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Delivering peptides and proteins to tumors

Tumor cell physiology is complex and evolves throughout disease development. Understanding the molecular biology of tumor cells, their blood and oxygen supply, growth factors, secreted proteins and their interactions with other cell types are crucial parameters not only in our understanding of the disease but also in the development of treatments. Delivery of drugs – either small molecules or peptide/proteins – has been a major challenge to achieving a good therapeutic index.

Proteins and peptides make up a significant percentage of the molecules developed for the treatment of cancer and one of the major advantages of these molecules is specificity for their target protein. Because of their larger size in comparison with traditional small molecules, peptides recognize and bind to multiple domains. However, one of the key problems with these molecules has been their instability in the bloodstream. Thus, designing and developing new technologies that will lead to efficient delivery of peptides and proteins to tumors is essential in achieving good therapeutic index.

In a recent issue of Drug Discovery Today, Torchilin *et al.* described the latest developments in this area [1]. Several technologies have been used to deliver peptides and proteins to their target tissue with an improved therapeutic index. One such method of delivery of unstable peptides and proteins is by slow release using a biodegradable implantable device [2] and some of this technology has already entered into clinical use [3]. Because peptides have a short half-life and are vulnerable to degradation by enzymes, they have to be protected for efficient delivery. Torchilin *et al.* explained that peptide conjugation with long polymers seems to help prevent rapid elimination with polyethylene glycol currently the most popular polymer to be combined with peptides and proteins for efficient delivery to tumor tissue [4]. Tumor blood vessels are more permeable to macromolecules, allowing peptides to diffuse easily into the interstitial tumor space [5]. The lymphatic system does not work well in draining such macromolecules, and hence the peptide molecules are retained for a longer period in the tumor tissue leading to an increase in the therapeutic index.

It has been suggested that peptide and protein delivery can be achieved more efficiently if they are protected in lipid balls termed 'liposomes' [6]. Liposomes that can act as carriers for either small molecules or peptides/proteins have received much attention over the past few years [5]. They are simple delivery vehicles that are stable and protect peptide and proteins from enzymatic degradation, with the only disadvantage being their nonspecific delivery, although recent formulations can be targeted to specific cell types.

Once tumor-specific peptides or proteins are delivered, they have to cross the membrane to bind to, and exert their effect on, a particular protein target. Peptides can be taken up by endocytosis and absorption can be enhanced by the addition of an antennapedia amino acid sequence. The peptide must find its target among the thousands of proteins within a cell, but once peptides reach their target, biological action is exerted in an effective manner (degradation by lysosomes is a concern but can be overcome by polymers). It is clear that peptides can be effective molecules in disease therapeutics, but only within the context of appropriate technology and design.

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