Deregulation of Osmotic Regulation Machinery Explains and Predicts Cellular Transformation in Cancer and Disease

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Osmotic regulation is a hugely important homeostatic system in all cells. Cells respond to osmotic stresses by activating or upregulating proteins involved in the transportation of charged ions, primarily Chlorine, Potassium, Sodium, and Calcium. Additionally, the movement of ions and osmotically obliged water are necessary for many of the cellular hallmarks exhibited in the transformations associated with disease states such as cancer. In particular, the aberrant expression of ion channels are hallmarks for increased proliferative and invasive behaviours ([1, 2]). We present a formal model of the osmotic regulation machinery within a mammalian cell. The model can provide a mechanistic explanation for the behavioural changes observed in highly diverse cellular systems of murine premetastatic Lymph Node stromal cells, and Lung Cancer Fibroblasts. The model explains phenotypic transformations within each cell types, and predicts behaviour from datasets not involved in its generation. Furthermore, we use the model to predict key proteins involved in each transformation, and propose experiments to alter the behaviour of cells in controllable ways.

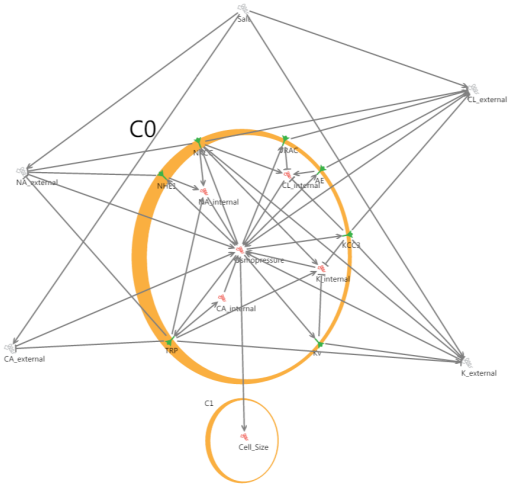

Figure 1: The model of osmoregulation as rendered by BMA. Phenotype nodes not shown for clarity.

A qualitative network of key channels, ions, and transporters was constructed using the BioModelAnalzer (http://biomodelanalyzer.research.microsoft.com/, [3, 4]). As osmoregulation achieves a homeostasis, the model was verified both through stability analysis (which proves the existence of a global attractor) and simulation. Initially a specification was constructed from the literature, and then refined against microarray data from resting fibroblast reticular cells (FRCs) in the lymph node [5].

To model the response of the FRCs to upstream tumuors at different timepoints, a subset of the ion channels and transporters were deregulated. This in turn caused wide-spread, coordinated changes in other channels through osmotic pressure alterations, and subsequent changes in cellular phenotypes. The model was found to accurately predict the changes observed in the FRCs, and subsequent validation of expression changes supported the model findings.

References

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