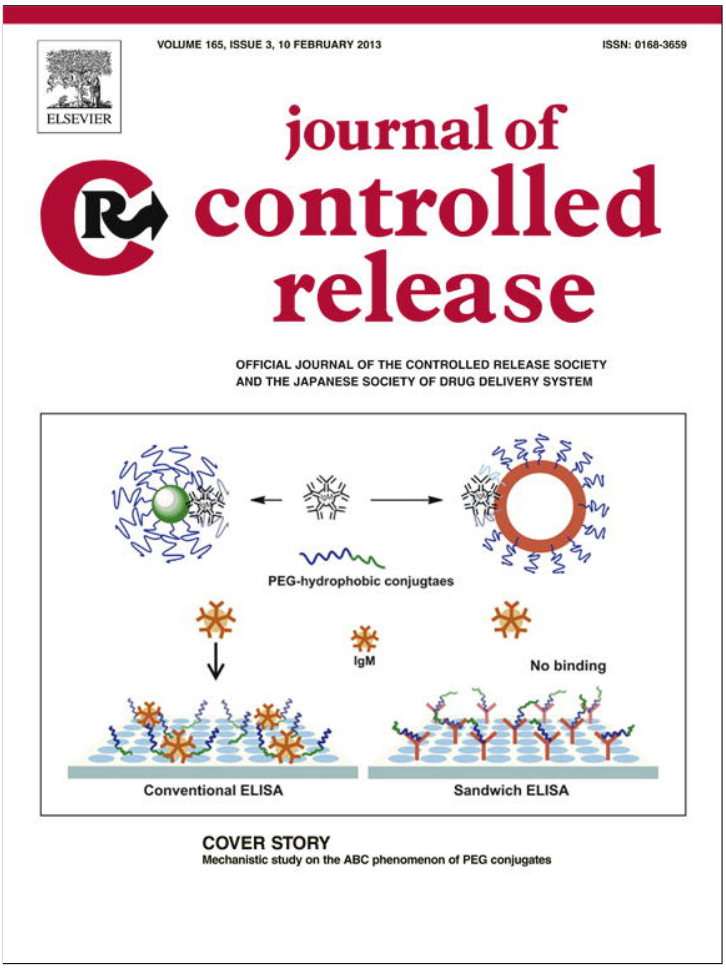

Journal of Controlled Release 165 (2013) 234

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover story

Mechanistic study on the ABC phenomenon of PEG conjugates

Poly(ethylene glycol) (PEG) has been used widely as an important excipient in pharmaceutical formulations. Since the 1970s PEG has also been widely used to modify protein drugs or liposomes, known as PEGylation, and enhance their therapeutic efficacy. PEGylation has been useful for increasing the blood circulation times of the modified protein drugs and drug delivery vehicles. PEG is believed to protect proteins from enzyme degradation, renal clearance, and interaction with cell surface membranes. These attributes contribute to improved pharmacokinetics and reduced adverse immunological effect.

There has been no report on the generation of antibodies to PEG present on the PEGylated conjugates. Recent studies, however, have reported that antibodies against PEG have been generated by injections of PEGylated proteins and PEGylated liposomes (PEG-liposomes) in animal models [1]. This led to investigations of immune responses by the PEG-liposomes, and the faster removal of the subsequent PEG-liposomes from blood circulation is now known as the accelerated blood clearance (ABC) phenomenon [2]. It is not unusual to observe increased IgM production after the first dose of PEG-liposomes. The produced IgM antibody binds to subsequently administered PEG-liposomes, leading to enhanced uptake in the liver and thus, eliminating the intended long-circulation property. Studies on PEG-liposomes concluded that the produced IgM was PEG-specific, i.e., anti-PEG IgM. Contrary to PEG-liposomes, however, PEG-containing polymer micelles did not show the ABC phenomenon [3].

