OSSD Paperpick

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Main paper

Sequential inverse dysregulation of the RNA helicases DDX3X and DDX3Y facilitates MYC-driven lymphomagenesis

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SUMMARY

DDX3X is a ubiquitously expressed RNA helicase involved in multiple stages of RNA biogenesis. DDX3X is frequently mutated in Burkitt lymphoma, but the functional basis for this is unknown. Here, we show that loss-of-function DDX3X mutations are also enriched in MYC-translocated diffuse large B cell lymphoma and reveal functional cooperation between mutant DDX3X and MYC. DDX3X promotes the translation of mRNA encoding components of the core translational machinery, thereby driving global protein synthesis. Loss-of-function DDX3X mutations moderate MYC-driven global protein synthesis, thereby buffering MYC-induced proteotoxic stress during early lymphomagenesis. Established lymphoma cells restore full protein synthetic capacity by aberrant expression of DDX3Y, a Y chromosome homolog, the expression of which is normally restricted to the testis. These findings show that DDX3X loss of function can buffer MYC-driven proteotoxic stress and highlight the capacity of male B cell lymphomas to then compensate for this loss by ectopic DDX3Y expression.

Commentary

Sex, life, and death in MYC-driven lymphomagenesis

Chi V Dang

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Gong et al. (2021) demonstrate that MYC-induced proteotoxic stress could be relieved by inactivating RNA helicase DDX3X for tumor initiation, and in male MYC-driven lymphomas, the homologous helicase DDX3Y, encoded on the Y chromosome, is subsequently induced for disease progression.

My statement of significance is:

DDX3X and DDX3Y are a pair of sex-linked homologs that encode RNA helicases important in protein synthesis. DDX3X escapes X inactivation, while DDX3Y is mainly expressed in testis. This new paper demonstrates that the complex interplay between the X-linked and Y-linked homologs in males enables early development and subsequent progression of MYC driven B-cell lymphoma. The authors construct a two-stage model in which the ability of the MYC oncogene to efficiently drive tumor growth is first enhanced by mutations in DDX3X, which reduces protein toxicity, and second, by ectopic expression of DDX3Y, which restores protein synthesis in established lymphoma. In females, both expressed copies of DDX3X would need to be mutated to moderate proteotoxic effects of MYC mutations and facilitate initial tumor development. Furthermore, the absence of DDX3Y would not allow restoration of tumor progression. These findings demonstrate the unique roles of X- and Y-linked genes in the male-biased prevalence of lymphomas.