Comment on Redondo-Muñoz et al, page 169

**Gang of 3 in aggressive CLL?**

**Grzegorz S. Nowakowski** Mayo Clinic

In this issue of *Blood*, Redondo-Muñoz and colleagues demonstrate that VLA-4 and the 190-kDa isoform of CD44v constitute docking molecules on the surface of CLL B cells for MMP-9. The attachment of MMP-9 to the surface of CLL B cells appears to alter their migration.

The current work by Ono and colleagues in Shaun Jackson’s group implies that myosin-IIA complexes play a key role not only in the birth of the platelet, but also in the endgame of hemostatic plug formation and thrombus consolidation in the vessel wall. Because the thrombus is attached to the vessel wall, the contraction will pull the thrombus toward the lesion, simultaneously cementing the breach and facilitating blood flow through the vessel. In the context of atherothrombotic disease, the extent of the contraction may affect the resistance of platelet–rich clots to fibrinolytic agents and to antiplatelet drugs.

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

**REFERENCES**


**NEOPLASIA**
also under development for the treatment of human cancer, may have an impact on the surface binding of MMP-9.

An interesting technical achievement by Redondo-Muñoz and colleagues is the very high efficiency of siRNA transfection of primary CLL B cells with little induction of apoptosis. Transfection of primary CLL B cells is technically challenging and typically observed low transfection frequencies have been a major obstacle in CLL research. The transfection strategy used by the authors, if reproducible by other researchers, may be a significant step forward.

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

Comment on Stegenga et al, page 82

Glucose, insulin, coagulation: endotoxin as exohormone

John C. Marshall ST MICHAEL’S HOSPITAL UNIVERSITY OF TORONTO

In this issue of Blood, Stegenga and colleagues at the University of Amsterdam report an elegant series of studies probing the independent effects of glucose and insulin on endogenous inflammatory and coagulant responses in a well-characterized model of acute inflammation—bolus endotoxin challenge in human volunteers.

Diabetes mellitus affects more than 170 million people worldwide, or 2.8% of the population of the planet; its prevalence is expected to rise to 4.4% by 2030. The morbidity of diabetes is linked to a spectrum of procoagulant and inflammatory derangements. Conversely, abnormalities of glucose regulation are common to a number of acute and chronic inflammatory disorders. By clamping plasma levels of glucose or insulin at normal or elevated levels, Stegenga and colleagues demonstrate that glucose and insulin differently regulate neutrophil and coagulant response to endotoxin challenge. Hyperglycemia alone inhibits the release of neutrophil elastase and enhances levels of thrombin:antithrombin (TAT) complexes, whereas hyperinsulinemia reduces plasminogen activator (PA) activity and increases both the level and the activity of plasminogen activator inhibitor type 1 (PAI-1). Neither significantly alter circulating levels of key cytokines whose release is induced by endotoxin, nor do they affect neutrophil numbers or markers of endothelial-cell activation. The effects are specific to the regulation of coagulation, and both promote a net procoagulant state.

These are important studies, but their interpretation is complicated. Endocrine interactions are dynamic: elevated or depressed levels of one hormone evoke a response that modulates levels by altering the release of that hormone, or by inducing the release or inhibition of a counterregulatory hormone. These dynamic interactions were inhibited in this study, both by the clamp technique and by the pretreatment of study subjects with somatostatin to inhibit endogenous insulin release. Nonetheless, 3 key conclusions emerge.

First, hyperglycemia alone supports a procoagulant state by increasing levels of soluble tissue factor and TAT complexes. This observation provides a further rationale for maintaining strict euglycemia in critically ill patients.

Second, insulin alone, independent of endotoxin, supports a procoagulant state through the induction of PAI antigen and activity, and inhibition of plasminogen activator activity. Thus, exogenous insulin may prove insufficient to reverse the procoagulant state associated with hyperglycemia.

Third, and perhaps most intriguing, is the insight that arises from the characterization of the interaction of an endogenous hormone, insulin, with what might legitimately be considered an exogenous hormone, endotoxin. When data from the current report are compiled with those from the authors’ earlier studies in volunteers who had not received endotoxin, it becomes apparent that endotoxin, itself a potent inducer of a procoagulant and proinflammatory state, synergizes with insulin to further increase levels of t-PA antigen and plasminogen activator activity (see figure). Endotoxemia is common in critical illness in which derangements of glucose-insulin homeostasis are particularly prominent, and insights such as those provided by Stegenga et al underline the challenges of modulating the hormonal milieu in a complex and vulnerable patient population.

Scientific experimentation is inherently reductionist, and imperfect in its capacity to encompass the nuances of diseases that arise within the complexity and intrinsic variability of whole organisms. Nonetheless,
Gang of 3 in aggressive CLL?

Grzegorz S. Nowakowski