Exploring the role of CEMIP in Alport syndrome

Sofia Spataro¹, Filippo Donati¹, Jacopo Sgrignani², Andrea Cavalli², Marco Prunotto¹, Leonardo Scapozza¹

¹School of Pharmaceutical Sciences, University of Geneva, Switzerland
²Università della Svizzera Italiana, Institute for Research in Biomedicine, Switzerland

sofia.spataro@unige.ch

Alport syndrome is caused by mutations in collagen type IV, an essential component of the basal lamina found in the ear, in the eye and in the kidney. The current therapeutic intervention aims to treat the symptoms and reduces the disease progression but does not target the collagen downstream pathway. This pathway includes DDR1 as collagen receptor and the CEMIP protein, known to be involved in the hyaluronic acid (HA) depolymerization. Could the DDR1/CEMIP/HA axis be a new way to address the medical need in Alport syndrome?

To answer this question we want to better study and understand CEMIP by identifying amino acids essential for its activity. We introduced point mutations in the hCEMIP-containing vector by site-directed mutagenesis, targeting in particular amino acids found in the first GG domain and in the hypothesized catalytic site. The activity of the mutated hCEMIP versions was tested with a technique called “hyaluronic acid assay”, which consist in treating the transfected cells with a high molecular weight HA, followed by a purification of HA from the cells supernatant after incubation, and a migration on an agarose gel.

We show that not only a mutation in position 187, from an arginine to a cysteine, causes a reduction in the catabolism of HA as showed by Yoshida et al. in 2013 [1], but also a mutation in position 208 from an aspartic acid to an asparagine. This new insight enables to investigate possible inhibitors targeting ARG187 and ASP208, important amino acids for the function of CEMIP, and validates a strategy to investigate the second GG domain and other CEMIP domains. A better understanding of this complex protein will empower research not only for Alport syndrome treatments but also in all the connected research areas where CEMIP has been found to have an essential function.