

## ● ● ● NEOPLASIA

Comment on Gelebart et al, page 5171

**Wnt-erizing mantle cell lymphoma**

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In this issue of *Blood*, Gelebart and colleagues show that the Wnt canonical pathway is constitutively active in mantle cell lymphoma cells and that selective inhibition of the pathway decreases malignant B-cell growth.

The Wnt signaling pathway is a highly conserved system that has a key role in embryonic development and in the growth and maintenance of normal tissues.<sup>1</sup> It has also been shown to have important roles in lymphopoiesis and hematopoiesis.<sup>2</sup> Dysregulated expression of components of the Wnt pathway can induce transforming events and are known to contribute to the pathogenesis of various malignancies.

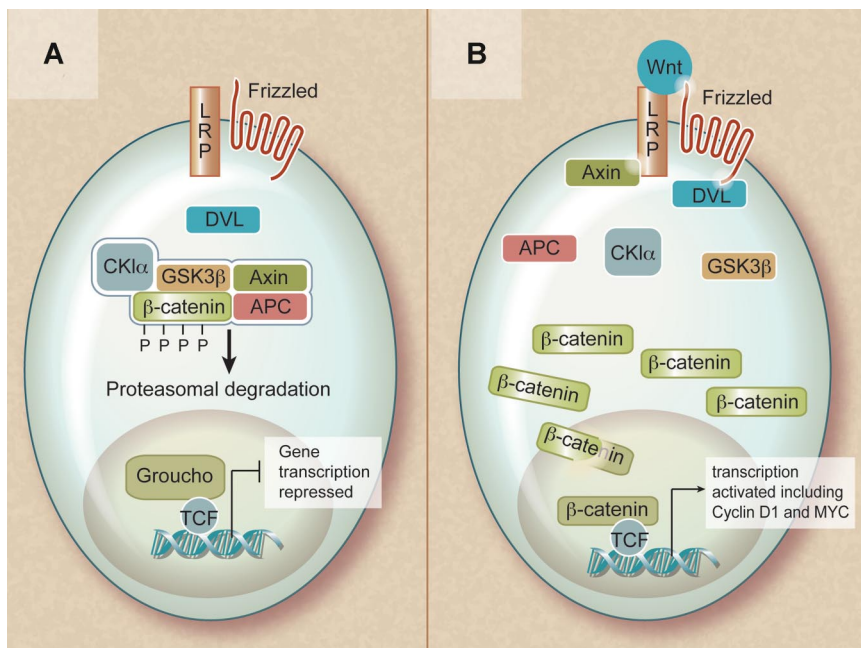
The Wnt family consists of secreted factors that bind to frizzled receptors (a family of transmembrane proteins) and low-density lipoprotein receptor-related protein coreceptors (LRP5 or LRP6) in the plasma membrane. In the absence of a Wnt ligand,  $\beta$ -catenin is found in a cytoplasmic complex with axin and adenomatous polyposis coli (APC) proteins and is targeted for ubiquitin-mediated degradation upon its phosphoryla-

tion by casein kinase 1 $\alpha$  (CK1 $\alpha$ ) and glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ). Consequently, in the nonactivated state, cytoplasmic  $\beta$ -catenin levels remain low and lymphocyte enhancer binding factor (LEF) and T-cell factor (TCF) in the nucleus interact with Grouchos to repress Wnt-specific target genes.

In contrast, when a Wnt protein binds to the receptor complex,  $\beta$ -catenin is no longer phosphorylated and targeted for degradation, resulting in accumulation of  $\beta$ -catenin in the cytoplasm and its translocation to the nucleus. In the nucleus,  $\beta$ -catenin regulates gene expression in cooperation with members of the TCF and LEF family of transcription factors. This results in the activation of multiple target genes, including *cyclin D1* and *c-MYC*, that instruct the cell to actively proliferate and remain in an undifferentiated state.

Mantle cell lymphoma is a well defined subtype of B-cell non-Hodgkin lymphoma and is characterized by dysregulated cyclin D1 gene expression.<sup>3</sup> This dysregulation is secondary to the t(11;14)(q13;q32) translocation that juxtaposes the proto-oncogene *CCND1* at chromosome 11q13, which encodes cyclin D1, to the immunoglobulin heavy chain gene at chromosome 14q32. Cyclin D1, which is not expressed in normal B cells, becomes constitutively overexpressed, resulting in deregulation of the cell cycle, alterations in DNA damage response pathways, and activation of cell survival mechanisms. However, overexpression of cyclin D1 alone is not sufficient for tumor formation, suggesting that dysregulation of additional signaling pathways may be critical for development of mantle cell lymphoma.<sup>4</sup>

Gelebart and colleagues have now shown that the Wnt canonical pathway is constitutively activated in a subset of patients with mantle cell lymphoma and that activation of the Wnt pathway appears to promote tumorigenesis. They found that Wnt3 and Wnt10 are highly expressed in mantle cell lymphoma and that  $\beta$ -catenin is localized to the nucleus and



Overview of the Wnt signaling pathway. (A) In the absence of a Wnt signal,  $\beta$ -catenin is captured within a destruction complex and phosphorylated. This results in ubiquitinylation and proteasomal degradation of  $\beta$ -catenin, ensuring repression of its target genes. (B) In the presence of a Wnt ligand, the destruction complex is inactivated and  $\beta$ -catenin translocates to the nucleus. In the nucleus,  $\beta$ -catenin becomes part of a transcriptionally active complex, ensuring efficient activation of its target genes. Professional illustration by Debra T. Dartz.

