The Role of the Putative DNA Sensor ZBP1 in Tumorigenesis

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Abstract
The DNA-binding protein ZBP1 (also called DAI or DLM1) was suggested to be a sensor of DNA in the cytosol. However, the role of ZBP1 in cytosolic DNA recognition is not well understood. Here we report that ZBP1 is involved in sensing of DNA damage in tumor cells. Zbp1-deficiency increased the survival of Eµ-Myc mice, a mouse model for Burkitt lymphomas. No apparent lymphomas were observed in Zbp1-deficient Eµ-Myc mice that survived longer than Zbp1+/-Eµ-Myc mice. Zbp1-deficient B-cell lymphoma cells expressed higher levels of markers for DNA damage and the DNA damage response. The enhanced DNA damage correlated with elevated levels of TNF-α and cleaved CASPASE 3, 7 and 8 in Zbp1-deficient tumor cells. Inhibition of the tumor suppressor ataxia telangiectasia mutated (ATM), which controls cellular responses to DNA damage, decreased the survival of Zbp1-deficient Eµ-Myc mice. Administration of blocking TNF-α antibodies reversed the lower tumor load in Zbp1/-Eµ-Myc mice. DLM1 or ZBP1 expression was upregulated and partially translocated to the nucleus in B-cell lymphoma of Eµ-Myc mice in response to DNA damage and in tumors of chronic lymphocytic leukemia (CLL) patients. In summary, we show that ZBP1 deficiency promotes DNA damage in tumor cells and suppresses B-cell lymphomagenesis in Eµ-Myc mice.

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