In this issue of Blood, Cao et al\textsuperscript{1} report on a novel mechanism of coagulopathy in acute promyelocytic leukemia (APL) induced by treatment with all-trans-retinoic acid (ATRA).

Over the last few decades, advances in the management of APL have transformed it from a leukemia with an abysmal prognosis to one with the best prognosis.\textsuperscript{2} Currently, it is reasonable to expect >90\% remission rates with long-term survival exceeding 80\%, even in high-risk APL.\textsuperscript{2} Remarkably, most of these improvements in clinical outcome have happened without intensification of conventional chemotherapy and with the use of combination of nonmyelotoxic differentiating agents such as ATRA and arsenic trioxide (ATO). Simultaneously, laboratory investigators have detailed the cellular and molecular pathogenesis of this leukemia. APL has become a model of the integration of basic and clinical investigation. Although challenges remain in the management of high-risk APL and relapsed APL, the greatest challenge is early mortality in newly diagnosed patients.

The distinctive and unique pattern of coagulopathy seen in APL remains the major cause of early mortality in newly diagnosed patients. In the real world, outside the context of clinical trials, early mortality approaches 17\% to 30\%, the majority of which is related to coagulopathy.\textsuperscript{3} These coagulopathy-related events cannot be attributed solely to delays in diagnosis and initiation of therapy.\textsuperscript{4} Conventional chemotherapy agents such as anthracyclines have been known to exacerbate the coagulopathy in APL, while differentiating agents such as ATRA and ATO improve it. However, even after initiating therapy with ATRA, there is considerable delay in the correction of coagulopathy and a discordance between laboratory parameters and clinical manifestations.

ETosis is a novel cell death pathway, neither apoptotic nor necrotic, that was first described in 2004 in the context of neutrophils and bactericidal activity.\textsuperscript{5} This process can be summarized as the initial breakdown of the nuclear and granule membranes within a cell leading to interaction of nuclear chromatin with antimicrobial peptides (AMPs) and enzymes (such as bactericidal/permeability increasing protein [BPI], elastases, and cathepsin G). The subsequent cell membrane breakdown leads to release of a web of extracellular chromatin enriched with AMPs and enzymes (such as bactericidal/permeability increasing protein [BPI], elastases, and cathepsin G). The subsequent cell membrane breakdown leads to release of a web of extracellular chromatin enriched with AMPs, BPI, and other enzymes that forms a sticky mesh (neutrophil extracellular traps [NETs]) in which bacteria are trapped and killed, while effectively limiting the systemic side effects of these toxic peptides and enzymes.\textsuperscript{6} It has also been recognized that NETs are involved in activation of coagulation. Similar to the ability of NETs to concentrate antibacterial peptides and enzymes, it has been demonstrated that they can also concentrate...
procoagulant proteins which, along with the disrupted and activated surface of cell membrane of the cell from which they arise, form a template for coagulation and fibrinolysis. The cell-free DNA (cf-DNA) released by the formation of NETs can also activate coagulation via the contact activation system.

More recently, Ma et al demonstrated a similar phenomenon of ETosis-induced cell death in malignant promyelocytes that was exacerbated by treatment with ATRA. Their data suggested that autophagy and an increase in cytokines such as tumor necrosis factor α and interleukin 6 following exposure to ATRA contributed to this phenomenon. In this issue of Blood, the same team extended those initial observations and demonstrated the effect of promyelocytic extracellular chromatin released due to ETosis and its impact on coagulation and fibrinolysis in APL following treatment with ATRA (see figure). Through a series of experiments, the authors demonstrate the presence of ETosis in malignant promyelocytes and the effect of ATRA in potentiating and inducing extracellular chromatin release in a time-dependent manner. They demonstrate that this effect was prominent in the first 3 days after exposure to ATRA and, beyond that time period, cell death was predominantly due to conventional apoptosis. They further correlated thrombin generation and a strong procoagulant effect to extracellular chromatin and cf-DNA generated by ETosis and the ability of DNAse1 to decrease thrombin generation by degrading cf-DNA. The use of anti–tissue factor antibodies could not reverse this. Additional experiments demonstrated the ability of promyelocytic extracellular chromatin to induce fibrin deposition, plasmin generation, and fibrinolysis. Paradoxically, it impaired clot lysis. Finally, the authors demonstrate the cytotoxic effect of promyelocytic extracellular chromatin on the endothelial cells that they come in contact with. This cytotoxic effect converts these endothelial cells to a procoagulant phenotype, provides additional surface area on which coagulation and fibrin deposition can happen, and may also contribute to loss of integrity of the endothelium.

Through the data in their paper, Cao et al demonstrate a novel mechanism of perturbation in coagulation and fibrinolysis in APL that is exacerbated on initiation of treatment with ATRA. The data suggest that targeting this novel mechanism could potentially address the problem of early coagulopathy-related mortality. The cytotoxic effects of promyelocytic extracellular chromatin on endothelial cells could also potentially explain the differentiation syndrome seen after initiation of therapy and apparent susceptibility to bleeding in the presence of what would be considered adequate hemostatic levels of platelets and coagulation factors.

REFERENCES


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APL: Oh! What a tangled web we weave

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