Targeting podocyte lipotoxicity in Alport syndrome
Dr. Alessia Fornoni, University of Miami (Florida, USA)
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Alport syndrome (AS) is a hereditary disease of glomerular basement membranes (GBM) linked to mutations in genes coding for different chains of collagen type IV. Although the GBM is primarily composed of laminin and Collagen type IV, the de novo production of the α1 chain of collagen type I (Col I) has been observed in experimental models of AS.

Discoidin domain receptor 1 (DDR1) is a unique receptor tyrosine kinase that is activated by extracellular matrix but that can also be activated by collagen. DDR1 deletion in Col4a3 knockout (KO) mice, a mouse model for AS, improves survival and renal function. Podocytes and their proper interaction with the GBM are crucial to maintain the permeability of the glomerular filtration barrier. Our in vitro and in vivo preliminary data indicate that DDR1 can be activated by collagen I in human podocytes. Furthermore, we demonstrate that Col I-induced or genetic activation of DDR1 causes cellular lipotoxicity, a phenomenon that we recently demonstrated to be a key determinant of podocyte injury in other glomerular diseases. In particular, we show that the uptake of free fatty acids (FFAs) is increased in Col I treated podocytes and requires the activation of DDR1 which will ultimately lead to intracellular lipid accumulation due to increased fatty acid (FA) uptake. This phenomenon is also reflected in Col4a3 KO mice, where increased DDR1 activity in kidney cortexes correlates with blood urine nitrogen (BUN) and is associated with increased lipid deposition and increased expression of scavenger receptor B, cluster of differentiation 36 (CD36), a protein involved in FA uptake, cholesterol absorption and activation of inflammatory pathways. Studies by others have shown that CD36 activation can be blocked by the clinically available compound Ezetimibe.

The goal of this proposal is to demonstrate a novel mechanism of podocyte lipotoxicity in AS that is amenable to therapeutic intervention through a repurposing strategy of Ezetimibe.

We will test the novel hypothesis that DDR1-induced podocyte injury in AS requires CD36 dependent fatty acid and cholesterol uptake and that inhibition of CD36-dependent lipotoxicity with Ezetimibe can prevent the progression of kidney disease in Alport syndrome.

We will address this hypothesis using a combined in vitro and in vivo approach to investigate the role of DDR1 in lipid induced podocyte damage and to determine if CD36 inhibition can prevent intracellular lipid accumulation and podocyte injury in Col4a3 KO mice. If our hypothesis is confirmed, repurposing strategies for the use of Ezetimibe to treat patients with AS should be fast and safe, as Ezetimibe is an already FDA-approved drug currently labeled for the treatment of patients with hypercholesterolemia.