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ATM deficiency: Revealing the pathways to cancer

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Genomic instability is a hallmark of cancer that can arise through the aberrant repair of DNA double strand breaks (DSBs) leading to the formation of chromosomal translocations, deletions, and inversions.[1] Although these lesions are often functionally inert they can have pathologic consequences by altering gene expression or encoding novel fusion proteins that participate in tumorigenesis by driving cellular transformation or improving tumor cell fitness. These chromosomal aberrations occur at increased frequency in cells with inherited or somatically acquired mutations that compromise DNA DSB repair.

The ataxia telangiectasia mutated (ATM) serine/threonine kinase is activated in response to all DNA DSBs and regulates canonical DNA damage responses required for checkpoint activation and normal DSB repair.[2] ATM is somatically inactivated in some tumors, and germline inactivation of ATM leads to ataxia telangiectasia (A-T), a syndrome that is marked by DNA DSB repair defects and genome instability. ATM-deficient humans and mice frequently develop lymphoid tumors with chromosomal translocations having breakpoints at antigen receptor loci. These lesions are indicative of aberrant repair of DSBs generated by the RAG endonuclease during antigen receptor gene assembly in developing lymphocytes.[3] Indeed, many non-transformed lymphocytes in ATM-deficient humans and mice have cytogenetically detectable translocations involving antigen receptor loci. Moreover, Atm-deficient mice that are deficient in RAG also generate lymphoid tumors with chromosomal aberrations, but they do not involve antigen receptor loci. Thus, ATM deficiency increases the frequency of aberrant DSB repair that leads to the formation of chromosomal lesions that can contribute to cellular transformation and tumor fitness.

Atm-deficient mice develop T cell acute lymphoblastic leukemia (T-ALL) with a high frequency of t(12;14) translocations that involve the *Tcrα/δ* locus on chromosome 14 and a region of chromosome 12 near the *Tcl1* gene. In A-T patients, translocations that result in the increased expression of TCL1 promote leukemogenesis. However, in Atm-deficient mice, the T-ALL t(12;14) translocations frequently delete the *Tcl1* gene, suggesting that these translocations promote leukemogenesis in other ways. This region of mouse chromosome 14 also includes the dosage-dependent tumor suppressor *Bcl11b*, a single copy of which is deleted by the t(12;14) translocations found in murine T-ALL. Moreover, a single copy of *BCL11b* is frequently inactivated in human T-ALL, suggesting that BCL11b may be an important suppressor of this disease.

Here, Ehrlich et al. develop genetically modified mice to address the role of Bcl11b haploinsufficiency in leukemic transformation.[4] The Lck-Cre transgene is used to delete a single floxed *Bcl11b* allele in thymocytes from both wild type and Atm-deficient mice. This leads to Bcl11b haploinsufficiency in developing and mature T cells in these mice. In wild type T cells, Bcl11b haploinsufficiency does not cause T-ALL, nor does it increase the incidence of T-ALL on an Atm-deficient background. However, the T-ALL that arises in Atm-deficient mice with T cells haploinsufficient for Bcl11b does not exhibit the classical t(12;14) translocations. Thus, while haploinsufficiency of Bcl11b alone is not sufficient for promoting leukemogenesis, the inactivation of a single copy of Bcl11b is an important contributor to this disease. Whether Bcl11b haploinsufficiency drives transformation only in combination with other lesions, or whether Bcl11b haploinsufficiency improves T-ALL fitness cannot be determined from this study.

It is intriguing that Erlich, et al. did not observe t(12;14) translocations that inactivate the functional copy of *Bcl11b* in T-ALL that forms in Atm-deficient mice with Bcl11b haploinsufficient T cells. In this regard, it is possible that complete deficiency of Bcl11b may have no added advantage for tumorigenesis. However, these findings raise the possibility that while inactivation of a single copy of *Bcl11b* promotes T-ALL, inactivation of both *Bcl11b* copies may be deleterious to transformed cells. Indeed, inactivation of both copies of *Bcl11b* in developing thymocytes affects the differentiation and survival of these cells.[5] Thus, in contrast to other haploinsufficient tumor suppressors, such as the histone variant H2AX, where complete loss increases tumorigenesis, loss of a one or both alleles of Bcl11b may have very different effects on the formation of T-ALL.[6,7]

While it is clear that genome instability is important for cancer, the effects of different lesions and combinations of lesions on driving transformation and evolving tumor fitness is not clear. This study by Erlich, et al. provides an important example of how model systems with DNA DSB repair defects (in this case, ATM deficiency) can be utilized to elucidate pathways required for cellular transformation and tumor fitness and define the manner in which these pathways function.

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