Gene Module Regulatory Network Analysis of Follicular Lymphoma Transformation

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Short Abstract — We constructed a gene module regulatory network underlying transformation of follicular lymphoma (FL) to diffuse large B-cell lymphoma (DLBCL) from microarray data. Modules that significantly discriminate between FL and DLBCL were identified by supervised classification, in addition to modules that discriminate between transforming and non-transforming FL. Core modules show expression signatures of cellular differentiation states, proliferation, deregulation of mitochondrial function, and increased proteasome activity impacting the cell cycle. Our module network generates hypotheses regarding processes driving transformation, including a role for Pax5. It further suggests that Bortezamib (a proteasome inhibitor) and Ecteinascidin-743 may have therapeutic benefits for treatment of FL/DLBCL.

***Keywords* — Follicular lymphoma, gene regulatory network, diffuse large B-cell lymphoma, microarray analysis.**

I. Purpose

Transformation of FL to DLBCL is common, and associated with worse prognosis. Mechanisms underlying transformation are poorly understood, and implicate multiple pathways. Several studies have investigated gene expression changes in FL transformation (e.g. [1,2]). To better understand the transformation process, we constructed a gene module regulatory network from microarray data on FL and DLBCL samples.

II. Results

We used ~13000 microarray probes from 88 FL/DLBCL clinical samples [1], to generate a transcriptional regulatory network of lymphoma, consisting of 200 modules [3]. Modules that significantly discriminate between FL and DLBCL were identified by supervised classification, in addition to modules that discriminate between FL that transform, and FL that are not known to transform. A network of regulatory modules was constructed with a directed edge between pairs of modules if a gene in one module served as a regulator of the other module. Known aspects of FL/DLBCL transformation, such as changes attributable to infiltrating T-cell populations were identified and served as internal validation.

Our approach identified modules of genes by virtue of a shared regulatory program [3]. From the module network, we were able to generate specific hypotheses regarding regulation of processes involved in lymphoma transformation, and to identify putative upstream targets for therapeutic intervention. Core discriminant modules associated with transformation showed expression signatures of cellular differentiation states, proliferative drive, deregulation of mitochondrial function, and increased proteasome activity impacting the cell cycle. The central proteasomal involvement suggests that there may be therapeutic benefits from proteasome inhibitors such as Bortezamib. Significant modules in the network were enriched for genes coordinately expressed in stem cells relative to normal cells, less differentiated cancer types. Our network implies that loss of Pax5 expression has a role in transformation. Abrogation of Pax5 activity has been shown in mice to induce reversion of committed B-cells to a more pluripotent state [4]. One corollary is that most FL cells may possess the potential for transformation, not just a small reservoir of "cancer stem cells". We also found inflammatory-like signatures characterizing transformation, concordant with other studies [5].

Module network analysis of expression data in lymphoma transformation recovered known aspects such as changes in T-cell infiltration and proliferative drive. We found a "stem-cell like" signature in the more aggressive cancer, with a role for Pax5 in transformation. Finally, we were able to generate specific hypotheses, including potential therapeutic response to proteasome inhibitors.

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