

Smart polymeric micelles as nanocarriers for gene and drug delivery

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Block copolymers with amphiphilic character, having a large solubility difference between hydrophilic and hydrophobic segments, are known to assemble in an aqueous milieu into polymeric micelles with a mesoscopic size range. These micelles have a fairly narrow size distribution and are featured by their unique core-shell architecture, where hydrophobic segments are segregated from the aqueous exterior to form inner core surrounded by a palisade of hydrophilic segments. Recently, progressive interest has been raised in the application of these block copolymer micelles as novel carrier systems in the field of drug targeting because of the high drug-loading capacity of the inner core as well as of the unique disposition characteristics in the body [1,2]. Body distribution of drug-loaded polymeric micelles may be determined mainly by their size and surface properties and are less affected by the properties of loaded drugs if they are embedded in the inner core of the micelles. In this regard, the design of the size and surface properties of polymeric micelles have crucial importance to achieve modulated drug delivery with remarkable efficacy. A major obstacle to targeting by colloidal carrier systems, including polymeric micelles, is the non-specific uptake by reticuloendothelial systems (RES), and the property to avoid RES-recognition is strongly needed for these systems to achieve longevity in blood circulation.

A variety of hydrophilic polymers with a flexible nature can be selected as shell-forming segments of the micelles,

which assemble into the dense palisades of tethered chains to achieve effective steric stabilization propensities. Core segregation from aqueous milieu is the direct driving force for micellization and proceeds through a combination of intermolecular forces including

hydrophobic interaction, electrostatic interaction, metal complexation, and hydrogen bonding of constituent block copolymers. A variety of drugs with diverse characteristics, including genes and proteins, can be incorporated into the core by engineering the structure of the core-forming segment of the block copolymer so that one can expect a sufficiently strong interaction with drug molecules. Compared to surfactant micelles, polymeric micelles are generally more stable with remarkably lowered CMC and have a slower rate of dissociation, allowing retention of loaded drugs for a longer period of time, and eventually, achieving higher accumulation of a drug into the target site. Furthermore, polymeric micelles have a size range of several tens of nanometers (mesoscopic size range) with a considerably narrow distribution. This feature in size is similar to that of viruses and lipoproteins, natural nanometric-scaled vehiclenanocarrier systems, and is certainly a crucial factor in determining their body disposition, especially when an Enhanced Permeation Retention effect (EPR effect) is involved. Indeed, Longevity in blood circulation as well as enhanced tumor accumulation through EPR effect was observed for doxorubicin- [3] and cisplatin-loaded

micelles [4], achieving significant tumor regression. Note that doxorubicin-loaded polymeric micelles are now in phase I/II clinical trial at National Cancer Center Hospital in Tokyo.

Recently, smart polymeric micelles with core structure responding to external stimuli have successfully been prepared. Polymeric micelles from doxorubicin-conjugated block copolymer poly(ethylene glycol)-poly(aspartame hydrazine doxorubicin) [PEG-p(Asp-Hid-DOX)] were contrived to retain drugs at physiological condition, pH7.4, and release drugs as pH decreased below 6.0 corresponding to the conditions in intracellular endosomes and lysosomes, which was controlled by pH-sensitive imine bond between drugs and polymer chains [5]. The intracellular drug release profile was clearly evidenced by the laser confocal fluorescence microscopy, corresponding nicely to their impressive in vivo anticancer activity ongoing by tumor-bearing animals. Physical stimuli can also be applied to tune the biological activity of polymeric micelles. In this regard, we have prepared photo-activating micelles entrapping dendrimer porphyrin in the core for the use in photodynamic therapy (PDT), which is known to be a very promising treatment of cancer and age-related macular degeneration (AMD) [6]. Dendrimer-entrapped micelle underwent appreciable cellular uptake as confirmed by laser confocal microscopy, and revealed remarkably higher PDT efficacy, evaluated from IC₅₀ value under photoirradiation, compared to protoporphyrin as a control and dendrimer porphyrin itself. Indeed, this micelle achieved highly improved PDT efficacy compared to commercial photosensitizer in the treatment of AMD model developed in experimental animals, suggesting the high clinical potential of this micelle as environment-sensitive delivery system of photosensitizers for PDT.

Functionalization of the outer

surface of the polymeric micelle to modify its physicochemical and biological properties is of great value from the standpoint of designing micellar carrier systems for receptor-mediated drug delivery. This can be accomplished in a regulated fashion by constructing the micelles from a variety of end-functionalized block copolymers. Polymeric micelles having sugars and peptides on their periphery have recently been prepared to explore their utility in the field of gene and drug delivery [7].

Focus of this presentation will also be placed on the use of polyion complex (PIC) micelles as novel carrier systems for delivering gene and related compounds. Indeed, blood circulation time of plasmid DNA was substantially prolonged by incorporating into PIC micelles, and eventually, expression of reporter gene in liver was confirmed [8]. Furthermore, disulfide crosslinking of the micelle core allows selective release of incorporated plasmid DNA in cellular cytoplasm, achieving high gene expression responding to reductive environment of intracellular compartment [9,10]. This concept of utilizing polymeric micelles as gene carrier has recently been expanded to their use as the carrier for siRNA and its vector. Indeed, clear gene silencing by siRNA was achieved by the use of polymeric micelles as the carrier in physiological medium containing substantial amount of serum proteins. The detail will be presented in this presentation.

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