Synopsis of Original Research Paper

Scaffold conversion of tight junction enhancers into ready-to-use compounds based on 3D-structure of PDZ domains

Hidekazu Hiroaki

Laboratory of structural and molecular pharmacology, Graduate school of pharmaceutical sciences, Nagoya University

Tight junction (TJ) is an inter-cellular adhesion machinery that is maintained by epithelial cells in a dynamic equilibrium between biogenesis and degradation. Biogenesis of TJ is mainly proceeded by ZO-1 (and its paralogs ZO-2/3), whereas TJ degradation is promoted by LNX1. In detail, two PDZ domains in ZO-1 and LNX1 are competing each other among molecular interaction against claudins' C-termini. Inhibition of either ZO-1 or LNX1 interaction to claudin may result in TJ-opening or TJ-closure, respectively. In this study, we screened compounds from natural products that binds ZO1-PDZ1. We found glycyrrhizin binds ZO1-PDZ1 with a reasonable affinity, while baicalin, baicalein, hesperetin and naringenin exhibited weak affinity against ZO1-PDZ1. Among these four flavonoids, baicalin and baicalein showed significant reduction CLD-2 from the intercellular membrane between two adjacent cells. Naringenin exhibited a marked increase in CLD-2 density between two adjacent cells. Baicalin and baicalein are candidates for drug absorption enhancers, whereas naringenin is a promising candidate for TJ barrier enhancer.