E2F1 and p53 because deletion of these genes rescued the defects in thymocytes lacking p57 (see figure). This critical role of the p57-E2F1-p53 axis in thymic development is remarkably similar to its functions in brain development.2

p53 is mutated in most human cancers, and inactivation of the p53 tumor suppressor pathway is critical for oncogenic transformation. Mice lacking p53 succumb to thymic lymphomas and other cancers by 6 months of age.8 Matsumoto et al demonstrate that T cell–specific loss of p57 leads to a differentiation block at the DN3 stage and p53 hyperactivation, which accelerates lymphoma development in a p53-null background. This reveals a critical tumor suppressor function for p57 in T lymphocytes. Inactivation of the TCRβ gene enhancer in mice leads to a block in T-lymphocyte development at the CD4+CD25− (DN3) stage, where recombination-activating genes (RAG) are expressed, and dramatically accelerates lymphogenesis in a p53-null background.9 These lymphomas display evidence of RAG-dependent chromosomal translocations and amplifications associated with human hematologic malignancies, suggesting that mutations that lead to a block in lymphocyte development, at a stage associated with continued expression of RAG genes, can act as a potential precarcinogenic event.9 Based on the findings of this study, it is likely that persistent RAG expression in the thymocytes lacking p57 that are blocked at the DN3 stage may activate the DNA damage checkpoint, leading to the observed p53 hyperactivation, which acts as a tumor suppressor whose loss leads to rapid lymphoma development. Hence the differentiation block in T cells lacking p57 is possibly a critical mediator of the accelerated lymphoma development in a p53-null background. Loss of the CKI p57 leads to increased Cdk activity, which raises the question of the Cdk substrates in this context. Cdns are known to phosphorylate p53, E2F1, and definitely Rb (which represses E2F1 transcriptional activity), but it cannot be excluded that there are lymphogenesis-specific Cdk substrate(s) to be uncovered. Because the knock-in of the p27 gene into the p57 locus corrected the defects in hematopoietic stem cells lacking p57,10 it would be interesting to check whether development of T cells lacking p57 can be similarly rescued. Future studies to determine the mechanism by which p57 loss leads to a differentiation block in thymocytes will be instructive for understanding its role in normal T-cell development as well as lymphogenesis.

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Comment on Tellier et al, page 3462

The missing link in early follicular lymphoma development

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In this issue of Blood, Tellier et al report on extremely rare t(14;18)-positive cells within reactive lymph nodes of normal individuals. They convincingly show that these cells preferentially reside as nonproliferating cells in germinal centers.1

Using primitive nested polymerase chain reaction methodologies, Limpons et al was the first to find t(14;18)-carrying cells in reactive lymphoid tissues of otherwise healthy persons.2 Later work by the same and other groups showed that these rare translocations can be regularly found in blood B cells of normal adults with some associations to age and exposure to pesticides.3 The risk in developing follicular lymphoma is estimated to be very low; however, recent data showed that individuals with a frequency of >1 translocation-positive cell in 104 leukocytes (approximately 1 in 500 B cells) have a 23-fold increased risk in developing follicular lymphoma over a period of 15 years.4

The t(14;18) is derived from erroneous recombination of variable, diverse and joining (VDJ) gene segments in precursor B cells, and previously it was thought that circulating t(14;18)+ cells should be naive B cells. In 2007, Roulland et al provided a surprising publication showing that these cells, just like follicular lymphoma cells, represent memory B cells that have undergone somatic hypermutations and abortive class switching, proving that they are postgerminal center memory B cells.5

In 2002 Cong et al identified a novel entity called “follicular lymphoma in situ” in which individual germinal centers of otherwise normal lymph nodes are heavily colonized by translocation-positive B cells.6 This in situ lymphoma is found in ~2%-3% of all individuals in which lymph nodes are removed for other reasons than lymphoma diagnostics.7 These rare lesions have already accumulated several genetic alterations underlying to follicular lymphoma and obviously may have little to do with the circulating t(14;18)+ cells that are present in so many normal adults.8,9 Tellier et al provide an important missing link between these circulating t(14;18)-positive
memory B cells in healthy individuals and their origin from bone marrow precursor B cells by the in situ analysis of t(14;18)+ cells in lymph nodes of healthy individuals. As in peripheral blood, these cells are identifiable in a sizeable proportion of individuals. Using triple staining for CD20, CD10, and B-cell lymphoma 2 (BCL2) and cell sorting for CD20, CD10, and C-X-C chemokine receptor 4 (CXCR4; a marker of centroblasts), translocations are mainly seen in the CXCR4 dim staining centrocytes. Moreover, by labeling for carboxyfluorescein succinimidyl ester (CFSE) before in vitro B-cell stimulation and flow sorting, they are exclusively found in the strongly CFSE-positive nonproliferating cells. The authors suggest that this nonproliferating state is caused by aberrant BCL2 overexpression.

The current paper suggests a preferential homing to germinal centers where these cells undergo somatic mutations and class switching and also further steps in the development of (pre)malignant clones, incidentally giving rise to a follicular lymphoma in situ (see figure). The next, even more challenging step will be to get these rare cells in hand to further investigate them by mutation analysis and in functional assays.

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

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A(never) day in the life of neonatal platelets

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In this issue of Blood, Liu et al demonstrate that neonatal platelets survive longer than their adult counterparts, which provides the rapidly growing fetus and neonate with a mechanism to expand platelet mass and maintain hemostasis during the transition from fetal to adult hematopoiesis.1

Thrombocytopenia, which may contribute to intracranial hemorrhage in preterm neonates, is a major clinical problem encountered in the neonatal intensive care unit. Significant intracranial bleeding can lead to hydrocephalus, seizures, neurologic deficits, and death. The current treatment of thrombocytopenia in preterm neonates is platelet transfusions, but the risks of this therapy include viral infections, transfusion-related acute lung injury, and volume overload. 2 New therapies are urgently needed, but first a basic understanding of neonatal thrombopoiesis is needed. In their article, Liu et al reveal a novel biological strategy for maintaining platelet homeostasis in neonates that is independent of the rate of platelet production.3

Using a mouse model for neonatal thrombopoiesis, the authors found an approximate doubling of the platelet count during the newborn period despite a 5-fold increase in

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