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Molecular glues: Adhesion-mediated control of biomolecular functions

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Abstract

"Glue" is an indispensable tool to fix objects in contact. We envisioned if such glue is realized in molecular scale, and can be utilized for biomacromolecules such as proteins, nucleic acids, and so forth. Toward this goal, we designed dendritic macromolecules having multiple guanidinium ion (Gu^+) pendants at their periphery. Thanks to multivalent salt-bridge formation with oxyanions such as carboxylate and phosphate, which exist ubiquitously in biomacromolecules, the dendritic molecules can tightly adhere to the surface of biomacromolecules, where the association constant reaches at nearly 10^8 M^{-1} even under physiological conditions. We also found that the dendritic "molecular glues" can freeze dynamic nature of protein assemblies by gluing their components together, and control their functions. For example, microtubule, which is a homotropic assembly of tubulin proteins, is stabilized against depolymerisation when treated with molecular glues. Besides, molecular glues can also stabilize a heterotropic protein conjugate of actin and myosin (actomyosin). In the presence of ATP, actomyosin shows sliding motion, which gives rise to muscle contraction. However, once molecular glues attach to the assembly and stabilize it, the ATP-driven sliding motion is completely arrested. In addition to the stabilization capability for protein assemblies, one of the molecular glues shows a high performance in migrating into living cells. Taking this property into account, we successfully delivered proteins or nucleic acids inside the cells by utilizing molecular glue as a carrier. This delivery system can be applied to serum existing conditions, suggesting its potential for *in vivo* practical use.

Biography

Kou Okuro is an assistant professor of Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, Japan. He completed his Ph.D for development of “molecular glue” designed for non-covalent chemical modification of biomacromolecules under the direction of Prof. Takuzo Aida at the University of Tokyo (2011). His research interests include biomimetic chemistry and chemical biology for medicinal and clinical application.