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**PIDs and cancer: an evolving story**

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Analysis of overall and site-specific cancer risk in patients with primary immunodeficiency diseases (PIDs) may shed light on the role played by the immune system in controlling malignancies. The association of PID and cancer has been known for many years. However, until recently, data on cancer risk in patients with PID have mostly derived from volunteer reporting to PID registries or from single-center studies. In this issue of *Blood*, Vajdic et al report on 1132 patients with PID whose data were entered into the Australasian Society of Clinical Immunology and Allergy (ASCIA) PID Registry and matched with those of the Australian National Death Index and of the Australian National Cancer Database. Because registration of primary invasive cancers is mandatory in Australia, the study by Vajdic et al represents the first large population-based analysis of cancer risk in PID, relative to the general population.

Patients with PID were found to have a 1.6 excess standardized incidence rate (SIR) of cancer. The risk was higher for non-Hodgkin lymphoma, leukemia, and thymic and stomach cancer. When PIDs were divided into major subgroups based on the nature of the immune defect, an increased risk of cancer was confirmed only for patients with predominantly antibody deficiencies, immune-deficiency syndromes, and diseases of immune dysregulation.

Previous studies had shown that patients with iatrogenic or acquired immunodeficiency are at higher risk for a variety of solid tumors with an infectious etiology, indicating that cell-mediated immunity is essential in the surveillance against such tumor-promoting agents. In contrast, Vajdic et al found that of all cancers with possible infectious origin, an increased SIR in patients with PID was identified only for stomach cancer. An increased risk of stomach and colon cancer among PID patients with antibody deficiencies had been previously reported. Vajdic et al conclude that patients with primary antibody deficiency may be at higher risk for a narrower range of malignancies than patients with iatrogenic or acquired immune deficiency, presumably because their cell-mediated immunity is intact.

Overall, the report by Vajdic et al illustrates the importance of investigating patients with rare disorders to better understand the pathophysiology of cancer. However, this study has several limitations. Only a minority of patients with PID were reported to the ASCIA PID Registry, no active follow-up was performed, and no quality control of the specific PID diagnosis was attempted. Because of the rarity of PIDs, underreporting or misreporting of patients may introduce a significant bias in the assessment of risk of cancer. Furthermore, some forms of PIDs are very severe, and require radical intervention with hematopoietic cell transplantation early in life to prevent death. If successful, this treatment is curative, thus impacting on the actual incidence of cancer in PIDs. This may explain the difference of SIR of cancer between the cohort of PID patients studied by Vajdic et al and patients with iatrogenic or acquired immune deficiencies. Finally, the criteria in use to classify PIDs are not adequate to describe the mechanisms of susceptibility to cancer in various forms of PID (see figure). For example,
PIDs with combined T- and B-cell deficiency include defects of DNA repair that carry a well-defined risk of transformation due to genomic instability, not just a lack of effective immune surveillance.10 Nonetheless, the study by Vajdic et al demonstrates the power of linking data derived from population-based and disease-specific registries to gain insights into the pathophysiology of cancer. With the development of PID registries in many areas of the world, the findings of this study are expected to be confirmed or challenged. Regional differences in the incidence of cancer among patients with PID might also emerge because of the distribution variability of various types of PID, exposure to tumor-promoting pathogens, and frequency of genetic variants conferring cancer susceptibility among different populations.

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REFERENCES


A new window on c-Myb function

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The c-Myb transcription factor is required for adult hematopoiesis.1 c-Myb is abundantly produced by hematopoietic stem cells and progenitors and is down-regulated in terminally differentiated hematopoietic cells. Expression of c-Myb increases in naive T and B lymphocytes after activation but little is understood about c-Myb function in mature lymphocytes.2 In this issue of Blood, Nakata and colleagues report that c-Myb is crucial for optimal development of human Th2 cells and demonstrate that c-Myb is important to establish autoregulation of GATA-3 expression during Th2 differentiation.3

CD4 helper T cells are critical for defense against a variety of pathogens. Depending on the cytokine environment after T-cell receptor–mediated activation, CD4 T cells differentiate into several types of helper T (Th) cells including Th1, Th2, and Th17 helper cells that are defined based on the cytokines that they produce.4 Interleukin-4 (IL-4)–mediated activation of signal transducer and activator of transcription 6 (STAT6) in activated CD4 T cells leads to expression of GATA-3, which is a transcription factor that is critical for differentiation of Th2 cells. The ability of exogenous GATA-3 to induce Th2 differentiation in the absence of IL-4 or STAT6 suggested that GATA-3 is able to mediate an autoregulation loop during Th2 differentiation.4 c-Myb has been reported to directly regulate transcription at the GATA3 locus in mouse thymocytes and to be important for CD4/CD8 lineage decisions.5 Nakata et al used short hairpin RNA (shRNA)–mediated silencing to identify potential c-Myb target genes in human effector/memory (CD4+CD45RO+) CD4 T cells and determined that mRNAs encoding GATA-3 and Th2 cytokines were decreased in the absence of c-Myb. Subsequent silencing of c-Myb expression in CD4+ naive (CD45RO−) and effector/memory T cells cultured under Th1- or Th2-promoting conditions led to decreased GATA-3 and Th2 cytokine production while expression of T-bet and interferon-γ was spared. Thus, c-Myb appears to be important for the differentiation and maintenance of CD4+ T cells with a Th2 phenotype. GATA-3 mRNA is transcribed from 2 alternative promoters, exon 1a and exon 1b. The exon 1a promoter is directly regulated by Notch signaling and is crucial for GATA-3 expression in mice during Th2 differentiation.5,6 Nakata et al determine that GATA-3 mRNA in activated naive and effector/memory human CD4 T cells parallels increased c-Myb expression during growth under Th2-promoting conditions and, perhaps surprisingly, is almost entirely transcription from the exon 1b promoter. Whether this difference in promoter use reflects a difference between the human and mouse systems requires clarification. Nakata and colleagues demonstrate that a conserved Myb-binding site in the exon 1b promoter is crucial for activation of exon 1b promoter/reporter constructs in primary human CD4 T cells. Silencing of endogenous c-Myb expression abrogated transcription from exon 1b promoter/reporter constructs and chromatin immunoprecipitation (ChIP) assays identified c-Myb bond to the endogenous exon 1b promoter in naive CD4 T cells grown under Th2-promoting, but not Th1–promoting, conditions. c-Myb was not found to be associated with exon 1a promoter chromatin. Thus, the GATA-3 exon 1b promoter appears to be a direct c-Myb target in human Th2 cells. Nakata et al further establish that GATA-3 also interacts with the exon 1b promoter near the c-Myb-binding site. GATA-3 alone has little ability to transactivate the exon 1b promoter but c-Myb and GATA-3 cooperate on the exon 1b promoter, suggesting that GATA-3 could establish an autoregulatory loop in the presence of c-Myb during the differentiation of Th2 cells. Few bona fide c-Myb target promoters have been established and little is actually understood about how c-Myb functions as a transcription activator. Nakata et al determined that GATA-3 does not bind to the exon 1b
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