

Lipids Influence the Size-Selective Permeability of Copolymer Vesicles

This report features the work of Hsin-Cheng Chiu and his co-workers published in *Adv. Funct. Mater.* **22**, 2267 (2012).

Because of both their environmentally innocuous processing without an organic solvent and their practical applications in pharmaceutical, agricultural and cosmetic industries, the synthesis and micellization behavior of amphiphilic copolymers and their derivatives have been extensively investigated for more than twenty years. Among these amphiphilic copolymers, those based on tertiary-amine methacrylates provide abundant variations and prospective applications because of their nature of responding to stimuli during micellization. The transmembrane permeability is another important factor in the design of functional polymer vesicles; this property is achievable simply with the incorporation of pore-forming proteins within the vesicular membranes.

Chiu *et al.* developed integrated lipid-copolymer vesicles from the self-assembly of a lipid-containing copolymer composed of poly(acrylic acid) (PAAc) functionalized with 1,2-distearoyl-*rac*-glycerol distearin.²

³ The formation of these novel lipid-polymeric vesicles is governed largely by the balance of the hydrophilic and hydrophobic fractions of the amphiphilic copolymers employed. Specifically, the formation of vesicles was driven by the hydrophobic packing of the distearyl tails of the distearin (DSA) residues within the copolymer into the bilayer structure, shown in Fig. 1. The unionized PAAc backbone segments enhanced the stability of the vesicles via an extensive entanglement of chains, hydrogen bonds and spatial connections of the closely packed lipid regions that they surrounded. These slightly hydrated, unionized PAAc domains play a responsive role in triggering the morphological modifications of the vesicular membranes upon alteration of an external pH. With the polymeric vesicles produced in an aqueous solution of pH 5.0, those ionized AAc units resided mostly on the outer and inner surfaces of the vesicle membranes; the mechanism of

electrostatic repulsion thus prevented the vesicles from aggregation. The novel lipid-containing polymer vesicles thus formed underwent major structural transformations when the pH of the solution was altered from 5.0 to 8.0. Images from a laser-scanning confocal microscope (LSCM) indicated that the permeability of the membrane vesicle to hydrophilic cargoes of varied size was regulated simply on adjusting the pH of the medium. Furthermore, the size-selective susceptibility of the lipidic copolymer membrane was tuned with the DSA content of the copolymers; decreasing the DSA content produced an increased gauge size of the membrane permeability.

An even more intriguing discovery in this work¹ is a mechanism for the locking and opening of pores of the lipidic-copolymembr vesicles through the regulation of ions in solution. An application of such lipidic-copolymer vesicles as shipping cargoes of biomolecules in bio-environments is hence promising. The immobiliza-

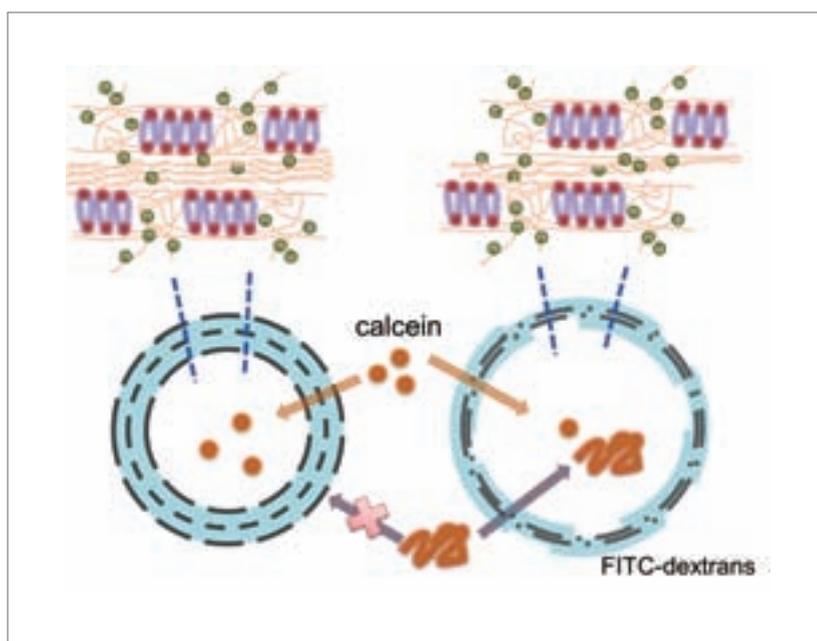


Fig. 1: Schematic illustration of polymer-vesicle assemblies equipped with size-selective permeability evolving with pH from the self-association of hydrophobically modified PAAc (poly(AAco-DSA)). The concept of drawing is adapted from Ref. 1.

tion of the vesicle structure (locking function) with Ca^{2+} ions was caused primarily by a partial cross-linking of the polymer chain segments arising from the electrostatic attraction of divalent cations with the ionized carboxylate groups of the AAc residues. In contrast, this locking action of Ca^{2+} ions on the vesicle structure and permeability was readily reversed on further addition of, for example, ethylenediaminetetraacetic acid (EDTA) into the aqueous vesicle suspensions at concentration 3.0×10^{-3} M. The capability of the resultant vesicles to undergo a transformation of the membrane structure and the corresponding regulation of the permeability in response to an altered external pH were then restored. This condition was caused primarily by the replacement of AAc carboxylates with EDTA for cationic chelation and, thus, the reversal of the locking action in the vesicle structure.

As revealed by synchrotron small-angle X-ray scattering (SAXS) at SWAXS end station **BL23A** of NSRRC, an environment of large pH caused the hydration and swelling of the vesicle membranes, within which the lipid residues were arranged into a morphology of lamellar islets surrounded by PAAc chain segments piled in a primary stack of four or five layers. This struc-

tural transformation produced an increasingly enhanced permeability of the vesicular membrane to hydrophilic solutes of increased molecular mass between 600 and 70000 g mol^{-1} . The SAXS result clearly indicated that the most ordered vesicle structure was realized with a lipidic copolymer of least DSC content of vesicles of PAAc-d8, with 8 mol % of DSA. Decreasing the DSA content resulted in a prominent lamellar stacking feature of the vesicles. The permeability of the vesicle membrane consequently became more sensitive to an alteration of the pH in the environment. The SAXS result helped to elucidate a close dependence of the vesicle structure, especially the extent of hydration and the swelling of the vesicle membranes, on the permeability of the membrane to hydrophilic solutes. Further and related information is presented in their publications.^{1, 2, 3}

References

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