Network Modeling of Focal Adhesion-Invadopodia Transitions

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Short Abstract — A central and unresolved question in cancer is how deregulated signaling leads to acquisition of an invasive cellular phenotype. Based on known properties of invasive cancer cells, we modeled the invasive transition as a theoretical switch between focal adhesions (FA) and ECM-degrading invadopodia and built molecular interaction network models of each structure. To identify upstream signaling regulators, we added first degree binding partners and applied graph theoretic analyses to identify hubs. By comparing the results to clustered human tumor signaling state data, several hubs were chosen for further analysis as potential interacting signaling molecules in head and neck squamous cell carcinoma (HNSCC) and validated as regulators of both FA and invadopodia.

***Keywords* — Invadopodia, focal adhesion, network model, graph theory, signaling hubs.**

I. Purpose

THE goal of our study was to identify signaling molecules that promote the invasive phenotype. At the cellular level, the invasive phenotype can be characterized as a shift in the dynamics and assembly of two cytoskeletal structures: non-invasive focal contact-type adhesions (FA) and invadopodia, actin-rich cellular protrusions with associated extracellular matrix (ECM)-degrading proteinases [1, 2]. The number of proteins known to be involved in the formation of invadopodia and focal adhesions has expanded; however, little is known about the upstream signals that trigger formation of invadopodia instead of the non-invasive FA. Interestingly, phorbol ester treatment of vascular smooth muscle cells has been shown to induce the formation of invadopodia-like podosomes at sites of focal adhesion disassembly, suggesting a direct transition between the two structures, induced by deregulated signaling [3]. Nonetheless, our understanding of this invasive switch remains minimal due to the complexity of both structures and the signal inputs. To identify key molecules and signaling states that drive the transition between FA and invadopodia, we used a network modeling approach. We built molecular interaction networks for FA and invadopodia based on lists of molecules derived from the literature and database-mining, and used a graph theoretic approach to identify regulatory signaling hubs of each network [4].

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II. Results

A number of signaling hubs were found to be central to both invadopodia and FA networks. These were prime targets for experimental testing. We compared the identified hubs to signaling state reverse phase protein array data obtained from human head and neck squamous cell carcinoma and identified clusters of molecules that correlated with recurrence. These poor prognosis clusters formed the selection basis for further in vitro studies to test for FA-invadopodia transition changes.

III. Conclusion

The combination of literature-derived network modeling and graph theory analysis with biological data is a promising approach to connect signaling states with specific cellular phenotypes.

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