Nature Reviews Nephrology | Published online 17 Jul 2017; doi:10.1038/nrneph.2017.106

CELL BIOLOGY

Connexin connections in GN

Expression of the gap junction protein connexin 43 (Cx43) is upregulated in chronic kidney disease (CKD). Kavvadas *et al.* further examined the relationship between Cx43 and kidney injury: "Our goal was to test the efficiency of Cx43 blockade in a severe model of CKD that corresponds to the human pathology and to try to identify the molecular mechanisms of Cx43 actions," says Panagiotis Kavvadas.

The researchers examined the effects of downregulating Cx43 expression *in vivo* using genetic and pharmacogenetic approaches in a mouse model of severe glomerulonephritis (GN) induced with nephrotoxic serum. The adverse effects of nephrotoxic serum on renal structure, function, inflammation and fibrosis were ameliorated in mice with a heterozygous deletion of *Cx43* compared with wild-type mice. Importantly, reducing Cx43 expression in wild-type mice using antisense oligonucleotides delayed the development of nephrotoxic serum-induced GN.

As Cx43 is highly expressed in injured podocytes, the investigators studied the effects of modulating Cx43 function *in vitro* in a podocyte cell line. Upregulation of Cx43 expression (induced by TGFβ treatment) in these cells resulted in podocyte dedifferentiation and apoptosis, which was blocked by pretreatment with Cx43 blocking peptides. Blocking purinergic signalling mimicked the results of Cx43 blockade, suggesting that the effects of Cx43 on podocytes may be mediated through this pathway. "The deleterious role of Cx43 in GN may not be exclusively due to the pro-inflammatory capacity of Cx43 but may also be due to a pro-apoptotic role in the main cellular target of the disease, the podocyte," suggests Kavvadas. "Combined therapies involving Cx43 targeting could provide an alternative therapeutic strategy to treat CKD."

Grant Otto

> "The deleterious role of Cx43 in GN may [be partly] due to a pro-apoptotic role in … the podocyte"

ORIGINAL ARTICLE Kavvadas, P. *et al.* Decreased expression of connexin 43 blunts the progression of experimental GN. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2016111211 (2017)

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