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Abstract Text:

Modeling Intraglomerular Transport in Diabetic Kidney Disease

Diabetic kidney disease (DKD) is among the severe complications of diabetes and is the primary cause for end-stage kidney failure. Hyperglycemia is the condition of excess glucose that can lead to diabetic complications and contribute to the loss of kidney function. Each kidney includes thousands of glomeruli that are comprised of a network of capillaries through which blood is filtered. The glomerular filtration barrier is a highly specialized microvascular interface made up of glomerular endothelial cells, basement membrane, and podocytes. Podocytes are terminally differentiated epithelial cells that form the outermost layer of the glomerular filtration barrier and normally prevent leakage of protein, such as albumin into the urine. Mesangial cells form the central stalk of the glomerulus and are known to interact closely with other cells including podocytes. Podocyte depletion and damaging structural changes around the mesangial cells are key predictors of DKD progression. There is evidence suggesting that the tissue damage is caused by signaling pathways and interactions between podocytes and mesangial cells. However, these are several interconnected pathways, and the tissue damage is not immediately detectable with non-invasive clinical methods until after proteinuria develops. Hence, a quantitative approach is used to understand and predict and design therapies to slow the progression of DKD before significant podocyte damage occurs.

The objective of this study is to model the transport of glucose from the glomerular microvasculature to the cells that comprise the tissue as well as the transport of key biochemicals that respond to glucose in glomerular injury. We focus specifically on the roles of angiotension II (ANG II) and transforming growth factor beta 1 (TGF-β) on effects in podocytes and mesangial cells within a glomerulus.

Elevated ANG II levels have been associated with several deleterious effects on podocytes. We developed an ODE-based model of glucose-stimulated ANG II dynamics in podocytes. TGF-β increases in hyperglycemic conditions via a mechanism mediated by ANG II and has been shown to play a key role overexpression of extracellular matrix proteins in the mesangial space and thickening of the glomerular basement membrane, eventually leading to podocyte loss. We extended our podocyte ANG II model to predict the downstream effects of glucose and ANG II on TGF-β production and tissue damaging behaviors. The model accounts for the production of TGF-β by glucose and ANG II that is synthesized by glucose-dependent as well as glucose-independent mechanisms. We combined the reaction network model with transport equations to study the movement of albumin and glucose through different layers of the filtration barrier using a PDE-based model. Small molecules can travel directly through the filtration barrier or indirectly through the mesangium and then into the filtration barrier. Macromolecules such as albumin cannot travel through the filtration barrier until significant damage occurs that modifies the permeability of the barrier to macromolecules. The model shows how high glucose affects the mesangial cells as glucose moves through and stimulates various biochemical networks in a glomerulus and how the structure of the tissue is damaged gradually over time. This work in progress can be developed into a digital twin type of model and will be connected into an agent-based multiscale modeling platform.