Coupled multiscale modeling and pathway analysis for prediction of drug efficacy in cystic kidney diseases

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Extensive research has uncovered many genetic changes associated with autosomal dominant polycystic kidney disease (*ADPKD*) and effects of ADPKD mutations on signaling pathways. However, we still do not know the precise sequence of events that lead to cyst initiation. One of the key changes during the initiation of cysts is abnormal expression of the juvenile cell adhesion molecule cadherin-8. We examined two hypothetical cell-level mechanisms by which abnormal expression of cadherin-8 could initiate cyst formation: i) reduction of cell-cell adhesion, which then leads to changes in cell proliferation or ii) direct reduction of contact inhibition of proliferation with no change in cell-cell adhesion. To test these mechanisms we built a 3D virtual-tissue (*VT*) computer model of the renal tubule using the CompuCell3D (*CC3D*) modeling environment (Swat et al., 2012). Our VT simulations showed that while both mechanisms could initiate cyst formation, only the loss of adhesion mechanism produced morphologies matching *in vitro* cadherin- 8 induced cysts (Belmonte *et al.*, 2016).

Concurrently, we used the Transcriptogram method for whole-genome gene expression analysis to analyze microarray data from cell lines developed from cell isolates from normal kidney and from both non-cystic nephrons and cysts from the kidney of a patient with ADPKD. We identified novel pathways altered in ADPKD. Transcriptogram significance metrics identified increased expression of cGMP phosphodiesterases as the highest priority pathways for study (de Almeida et al., 2016). Our modeling and experimental efforts then focused on cGMP phosphodiesterase inhibitors, a class of drugs already FDA approved for other uses.

Using pathway analysis we linked the cell behaviors known to drive cyst formation with increased cGMP phosphodiesterase expression and constructed models of these pathways using Cell Designer. We are currently calibrating these pathway models using biological data. Preliminary *in vitro* and mouse model testing of phosphodiesterase inhibitors to reduce cyst formation have shown efficacy. We will next incorporate these pathway models into our CC3D VT cystogenesis model to predict drug effects on cyst formation.

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