

Mechanisms of Dynamic Chromatin Reorganization Regulating B Cell Differentiation and Lymphomagenesis

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Abstract: Germinal center (GC) B-cells manifest many hallmarks of cancer cells explaining why a majority of lymphomas arise from B-cells transiting the GC reaction. GC B-cells oscillate between two main phenotypic states: i) proliferative and mutagenic centroblasts, and ii) quiescent centrocytes, which exit the GC reaction to undergo subsequent terminal differentiation. These distinct phenotypic states are encoded through opposing epigenetic mechanisms. The transition from centroblast to centrocyte is determined by signaling through the “immune synapse”. It is not known how the immune synapse reprograms chromatin to enable the switch between these opposing epigenetic forces. Our preliminary data indicate molecular mechanisms by which histone H3 phosphorylation, downstream of immune synapse signaling, can potentially disrupt and reshape chromatin states. Thus, we hypothesize that immune synapse mediated H3 phosphorylation controls this critical GC epigenetic switch. Activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCLs) are aggressive lymphomas that reflect post-GC B-cells, and harbor mutations that induce strong immune-synapse signaling. Targeting of proximal signaling factors (e.g. ibrutinib) is only modestly effective in these tumors, and more effective therapy remains a critical unmet need. We predict that ABC-DLBCLs are addicted to H3 phosphorylation and its corresponding epigenetic effects, mediated by the kinase MSK, and will be selectively killed by its inhibition, since it represents the convergence of many branches of immune synapse signaling. This team is uniquely suited to address these conceptual and cancer treatment-directed questions with expertise in lymphoma biology, epigenetics, histone biochemistry, biophysics, and computational epigenomics.