transcriptionally active in mantle cell lymphoma cell lines. Fifty percent of biopsy specimens from mantle cell lymphoma patients showed nuclear localization of  $\beta$ -catenin, and this correlated with an increase in the inactive form of GSK3 $\beta$ . The functional relevance of the Wnt canonical pathway in mantle cell lymphoma was further confirmed by selective inhibition of  $\beta$ -catenin resulting in decreased growth of the malignant B cells. These findings are supported by previous gene expression profiling studies that showed that several genes from the Wnt signaling pathway were up-regulated in mantle cell lymphoma cells.<sup>5</sup>

These results suggest that the Wnt pathway promotes malignant cell growth in mantle cell lymphoma and the Wnt pathway may therefore be a target for therapeutic intervention. Small molecule inhibitors and monoclonal antibodies targeting this pathway are being

developed and may be beneficial in treating mantle cell lymphoma in the future.

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

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## ● ● ● HEMOSTASIS

Comment on Verhaar et al, page 4935

# UV-C irradiation gives platelets a sunburn

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In this issue of *Blood*, Verhaar and colleagues report that, although UV-C irradiation is an attractive method to minimize microbial contamination of platelet concentrates, it directly activates platelet  $\alpha$ IIB $\beta$ 3 by reducing critical extracellular disulfide bonds, resulting in the aggregation of stored platelets.

**W**ith the largely successful advent of viral testing, bacterial contamination has become the major infectious complication of transfusion. This is particularly relevant for platelets that must be stored at 20°C to 24°C to preserve platelet function, unfortunately resulting in a permissive environment for growth of bacterial contaminants. In fact, microbiologic testing of platelet products has revealed contamination rates of between 1 in 2000 and 1 in 4000<sup>1</sup> as well as a risk of clinical sepsis from apheresis platelets that can be as high as 1 in 15 000 infusions.<sup>2</sup> Accordingly, platelet storage has been limited to 5 days to minimize the extent of bacterial growth.

Bacterial contamination of blood products can result from inadequate skin cleansing, from a small core of skin that sometimes enters the phlebotomy needle, and from contaminated blood collection packs.<sup>3</sup> Thus, obvious ways to reduce contamination are to improve skin disinfection, to discard the first 15 to

30 mL of collected blood, and to culture or otherwise screen platelet products for the presence of bacteria.<sup>3</sup> Another approach is to inactivate the contaminating bacteria.

Photodynamic and photochemical methods using ultraviolet (UV) light have been developed to inactivate bacteria in platelet products by damaging their DNA and RNA. Thus, irradiating platelet concentrates containing psoralen derivatives with UV-A light (wave length 315–400 nm) induces pyrimidine crosslinks in bacterial DNA and RNA, preventing subsequent replication and transcription. In the SPRINT trial, transfused platelets that had been irradiated with UV-A in the presence of the psoralen amotosalen were as hemostatically effective as control platelets. However, the photochemical treatment resulted in lower platelet increments and shorter intervals between transfusions, suggesting that it had caused mild platelet injury.<sup>4</sup> Although UV-B irradiation (wave length 280–315 nm)

has been used primarily to prevent HLA sensitization and platelet refractoriness, it has been combined with the dye thionine and yellow light in a 2-step procedure to inactivate bacteria in platelet concentrates.<sup>5</sup> Enthusiasm for UV-B as a decontaminant, however, must be tempered by the report by van Marwijk Kooy et al, which found that UV-B irradiation causes platelet aggregation via oxygen radical-induced activation of protein kinase C.<sup>6</sup>

In contrast to UV-A and UV-B, UV-C irradiation (wave length 100–280 nm) reduces bacterial growth in platelet concentrates without the need for photosensitizing additives. However, Terpstra et al observed that when platelets suspended in 10% plasma were irradiated with UV-C light, there was dose-dependent LDH release, P-selectin expression, and phosphatidylserine exposure that was mitigated to some extent by increasing the plasma concentration to 30%.<sup>7</sup> In the work reported in this issue of *Blood*, the same group of investigators has studied the mechanism responsible for the decrease in platelet count that occurs during storage of UV-C-treated platelets. They found that relatively high-dose UV-C irradiation (1500 J/m<sup>2</sup>) caused immediate,  $\alpha$ IIB $\beta$ 3-dependent, platelet aggregation, implying that aggregate formation was the cause for the decreased platelet counts. Interestingly, UV-C-induced platelet aggregation was independent of platelet signal transduction. For example, it was unaffected by increasing platelet cAMP with forskolin, but it was associated with a marked increase in free thiol groups on the platelet surface, including free thiols in  $\alpha$ IIB $\beta$ 3. Incubating platelets with the reducing agent dithiothreitol has been known for decades to induce platelet aggregation, presumably by reducing critical but, as yet, unidentified disulfide bonds in  $\alpha$ IIB $\beta$ 3.<sup>8</sup> Thus, the authors speculate that disulfide bond photolysis induced by UV-C irradiation was responsible for the platelet aggregation they observed.

The bacteriocidal properties of UV-C radiation would make it seem an ideal solution for the infectious complications of platelet transfusion. But the chemistry responsible for its bacteriocidal properties also has unexpected but unavoidable novel consequences on platelet function. It's not easy to mess with Mother Nature.

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