

Elucidating the Etiologic Role of Linker Histone Mutations in Hematologic Malignancy

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Abstract: The genetic information encoded in DNA is packaged and interpreted by the cellular machinery within the context of chromatin. As the genome sequence remains largely unchanged throughout development, chromatin modifications represent a critical interface between the genome and regulatory inputs. Histone proteins are major constituents of chromatin; four core histone types make up the nucleosome particle, the basic unit of chromatin. The fifth type, linker histone H1, binds the nucleosome and the linker DNA between. Whereas the progress in understanding the function of core histones is significant in recent years, much of the linker histone H1 biology remains unknown. Mutations in linker histone H1 have been recently reported in 30% of follicular lymphomas and diffuse large B cell lymphomas. We have also found mutations in the tumor cells in 60% of classical Hodgkin lymphoma. While genomic data suggest strongly that these mutations provide an advantage to the tumor cells, the molecular basis of this remains unexplored. We found that linker histones self-associate, via RNA-dependent mechanism; the H1 mutations found in B-cell malignancy strongly impede such association. Building on these preliminary results, we propose to investigate the molecular details and functional consequences of H1 mutations in lymphoid carcinogenesis by bringing together leaders in the field of transcriptional regulation, chromatin, epigenetic regulation and lymphomagenesis.