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In this issue, Joshi and colleagues show that Notch-1 regulates cell cycle by targeting expression of cyclinD3 and Cdk4/6. This article adds to the growing body of literature pointing to aberrant Notch activity as a master controller during T-ALL pathogenesis.

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive leukemia with a poor outcome. The majority of human T-ALL has gain-of-function (activating) mutations in Notch-1, implicating Notch-1 as a central component in the pathogenesis of T-ALL. Notch proteins are widely expressed transmembrane receptors involved in many cellular processes such as differentiation, proliferation, and apoptosis. Notch-1 signaling is critical for normal T-cell development. However, aberrant regulation of Notch, leading to persistent activation, leads to unchecked cell growth. All members of the Notch family (Notch 1–4) have been implicated in tumorigenesis. Notch ligands are members of Delta-Serrate-Lag2 (DSL) family that are expressed on neighboring cells. Ligand binding causes a 2-step proteolytic cleavage of Notch that releases the active intracellular domain of Notch (N1C) from the cell surface membrane. The last cleavage step is mediated by γ-secretase complex. N1C translocates to the nucleus, where it functions as a transcription factor. In the canonical NOTCH signaling pathway, Notch binds to the transcription factor CSL, displaces transcriptional repressors, recruits activators, and thus increases transcription of target genes.

In the current study, Joshi et al demonstrate that Notch-1 regulates expression of components of cell-cycle machinery, which contribute to dysregulated cell growth. Specifically, they demonstrate that Notch-1 directly binds to the cyclinD3 promoter and increases cyclinD3 expression. In addition, Notch-1 increases expression of Cdk4 and Cdk6, the catalytic partners of cyclin D3. The Cdk4-cyclin D3 complex is essential for progression through G1/S phase of cell cycle. The authors also demonstrate that Cdk4 and cyclinD3 are increased, and the increase can be abrogated by use of inhibitors of γ-secretase (GSI). In further support of the concept that cyclinD3 is downstream of Notch, mice lacking cyclinD3 are protected from the development of leukemias induced by the activated, intracellular form of the Notch. Thus, their data support a direct role of Notch in regulating cell-cycle progression in which activating mutations of Notch would be able to enhance transformation by deregulating cell growth.

Because of its central role in T-ALL pathogenesis, Notch is an obvious therapeutic target. Since cleavage and release of N1C by γ-secretase is a critical step in Notch signaling, small molecular inhibitors of γ-secretase (GSI) have been proposed for use in T-ALL. Indeed, in vitro GSI administration causes cell-cycle arrest of T-ALL cell lines with activating mutations in Notch1. However, early clinical trials of GSI in refractory T-ALL have not shown significant clinical response. The current study suggests that combinatorial therapy with inhibitors of Notch and inhibitors of cell cycle may be beneficial to a subset of patients with T-ALL. However, targeting Notch signaling has additional complexities. For example, Notch can decrease expression of p27, a Cdk inhibitor; increase expression of

[Diagram: Schematic representation of Notch pathway interactions with the cell cycle. The ligand (DSL) binds to the extracellular domain of the Notch receptor. Following ligand binding, Notch is cleaved at the extracellular domain. The membrane-bound intracellular domain is then cleaved by the γ-secretase complex, releasing the active intracellular domain N1C. N1C moves to the nucleus, where it binds to CSL, recruits coactivators (CoA), and induces gene transcription. Target Notch genes include cyclinD3 and Cdk4, which promote progression through the cell cycle. Additional target genes are not shown.]
Myc; and upregulate of the PI3K–AKT signaling pathway. Thus, identification of additional Notch target genes and molecular characterization of T-ALL mutations will facilitate development of rational therapy for T-ALL patients.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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A role for ionizing radiation in myelomagenesis?

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Using data from the monoclonal-protein screening study on Nagasaki atomic bomb survivors, Iwanaga and colleagues report in this issue of Blood that ionizing radiation is associated with an elevated risk of MGUS, particularly for individuals exposed at younger ages.

Beyond age, sex, race, and a positive family history of multiple myeloma, no consistent extrinsic risk factors have been clearly linked to multiple myeloma. Previous studies evaluating the risk for multiple myeloma among individuals exposed to radiotherapy have generally not found evidence of excess risk, and the same has been true in prior studies of atomic bomb survivors.

A few studies have evaluated the relationship between monoclonal gammapathy of undetermined significance (MGUS) and ionizing radiation. For example, in a small retrospective study including 285 MGUS cases and 570 hospital-based controls, ionizing radiation was found to be associated with an increased risk of MGUS. In a prior study based on 6737 atomic bomb survivors, 112 developed MGUS reflected in a crude incidence rate of 164 per 100 000 person-years, and with a sharp increase in incidence after age 60. The MGUS incidence was not significantly associated with radiation dose, and the authors found that transformation from MGUS to multiple myeloma occurred at a significantly higher rate among radiation exposed (vs non-exposed) persons.

In the largest investigation to date, Iwanaga et al assess the relationship between MGUS and radiation exposure in Nagasaki atomic bomb survivors. Based on more than 50 000 study participants, a total of 1082 MGUS cases were identified (yielding an overall prevalence of 2.1%; 95% CI 1.9%-2.2%). Importantly, the authors found that individuals exposed to radiation at age 20 years or younger had a higher prevalence of MGUS comparing those exposed at a distance within 1.5 km (vs >3.0 km). Very similarly, among individuals exposed at age 20 years or younger, the prevalence of MGUS was higher in individuals exposed to more than 0.1 Gy (vs <0.01 Gy). However, in contrast, among those exposed at age 20 years or older, the exposure distance and the dose intensity yielded no statistical association with regard to MGUS. Thus, individuals exposed at younger ages had a higher risk for MGUS when exposed to higher radiation doses. Finally, when evaluating the risk of developing multiple myeloma among MGUS cases, there was no statistical association with regard to radiation exposure.

The findings of the study by Iwanaga et al are important for several reasons. Their results indicate that ionizing radiation exposure might play a role in the causation of plasma cell disorders. Given that we currently lack insight into mechanisms underlying the development of plasma cell disorders, this is an intriguing observation that potentially could facilitate the discovery of biological mechanisms involved in myelomagenesis. For example, ionizing radiation induces chromosomal and genomic instabilities and chromosomal abnormalities are indeed commonly found in MGUS and multiple myelomas. Furthermore, as pointed out by the authors, beyond the observed association between radiation and MGUS risk, there are emerging data from other studies to support a role for genetic susceptibility, and immune-related and inflammatory conditions in the development of myelomagenesis. Interestingly, there has been recent evidence to suggest that radiation-induced inflammatory reactions and radiation-induced genomic instability may be interrelated with a predisposition to radiation carcinogenesis. Taken together, more research is needed to clarify underlying mechanisms of the observed excess of MGUS among persons exposed to ionizing radiation.

From a general clinical perspective, the study by Iwanaga et al addresses an important question related to the rapidly growing use of computed tomography (CT) in clinical practice during recent years. Indeed, increasing attention has been focused on the potential for radiation exposure from CT to induce cancers. This is a particular concern for children since they have increased organ radiosensitivity and a long lifetime to potentially develop radiation-related cancer. Along the same lines, it would be interesting to assess the prevalence of MGUS among individuals exposed to CT and other types of medical ionizing radiation at younger ages.

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Another Notch on the belt

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