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"The Role of ALCAM/CD166 in Diabetes and Diabetic Nephropathy"

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Diabetic nephropathy is considered a very serious micro-vascular complication of diabetes, whose treatment requires relevant financial costs that can impact strongly on health policies of a country. It is projected that the number of DN will increase with 13-20% by 2030. Complex pathogenesis makes DN a challenging important subject for future studies. Although not traditionally considered as a factor in diabetes, inflammation may be a novel central factor in DN progression. DN is characterized by an inflammatory milieu and in part caused by activation of PRRs. The role of ALCAM as PRR in inflammatory mechanisms that may evolve in DN was studied in this work.

In order to characterize expression of ALCAM in diabetic and non-diabetic patients, several biochemical assays were conducted in human serum. ELISA revealed upregulation of soluble ALCAM (sALCAM) in serum of type 2 diabetic patients compared to control and positive correlation with HbA1c in diabetic patients. Expression of ALCAM and markers of sclerosis were significantly higher in kidneys of diabetic patients compared to non-diabetic patients. ALCAM was located in podocytes and tubules of diabetic kidneys. Expression analysis of the ALCAM ligand S100B revealed increased expression in podocytes of type 2 diabetic patients compared to control, and S100B antigen expression in tubules of non-diabetic and type 2 diabetic human kidneys.

A functional relevance of these findings was studied employing mouse model of diabetic nephropathy. Diabetic ALCAM$^{-/-}$ mice showed lower levels of albuminuria and lower albumin-creatinine ratio (ACR) than diabetic WT mice. Furthermore, glomerular and tubular damage was significantly lower in ALCAM$^{-/-}$ mice compared to WT. Studies on tubular endothelial cells revealed an ALCAM-dependent increase in NF-κB activation upon S100B treatment with consequent upregulation of TGF-ß. ALCAM devoid TECs were completely protected from this mechanism. A minor and similar effect was seen after glucose treatment.

Surprisingly and in contrast to the protective mechanism of ALCAM knockout regarding diabetic nephropathy, ALCAM$^{-/-}$ diabetic mice showed a marked increase in

mortality, compared to WT diabetic mice. Although probably a decreased stress resistance due to the observed significantly reduced overall body weight in ALCAM$^{-/-}$ control and diabetic mice compared to WT mice, further explanations including possible protective ALCAM effects are under active study.

Taken together this work shows contribution of the PRR ALCAM to diabetic tubulopathy through NF-κB driven upregulation of TGF-ß upon S100B ligation.