Abstract #14 | Poster

DDX3X and DDX3Y dosage imbalance drives sex bias in Burkitt lymphoma.

K. Helian[1], C. Gong[1], J. Coleman[2], V. Aggarwal[1], J. Krupka[1], S. Brocklesby[1], R. Gilbertson[2], D. Hodson[1]

[1] *University of Cambridge, Cambridge Stem Cell Institute & Department of Haematology, Cambridge, United Kingdom*
[2] *University of Cambridge, CRUK Cambridge Institute & Department of Oncology, Cambridge, United Kingdom*

Burkitt lymphoma displays a striking male predominance, yet the biology underpinning this sex bias remains unclear. DDX3X, an X-linked RNA helicase that escapes X-inactivation, is recurrently inactivated in MYC-driven B cell lymphomas. Prior work shows that DDX3X loss constrains MYC-driven protein synthesis and proteotoxic stress but is accompanied by a compensatory upregulation of the Y-chromosome paralogue, DDX3Y. Why lymphoma cells select for loss of DDX3X, only to apparently restore DDX3 activity through induction of the near-identical Y-linked paralogue DDX3Y, remains an intriguing paradox.

Here we define how DDX3X and DDX3Y jointly shape lymphoid physiology and malignancy. Using conditional mouse genetics, we demonstrate a male-specific, selective advantage for *ddx3x* loss during MYC-driven lymphomagenesis, with no comparable advantage for *ddx3y* loss, and an absolute requirement to retain at least one DDX3 paralogue. In the physiological germinal center (GC), either paralogue supports GC formation, but DDX3Y alone incompletely sustains affinity maturation, consistent with inadequate total DDX3 dosage. Using engineered isogenic human BL models, we show that DDX3X is the dominant paralogue in lymphoid cells. However, when DDX3X is lost, DDX3Y is rendered essential, creating a tumor-specific, switched paralogue dependency. Critically, total DDX3 expression is restored to only a small fraction of the original level. DDX3X and DDX3Y display overlapping RNA interactomes and downstream translational targets. However, DDX3Y is less able to interact with EIF3 subunits, suggesting that it makes a weaker contribution to translation initiation. These findings point to total DDX3 dosage rather than paralogue-specific functions as the key determinant. Mechanistically, DDX3X suppresses DDX3Y expression via intron retention within the DDX3Y transcript, and DDX3X loss releases this cross-paralogue repression to permit partial DDX3Y compensation.

We propose a Goldilocks model in which male cells achieve a DDX3 dosage state that is low enough to blunt MYC-induced stress, yet sufficient for survival via induced expression of DDX3Y. This state of low DDX3 dosage is not achievable in female cells, explaining the male-skewed DDX3X mutation and identifying DDX3Y and its cross-paralogue regulatory circuitry as therapeutic vulnerabilities in male Burkitt lymphoma.