Synopsis of Original Research Paper

Scientific research on claudin-1- mediated macromolecular delivery by naturally derived compound

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Tight junctions (TJ) are intercellular barriers between epithelial cells that separate the internal and external environments of cellular sheets, and control invasion of foreign substances and a diffusion of solutes and water across the epithelium. Macromolecules such as biologics with high molecular weight and hydrophilicity are unable to diffuse through the lipid bilayer of the cell membrane. Control of TJ opening by attenuating the barrier function of TJ has proved to be attractive because it could allow safe and controllable transdermal administration of macromolecules.

MA026, a cyclic depsipeptide with 14 amino acid residues, is a natural product isolated from *Pseudomonas* sp. RtIB026 as an antiviral compound. It was recently suggested that MA026 binds to claudin-1. Because claudin is the essential component of tight junction complex, we investigated the effects of MA026 on TJ and found that MA026 opens TJ of MDCK II cell monolayer, reversibly. This result suggests that MA026 is a candidate for TJ reversible opener.

Here, we report the binding specificities and activity of MA026 toward claudin-1 and other claudin family proteins revealed by several methods, and the 3-dimensional structure of MA026. Our results not only reveal the mode of action of TJ regulator MA026 with novel binding site but also are useful for transdermal administration of large hydrophilic biologics.