DUSP4 deficiency caused by promoter hypermethylation drives JNK signaling and tumor cell survival in diffuse large B cell lymphoma

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The epigenetic dysregulation of tumor suppressor genes is an important driver of human carcinogenesis. We have combined genome-wide DNA methylation analyses and gene expression profiling after pharmacological DNA demethylation with functional screening to identify novel tumor suppressors in diffuse large B cell lymphoma (DLBCL). We find that a CpG island in the promoter of the dual-specificity phosphatase DUSP4 is aberrantly methylated in nodal and extranodal DLBCL, irrespective of ABC or GCB subtype, resulting in loss of DUSP4 expression in 75% of >200 examined cases. The DUSP4 genomic locus is further deleted in up to 13% of aggressive B cell lymphomas, and the lack of DUSP4 is a negative prognostic factor in three independent cohorts of DLBCL patients. Ectopic expression of wild-type DUSP4, but not of a phosphatase-deficient mutant, dephosphorylates c-JUN N-terminal kinase (JNK) and induces apoptosis in DLBCL cells. Pharmacological or dominant-negative JNK inhibition restricts DLBCL survival in vitro and in vivo and synergizes strongly with the Bruton's tyrosine kinase inhibitor ibrutinib. Our results indicate that DLBCL cells depend on JNK signaling for survival. This finding provides a mechanistic basis for the clinical development of JNK inhibitors in DLBCL, ideally in synthetic lethal combinations with inhibitors of chronic active B cell receptor signaling.