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Genome instability and DNA damage response in lymphoid malignancies

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Abstract

Lymphoid malignancies are characterized by the accumulation of DNA damage in the forms of point mutations, chromosomal translocations, deletions, and numerical abnormalities. Evidence suggests that structural abnormalities, such as DNA:RNA hybrids that form during faulty transcription or replication, serve as a trigger for genomic instability and checkpoint activation which can lead to cell cycle arrest and apoptosis. We postulate that a subgroup of aggressive lymphoid malignancies escape checkpoint activation through the upregulation of pathways and enzymes that can resolve these mutagenic abnormalities within the DNA.

Here we investigate the occurrence of DNA:RNA hybrids in lymphomas and benign lymphoid lesions. We show that unlike in benign lesions where DNA:RNA hybrid formation is frequent, DNA:RNA hybrids are relatively uncommon in a subset highly proliferative lymphomas. Further, we demonstrate that RNASEH2A (the catalytic component of the human ribonuclease H enzyme II which repairs DNA:RNA hybrids) is upregulated in this subset of predominantly aggressive lymphomas and inversely correlates with checkpoint activation. We hypothesize that RNASEH2A acts as a non-oncogene addiction gene in these malignancies, maintaining the survival of aggressive lymphomas in the setting of the increased cellular stress associated with the tumorigenic state. Our findings provide new and the valuable tools for uncovering the potential novel targets in preventing and treating the aggressive lymphoid malignancies.

Biography

Milena Vuica-Rossis an Assistant professor of Pathology at Johns Hopkins School of Medicine. She received her Medical Doctorateand Masters in Biomedicine from the School of Natural Sciences and Mathematics at the University of Zagreb, Croatia. She completed residency training program in Pathology, as well as fellowships in Immunology, Molecular Biology, Genetics and Hematopathology at the Johns Hopkins School of Medicine.