

Podocyte response to injury in Alport Syndrome: an answer from human amniotic fluid kidney progenitors

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Most kidney diseases leading to complete kidney failure originate when podocytes, the key cells in maintenance of the renal filtration, are lost. In Alport Syndrome, a hereditary form of glomerular nephritis, renal damage is caused by the inability of podocytes to synthesize the proper glomerular basement membrane (GBM), leading to podocyte injury and irreversible loss of kidney function.

Currently, there are no treatments that can effectively cure chronic kidney diseases (CKD). Dialysis and transplantation do not represent a definitive cure and existing pharmacological options are unspecific and not designed to treat podocytes but rather act systemically causing many side effects to the patients. The lack of knowledge about how podocytes respond to injury during disease progression, and consequently the lack of specific therapies, stems from the inability to propagate these ultra-specialized cells *in vitro*.

Therefore, the development of new systems allowing the study of podocyte biology that can lead to possible therapies and increase the chances of treating CKD is strongly needed. A new population has recently been identified of renal progenitors within the human amniotic fluid that can be easily differentiated into mature and functional podocytes, without the use of genetic manipulation thus eliminating some concerns over ethical problems. Dr. DaSacco hypothesizes that these cells are ideal for studying podocyte physiology and pathology and to understand the response to therapeutic compounds.

In this project, two main goals are proposed: *A.* To better understand the relation between genotype and phenotype in podocytes derived from amniotic fluid of Alport patients and healthy controls, with particular focus on GBM formation and deposition. *B.* To use our newly developed human podocytes in a three-dimensional culture system and perform disease-modifying studies, testing the effects of drugs and studying podocyte and endothelial cell biology. Such approaches may accelerate the understanding of renal response to injury and may ultimately contribute to new therapies that can slow down the progression of renal disease caused by GBM defects and podocyte loss in Alport Syndrome.