Stability of the actin cytoskeleton in podocytes

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Short Abstract — The maintenance of the morphology of podocyte kidney cells is essential for its function: help prevent the loss of protein into the urine. Among the hereditary diseases involved in nephrotic syndrome some impact the actin cytoskeleton or its interaction with the basement membrane.

In a simplified manner, the actin cytoskeleton is built upon polymerization of monomeric G-actin into F-actin fibers, which are then crosslinked to form bundles. We show that the proportion of actin in each of these ‘states’ is regulated by polymerization, bundling and depolymerization, and analyze how certain mutations and excessive stress potentially perturb such equilibrium.

Keywords — podocytes, actin cytoskeleton, stability analysis, kidney disease.

I. INTRODUCTION

PODOCYTE cells are highly differentiated epithelial cells. Their morphology consists of a large cell body, with primary processes emerging from it, to be branched into a large number of foot processes. The foot processes (FP) (~10⁳ per cell, each with area ~1µm²) establish contact with the basement membrane (BM). The region between FP of neighboring cells is termed ‘slit diaphragm’ (SD). The SD is structurally maintained by crosslinking of transmembrane proteins from neighboring cells, and the proper anchoring of the FP to the BM. The podocyte cytoskeleton in the cell body and primary processes is composed mostly of microtubules and intermediate filaments. In contrast, the FP are characterized by the high concentrations of actin, organized as contractile actin bundles [1].

Among the mutations involved in hereditary diseases that cause nephrotic syndrome are: a) mutations on SD related proteins (Nephrin, Podocin, CD2AP); b) mutations that affect the actin cytoskeleton structural properties (α-actinin 4 and non-muscle myosin IIA heavy chain); and c) mutations that affect the interaction between the FP and the BM (laminin β2 chain) [2].

Signaling from the SD is believed to promote actin polymerization [3]. Because a series of mechanisms are reported to enhance polymerization, such as phospholipids, small GTPases, and mild stress at focal adhesions, it is common to model actin polymerization as subject to a positive feedback loop [4]. We analyze the impact of such topology, which parameters are potentially perturbed by the listed mutations, and the stability of FP actin cytoskeleton.

II. RESULTS

In our model, the variables of interest are the fraction of monomers in each of the three states (G-actin, F-actin and bundles). The mechanisms modulating the exchange between the three states are illustrated in Fig. 1.

Figure 1. The positive feedback α is dependent on SD proteins, GTPases and stress. Mutations of α-actinin 4 and myosin are expected to perturb α2, while the coefficients β and β2 are dependent on interactions with BM and the external stress such as hypertension.

Analysis of our system reveal that a) some sets of parameters result in two stable points, one with high concentration of bundles, another where the cytoskeleton collapses (mostly G-actin); b) a stronger positive feedback may shift the system to a single equilibrium point, rich in bundles; c) reduction of the coefficients β and β2 may result in a cyclic behavior, with the cytoskeleton oscillating between F-actin rich and bundle rich states.

III. CONCLUSION

Our simple and compact model allows for analytical exploration of the potential impact of the several players involved in maintenance of the podocyte cytoskeleton and morphology. Because the parameters involved and extracellular conditions are not expected to be constant, the model can help elucidate the relationship between perturbations and cytoskeleton dynamics.

REFERENCES


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