In this issue, Professor Masayuki Yokoyama and his group present the result of their study on the mechanisms of the ABC phenomenon of PEGylated drug delivery systems [4]. Two types of PEG-containing polymeric micelles were prepared: the micelle with hydrophobic inner core (PEG-PBLA); and the micelle with hydrophilic inner core (PEG-P(Lys-DOTA-Gd)). The results showed that PEG-P(Lys-DOTA-Gd) did not induce IgM response and the ABC phenomenon. On the other hand, PEG-PBLA micelle did. Both types of polymer micelles have PEG outer shell, but the results were very different due to the difference in the core. It is interesting to note, however, that subsequent PEG-PBLA micelles exhibited no significant decrease in the plasma concentration in the wake of the ABC phenomenon. This is in stark contrast with PEG-liposomes showing rapid clearance from the blood at the same dose. This difference between polymeric micelles and PEG-liposomes needs to be explained.

The main proof of the PEG specific IgM antibody has been based on the results of conventionally performed ELISA. Sandwich ELISA, however, indicated no PEG specific IgM present in the ABC phenomenon induced sera. Sandwich ELISA further showed no binding of pure PEG (MeO-PEG-OH, MW of 5000 Da) but the binding of PEG-DSPE (PEG MW of 2000 Da) used in PEG-liposomes. The results of the two different ELISA experiments appear to be contradictory. But the results can be explained, if we assume that the induced IgM bind only to the exposed interface between the hydrophilic PEG main chain and a hydrophobic block. This observation can also explain the in vivo results.

The induced IgM may bind to both PEG-liposomes and PEG-PBLA micelle. The difference of the blood clearance behavior between the two carriers can be explained based on the PEG chain length and the surface area of the carriers. PEG-liposomes and PEG-PBLA micelles used PEG with molecular weights of 2000 Da and 12,000 Da, respectively. The diameters of PEG-liposomes and PEG-PBLA micelles are 150–200 nm and 70–110 nm, respectively. PEG-liposomes have a larger surface area with shorter PEG chains as compared with PEG polymer micelles. This suggests that more IgM can bind to each PEG-liposome and more IgM can be exposed to the environment. Thus, it is reasonable to assume that IgM-bound PEG-liposomes are easily captured by macrophages, while IgM-bound PEG polymer micelles can escape from macrophages.

While the mechanism proposed by Professor Yokoyama is a very reasonable one that can explain the current literature data, only further studies will confirm the suggested mechanism and/or provide more insights. Nevertheless, the current mechanistic study clearly indicates that the ABC phenomenon of PEGylated drugs or formulations, if observed, can be overcome by engineering of the interface between hydrophilic PEG and hydrophobic blocks.

References

[1] T.-L. Cheng, P.-Y. Wu, M.-F. Wu, J.-W. Chern, S.R. Roffler, Accelerated clearance of polyethylene glycol-modified proteins by anti-polyethylene glycol IgM, Bioconjugate Chem. 10 (1999) 520–528.
[2] T. Ishida, M. Harada, X.Y. Wang, M. Ichihara, K. Irimura, H. Kiwada, Accelerated blood clearance of PEGylated liposomes following preceding liposome injection: effects of lipid dose and PEG surface-density and chain length of the first-dose liposomes, J. Control. Release 105 (2005) 305–317.
[3] H. Ma, K. Shiraishi, T. Minowa, K. Kawano, M. Yokoyama, Y. Hattori, Y. Maitani, Accelerated blood clearance was not induced for a gadolinium-containing PEG-poly(L-lysine)-based polymeric micelle in mice, Pharm. Res. 27 (2) (2010) 296–302.
[4] K. Shiraishi, M. Hamano, H. Ma, K. Kawano, Y. Maitani, T. Aoshi, K.J. Ishii, M. Yokoyama, Hydrophobic blocks of PEG-conjugates play a significant role in the accelerated blood clearance (ABC) phenomenon, J. Control. Release 165 (2013) 183–190.

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0168-3659/$ – see front matter
http://dx.doi.org/10.1016/j.jconrel.2013.01.003