PML-RAR-alpha (fusion protein) retains both DNA-binding domains and ligand-binding domains of RAR-alpha (104). The fusion protein binds retinoic acid just as wild-type RAR-alpha binds retinoic acid. The fusion protein is thought to block cell differentiation by constitutively silencing retinoic acid-responsive genes involved in the control of differentiation of hematopoietic precursor cells (105). The silencing of these genes and the blocking of cell differentiation is reversed by administering retinoic acid (106). As reviewed by Nasr and de Thé (107) all-trans-retinoic acid induces the degradation of the PML-RAR-alpha fusion protein, and arsenic trioxide also provokes degradation of the PML-RAR-alpha fusion protein. Regarding the mechanism of action of arsenic trioxide, Goussetis et al. (108) find that it induces autophagy, a mechanism of cell death, while Shackelford et al. (109) find that arsenic trioxide induces apoptosis, another mechanism of cell death. Thus, when the combination of all-trans-retinoic acid and arsenic trioxide is used to treat PML, relief from cancer may result from killing of the cancer cells, but also by promoting the cancer cells to undergo cell differentiation to become non-transformed cells.

3. Methodology tip – platelets and blood clotting

Platelet transfusions are used in treating acute promyelocytic leukemia and the myelodysplastic syndromes. The relevance of platelets to blood clotting is as follows. The blood clotting pathway is initiated when a wound releases tissue factor, and tissue factor is exposed to the bloodstream. Tissue factor resides in the walls of blood vessels (110,111). Following a rapid cascade of enzymatic events, prothrombin (catalytically inactive) is converted to thrombin (catalytically active). Thrombin, in turn, catalyzes the activation of fibrinogen and as well as the activation of platelets (112). In other words, thrombin activates two branches of the blood clotting cascade (fibrinogen; platelets). The result is a blood clot, which takes the form of a network of cross-linked fibrin, where platelets are cross-linked to the fibrin.

[104] Segalla S, Rinaldi L, Kilstrup-Nielsen C, et al. Retinoic acid receptor alpha fusion to PML affects its transcriptional and chromatin-remodeling properties. *Mol Cell Biol*. 2003;23:8795–808.

[105] Segalla S, Rinaldi L, Kilstrup-Nielsen C, et al. Retinoic acid receptor alpha fusion to PML affects its transcriptional and chromatin-remodeling properties. *Mol Cell Biol*. 2003;23:8795–808.

[106] Minucci S, Monestiroli S, Giavara S, et al. PML-RAR induces promyelocytic leukemias with high efficiency following retroviral gene transfer into purified murine hematopoietic progenitors. *Blood*. 2002;100:2989–2995.

[107] Nasr R, de Thé H. Eradication of acute promyelocytic leukemia-initiating cells by PML/RARA-targeting. *Int J Hematol*. 2010;91:742–747.

[108] Goussetis DJ, Altman JK, Glaser H, McNeer JL, Tallman MS, Platanias LC. Autophagy is a critical mechanism for the induction of the antileukemic effects of arsenic trioxide. *J Biol Chem*. 2010;285:29989–29997.

[109] Shackelford D, Kenific C, Blusztajn A, Waxman S, Ren R. Targeted degradation of the AML1/MDS1/EVI1 oncoprotein by arsenic trioxide. *Cancer Res*. 2006;66:11360–11369.

[110] Mackman N, Taubman M. Tissue factor: past, present, and future. *Arterioscler Thromb Vasc Biol* 2009;29:1986–1968.

[111] Mackman N. The many faces of tissue factor. *J Thromb Haemost*. 2009;7(suppl 1):136–139.

[112] Brody T. *Nutritional Biochemistry*. 2nd ed. San Diego, CA: Academic Press; 1999; pp. 524–539.