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Efficient and Safe Intra-cellular Transport of Targeted Nanomedicines: are we there Yet?

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Efficient transport of drugs into cells in the body is a key factor to achieve relevant therapeutic effects for most clinical applications. However, this aspect still represents a main obstacle for a considerable number of therapeutic agents, such as poorly soluble drugs, relatively large molecules, and many biological agents, which cannot gain access to the intra-cellular compartment per se. In such cases, coupling of therapeutic agents to molecules and/or supra-molecular carriers that display affinity toward biological surfaces in the body (a strategy known as drug targeting), holds promise to improve drug transport to those sites where the therapeutic action is required [1-3].

The development of strategies aimed to improving control of drug biodistribution at the cellular and/or sub-cellular level is, hence, a very active area of research. Affinity molecules can be chosen to favor adhesion to either broadly distributed or rather specific biological markers, depending on the degree of selectivity required for a particular clinical application. Drugs and/or their carriers can be targeted to distribution particular cellular receptors involved in endocytic transport or coupled to cell penetrating peptides, in order to achieve intracellular [1-3].

A priori, strategies that take advantage of cell surface receptors involved in transport of substances into cells may seem a preferable choice. For instance, this is the case for receptors of endocytic transport, a group of pathways by which cells engulf with their plasma membrane extracellular substances and objects, subsequently transporting these membrane-surrounded vesicles and their contents into the cell body. Drug delivery approaches exploiting said pathways present some advantages, such as the use of transport routes that are naturally present in the body and typically active, and minimal interference with the plasma membrane (as opposed to approaches that porate the plasmalemma) and, hence, maintenance of the selective distribution of ions and small molecules across this semipermeable barrier [4-6].

However, this approach is also restricted by a number of obstacles, including the presence and accessibility of adequate and specific receptors at the surface of cells that are targets of intervention, presence in the body of natural ligands able to bind to these receptors, therefore, competing for binding against targeted drugs and drug carriers, and potential side effects of disturbing pathways by which cells internalize important nutrients and/or signaling factors.

In many instances, the efficacy of drug uptake by endocytic pathways is also restricted by biophysical parameters, e.g., the size of the vesicular compartments that can form at the cell surface may be not permissive for uptake of drug carriers with certain geometrical features [7,8]. Furthermore, when internalized by endocytic pathways, drug carriers remain contained within membranous vesicles, e.g., endosomes and lysosomes, which may result in hydrolysis of certain drugs within these compartments and may also hider access of drugs to other sub-cellular locations, such as the cytosplasm, nucleus, etc [8-10].

Despite these downsides, targeting of endocytic receptors and subsequent endocytic transport of drugs and/or drug carriers are advantageous for a number of applications, including those where rapid efflux of drugs across the plasmalemma need to be minimized, those where the therapeutic action is required in endo-lysosomes, or those where the acidic pH of these compartments is taken as an advantage for triggering controlled release of drugs from pH-sensitive carriers [4,9-12].

On the other hand, a number of targeting strategies are built using charge-based interaction principles. This is the case for hydrophilic and slightly positively-charged polymers and peptides that provide affinity to the negatively-charged plasmalemma of cells [4,9,10]. These approaches do not require selection of a target receptor or fundamental knowledge of its properties and functions, do not involve tedious design of specific targeting moieties, are not affected by presence of competitor ligands in the body, and may avoid side effects of hijacking natural life-keeping pathways.

Yet, despite these advantages, charge-based targeting strategies suffer from lack of selectivity to precise destinations and are less prompt to optimization by manipulating natural cell mechanisms. Some of these approaches result in direct translocation of drugs and/or carriers across the cell membrane, which may disrupt the selective distribution of molecules at both sides of the plasmalemma. Other strategies still result in (passive) endocytic uptake, e.g., due to naturally and constant ongoing endocytic activity of cells, and are affected by the same obstacles described above.

Nevertheless, some therapeutic applications may benefit from charge-based targeting strategies, e.g., despite their intrinsic lack of selectivity, enhanced permeability and retention effect observed in tumors still favors accumulation of these systems in tumor regions, and potential side effects of cell membrane permeabilization may enhance the effects of cytotoxic drugs [3,4,11].

Therefore, after several decades of experimental design, it has become apparent that targeting strategies offer valuable advantages regarding improved intracellular delivery of therapeutic agents. However, one should be cautious when considering these approaches as efficient and safe in absolute terms, since each particular strategy offers both advantages and disadvantages and has to be evaluated under the light of the particular clinical application and therapeutic outcome required. Detailed characterization of the complex mechanisms governing the interaction of targeted drugs and carriers with the

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biological environment, are necessary steps toward achieving efficient drug targeted systems.

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