Cover Story

Albumin: A versatile carrier for drug delivery

Albumin is probably the most widely studied protein, and yet its application in drug delivery has been limited. That is until recently. In 2008 the Journal of Controlled Release (JCR) published a review article on albumin by Dr. Felix Kratz [1], and it became an instant sensation with more than 1600 downloads while the paper was available only on-line from May to November 2008. When the paper was available in hard copy in December 2008, the full text was downloaded more than 4300 times in the first year alone. It has been cited more than 120 times in the published articles to date. Dr. Felix Kratz, Head of the Division of Macromolecular Prodrugs at the Tumor Biology Center in Freiburg, Germany, is one of the leading scientists in applying albumin as a drug carrier. In this issue of JCR, he wrote another review article on albumin, which is an updated version of his previous article with much more in-depth analysis ranging from the existing albumin-based drug formulations to future applications [2].

Albumin, in retrospect, should have been one of the first molecules of choice for developing drug delivery systems from the early period of controlled drug delivery technologies. Yet, the use of albumin as a versatile drug carrier did not occur until decades later. Recently renewed appreciation on albumin as a useful drug carrier poses one question: why have so many scientists missed the beneficial properties of albumin for drug delivery? Dr. Kratz's research provides a partial answer to this question. When he began his work on transferrin-mediated drug delivery in 1989 to test the efficacy of acid-sensitive transferrin–doxorubicin conjugates, he used albumin as a negative control. Naturally, the expectation was that the transferrin–doxorubicin conjugate would be much more effective than the negative control, i.e., albumin–doxorubicin conjugate. Contrary to his expectation, however, there was no difference in efficacy between the two in a panel of tumor cell lines and in a breast cancer model in vivo [5]. There are two possible explanations for this observation. One is that the amount of transferrin receptors on the target cells was not sufficient enough to translate into a therapeutic advantage for a commonly used anticancer drug such as doxorubicin. This is of course assuming that the albumin has no beneficial effect in delivering drug to the target site. The alternative is that albumin was as effective as transferrin in delivering drug to the target site. The seminal research by Professor Maeda describing the enhanced permeation and retention (EPR) effect supports this alternative explanation. Dr. Maeda's early work on the EPR effect [3,4] has clearly shown that albumin accumulates in the tumor area as well as the antibody tested in the study. It is through this kind of cumulative, unexpected observations that the scientists began to appreciate the usefulness of albumin in drug delivery. Furthermore, identification of albumin-binding proteins, such as membrane-associated gp60 protein and secreted protein, acidic and rich in cysteine (SPARC), provides additional insights into the future application of albumin as a drug carrier. Overexpressed SPARC results in accumulation of albumin within the tumor interstitium, and membrane-associated gp60 receptor on the endothelial cells of tumor vessels allows transcytosis of albumin across continuous endothelium. Naturally, these albumin-binding proteins can be exploited for efficient targeted drug delivery to tumor by simple formation of drug–albumin conjugates.

It is likely that endogenous albumin, with the half-life of 19 days in the blood circulation, will play an important role for improving the pharmacokinetic profile as well as drug targeting properties of the many novel drugs ranging from small molecular drugs to peptide- and protein-based drugs. Currently, there are a number of albumin-based formulations already on the market as well as in clinical studies. Simple modification of drugs or drug delivery systems, e.g., with an albumin-binding fatty acid, can make them reach all parts of the body and significantly improve the pharmacokinetic properties. In the near future, it is highly likely that there will be a new generation of albumin-based drugs that improve their bioavailability as well as albumin-based tailor-made prodrugs that exploit the EPR effect for reduced side effect but with improved anticancer efficacy. Albumin, a seemingly inert protein, may be the one that will open up a new avenue for targeted drug delivery.

References

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