. Furthermore, there they must escape endosomal entrapment, and release their cargoes in a controlled manner, without affecting their functionality. Here we review recent efforts aiming at using biomolecules to confer these abilities to bare nanoparticles, to transform them into smart anticancer therapeutic nanosystems.

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Introduction

In spite of worldwide efforts to better understand, prevent, detect and treat cancer, this disease killed more than 8 million people in 2012. Furthermore, the global cancer burden is expected to nearly double over the next 15 years and therefore, unless more effective therapies are developed, cancer could be killing over 13 million people yearly by 2030 [1,2]. Surgery and radiotherapy remain the cornerstones of treatment for early-stage cancer, but their practicability and efficacy are limited when cancer cells have already metastasized, a pathological feature that accounts for 90% of human cancer deaths [3]. In those cases, therapeutic decisions depend on the type of cancer, metastatic burden, patient symptoms, and several predictive factors but, most frequently, they involve systemic administration of antineoplastic agents.

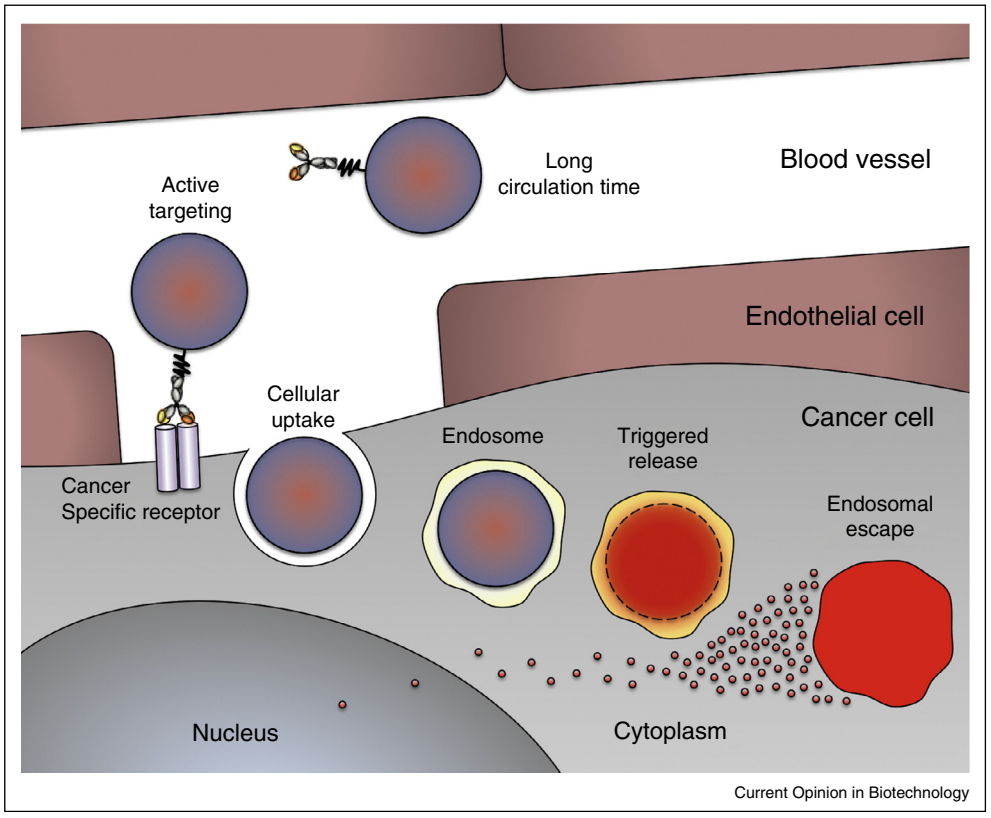
Tumors require feeding blood vessels to grow, and therefore intravenous administration is used to let chemotherapeutic drugs reach diseased cells dispersed throughout the body. However, to be effective, these agents must not only induce cell killing, but also do so in a selective manner. Unfortunately, developing drugs that meet these two requirements is proving very difficult, and virtually all cytocidal chemotherapeutic agents also harm healthy cells. This provokes undesired side effects that hinder progress towards effective treatments for the disease.

A possible way to reduce off-target toxicity is to load anticancer drugs into tumor-targeting nano-carriers that can be administered systemically and release their cargoes when diseased locations are reached. This strategy reduces the distribution volume of drugs *in vivo*, avoiding indiscriminate exposure of healthy tissues to these agents, and therefore side effects. Different types of particles may be used as core structural elements in these drug-transporting systems but, to achieve a therapeutic effect, they have to accumulate in tumors selectively and in appropriate numbers, for which multiple physiological barriers must be overcome first (Figure 1).

For instance, to achieve appropriate circulation times, these systems must avoid surface 'fouling' by nonspecific adsorption of serum proteins (i.e. opsonization), and the concomitant attack by cells of the reticuloendothelial system (RES) [4]. They must be able also to exit the vascular system at diseased locations, and establish strong physical contact with target cells there. Ideally, these systems should gain access into targeted cells and, once there, release their cargoes in a controlled manner, avoiding cellular mechanisms deployed to destroy or expel the latter. Of course such systems should be made of biodegradable parts, to limit their long-term post-operational stability and minimize the concomitant risks of toxicity.

On their own, bare nanoparticles (NPs) do not overcome such barriers efficiently, and therefore they constitute poor drug delivery systems. However, nature has provided nanotechnologists with a plethora of molecules that can be used as additional building blocks to transform

Figure 1



Ideal features for smart anticancer therapeutic nanosystems. These include long circulation time, selective tumor-cell targeting, and the ability to enter target cells, to escape endosomal entrapment and to trigger the release of cargoes in a controlled manner.

simple drug-loading bare NPs into multifunctional '*smart therapeutic nanosystems*' (STNS).

Biomolecules as core nanoparticle scaffolds

Proteins constitute good scaffolds for the construction of biocompatible, non-immunogenic or toxic, and biodegradable, nanoparticle cores. For instance, albumin [5,6], ferritin [7], and small heat shock proteins [8] have already been used for this purpose, the latter two forming hollow structures (nanocages) where cargoes can be encapsulated. Proteins can be modified chemically with ease, which facilitates their attachment to therapeutic agents and other building blocks of STNS [9,10]. Furthermore, genetic manipulation allows the creation of modular proteins with disparate functionalities that can be brought together into nanosystems assembled using these synthetic polypeptides. NPs made by the self-assembly of viral capsid proteins [11,12], or of the major vault protein [13] constitute examples of this.

Polysaccharides such as heparin, chitosan and hyaluronic acid are also desirable materials for the fabrication of NPs due to their good biodegradability and low immunogenicity. Facile methods to produce core NPs made out of these molecules have been developed [14•]. Furthermore, besides serving as structural scaffolds, some polysaccharides confer additional attractive properties to NPs, such as stealth and cell specific tropism (see below) [15].

Due to its remarkable molecular recognition properties, flexibility and structural features, DNA also constitutes a promising scaffold to design a variety of nanostructures. 'DNA origami' enables the production of small, sophisticated and well-defined structures that can accommodate a range of chemical moieties, proteins and other functional elements, making this molecule an interesting platform to create core structures for targeted drug delivery [16•]. Additionally, the combined use of DNA origami structures and proteins may lead to improved performance of STNS [17].

Structurally more complex NPs can be made using bacterially derived vesicles, called 'nanocells', which can be easily loaded with therapeutic agents of chemical and biological origin. Bacteria can be genetically modified to produce nanocells that bear desired new (or lack former unwanted) features [18,19]. Exosomes, which are endogenous nanocarriers that mammalian cells use to