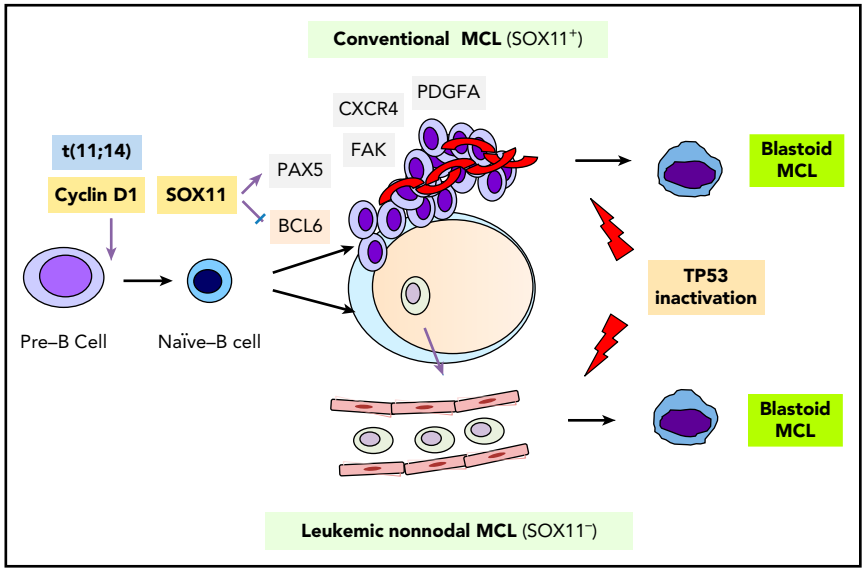

MCL pathogenesis and molecular subtypes. Classical MCL and leukemic, nonnodal MCL are derived from distinct B-cell populations and are transformed via distinct biological pathways. Both subtypes possess t(11;14) and may undergo blastoid transformation, which is frequently associated with disruption of TP53. Reprinted with permission from Puente et al.[2]

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THROMBOSIS AND HEMOSTASIS

Comment on Pilli et al, page 452

Hypoxia and thrombosis

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In this issue of *Blood*, Pilli and colleagues[1] report that the essential antithrombotic factor protein S is inversely regulated by the transcription factor hypoxia inducible factor 1 (HIF1). This is an important contribution to our understanding of the molecular basis of the augmentation of thrombosis by hypoxia.

An association between increased arterial and venous thrombosis and environmental hypoxia has been well described in the acquired prothrombotic condition polycythemia vera[2] and other conditions,[2] as well as in familial Chuvash polycythemia, a recessively inherited augmentation of hypoxia sensing.[3] Hypoxic cancer tissue may contribute to cancer patients' propensity to thrombosis.

Hypoxia is sensed and its effect transmitted to an array of physiological processes by HIFs. HIFs are dimers of posttranscriptionally oxygen-regulated HIFα and HIFβ subunits. There are 3 paralogs of HIFα (HIF1α, HIF2α/EPAS, and HIF3α) and 2 paralogs of the HIFβ subunit (ARNT and ARNT2).[4] HIFs directly regulate transcription of many known and yet to be discovered genes. HIFs have distinct tissue and gene specificity. For example, the ubiquitously expressed HIF1 upregulates >3% of genes in endothelial cells,[5] whereas the more tissue-restricted HIF2 is the principal transcriptional regulator of erythropoietin.[6] Levels of HIF dimers are regulated by the posttranslational stability of HIFα subunits.[7] In normoxia, these subunits are prolylhydroxylated and bind to VHL protein, targeting them for rapid destruction in the proteasome.[8] In contrast, in hypoxia, these HIFα subunits proteins are stabilized, resulting in increased transcription of HIF-regulated genes; similarly, homozygosity for the hypomorphic Chuvash polycythemia mutation VHL^{R200W} also leads to posttranslational stabilization of HIFα subunits at normoxia.[9]

The liver is the site of protein S synthesis. Pilli and colleagues report that in a liver cell line HepG2, the level of protein S decreases after hypoxic exposure. In further studies of mice with either a HIF1α gene knockout or a HIF1α gain-of-function mutation, they demonstrate that HIF1 downregulates protein S levels. The decreased protein S levels were associated with increased thrombin, consistent with a prothrombotic effect.

Unexpectedly, they describe that the transcript of HIF1α also increases under these hypoxia-augmenting conditions. The molecular basis of this observation remains to be clarified, as HIFs activate transcription of genes only by direct binding to their promoters; however, HIFs may also repress gene transcription indirectly by the transcriptional activation of microRNAs and repressors.

Hypoxia is common in many disease states, including cancer, wherein it accounts for unique HIF-mediated cancer cell energy generation (ie, the Warburg effect). The

hypoxic regulation of other prothrombotic and antithrombotic genes is currently under active investigation, and other hypoxia-controlled thrombotic mechanisms are expected to be uncovered.

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

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