1-JS1-3 Joint Symposium

Pharmacological approach and diagnosis for Alport syndrome

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Alport syndrome is a hereditary glomerular disease caused by mutation in the *COL4A3, COL4A4*, or *COL4A5* gene encoding type IV collagen alpha 3, alpha 4, and alpha 5 chains (alpha 3-alpha 5(IV)), respectively, which are components of the glomerular basement membrane (GBM). The most common mutations are those in *COL4A5*, which comprise more than 80% of AS-associated mutations. Mutant achains cannot form alpha 345(IV) trimer, which leads to abnormal GBM. In current therapeutic approaches for the management of Alport syndrome, inhibitors of the renin angiotensin system (RAS) are typically prescribed. Although early intervention by RAS blockade suppresses the progression of nephritis, patients with Alport syndrome taking RAS inhibitor eventually develop end-stage renal disease. Numerous basic studies have revealed the molecules that are associated with the progression of Alport syndrome. However, candidate drug targets have not been assessed in clinical applications, and a novel therapeutic strategy is urgently needed. We have established collagen alpha 345(IV) heterotrimer formation assay system that is amenable to high throughput screening (HTS) by using split luciferase compliment system (NanoLucTM) (Omachi, et al., Cell Chem. Biol. 2018). The assay provided evidence that compared with wild-type alpha 345(IV) trimer, the heterotrimer with mutant alpha 5(IV) had either intracellular trimerization defect or trimer secretion defect. We have started screening of natural compounds in our original library using alpha 5(IV) G1244D-expressing cellular system, and are trying to find potential candidate compounds to correct the mutant alpha 5(IV)-dependent defect of alpha 345 (IV) trimer secretion. Furthermore, we will also discuss the recent progress on the generation of new Alport mouse models with missense mutations in C57BL/6 and 129 strains that may be usable for future analysis of the in vivo efficacy of our candidate compounds.