Comment on Weeterings et al, page 3227

FVIIa: you’ve come a long way, baby!

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In this issue of Blood, Weeterings and colleagues report that binding to the GPIb/IX/V complex plays a role in mediating the platelet surface procoagulant effects of rFVIIa.

In 1997, our first article on the mechanism of action of recombinant activated factor VII (rFVIIa) in hemophiliacs1 was summarily rejected by Blood because the reviewers felt that the topic was not of interest to a general hematology audience. However, in the ensuing years, FVIIAs has become a hot topic, not only in hemophilia but also for its off-label use to manage intractable hemorrhage in a wide variety of clinical settings. Even with all of this interest, the mechanism of its hemostatic effect is still not fully understood.

Plasma-derived FVIIa was first used in 1983 to provide hemostasis in 2 hemophiliacs and PK, pre-kallekrein. Professional illustration by Debra Tyler Dartez.
This second figure is of thrombin generation on platelet surfaces. In normal hemostasis, FIXa combines with FVIIa on the activated platelet surface to activate FX. The FXa, in turn, combines with FVa to produce thrombin. The binding activity of FXa is mediated by negatively charged phospholipid, the GPIb/IX/V complex, and possibly other binding proteins that are unrecognized as of yet. Professional illustration by Debra Tyler Dartez.

Immunoglobulin (Ig) has long been known to have tolerogenic properties. Thus, antigens (Ags) conjugated to Ig elicit tolerance rather than immunity,1,2 and intravenous administration of pooled Ig from multiple donors, known as intravenous immunoglobulin (IVIg), is used in clinical practice to treat autoimmune and inflammatory diseases.3 The reason for these tolerogenic effects of Ig is not understood, but recently IVIg has been shown to enhance human regulatory T cells (Tregs).4,5 This, together with the observation that Fc fusion proteins of soluble receptors and other bioactive molecules are either poorly or nonimmunogenic, and antibody (Ab) variable regions (to which central tolerance should not exist) do not elicit robust autoimmune responses, led De Groot et al to postulate that the Ig molecule must contain regions or epitopes that are stimulatory to Tregs (ie, Tregitopes).

Using computational epitope mapping, the authors looked for consensus 9 amino acid regions in the human Ig molecule that would bind to multiple HLA class II molecules (on the premise that most Tregs are CD4-restricted). They identified 2 such clusters of major histocompatibility complex (MHC) binding motifs in the Ig molecule that could be presented to T cells. Predicted human Tregitope (hTregitope) sequences 167 and 289 were synthesized and were indeed shown to bind to multiple MHC class II molecules. Using a variety of Ags and culture conditions, the authors presented evidence that these Tregitope peptides activate as well as expand Tregs. The authors conclude that both natural Tregs (nTregs) and Ag-specific adaptive Tregs are affected. However, due to limitations of the experimental setup and the complexities of the human system, the distinction between effects on natural versus adaptive Tregs (as in humans, CD4+CD25\textsuperscript{high} cells are a mixture of both) and between the expansion of preexisting FoxP3\textsuperscript{+} cells versus their de novo conversion from conventional T cells is not always clear.

In the next step, the functional effects of Tregitopes on Ag-induced cytokine production and surface activation markers are documented using depletion experiments and Ag-MHC tetramers. The authors use a pool of immunogenic peptides derived from the complement component C3d (an autologous peptide) and targeted forms of FVIIa as future hemostatic agents.

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REFERENCES

Comment on De Groot et al, page 3303

Tregitopes switch on Tregs

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In this issue of Blood, De Groot and colleagues report the identification and functional characterization of Tregitopes, which are Treg-activating regions in the Fc portion of the IgG molecule. This important finding has the potential to bring understanding about a number of phenomena related to Ig, including tolerance to Ab variable regions, the tolerogenic properties of immunoglobulin–Ag conjugates, the weak immunogenicity of Fc fusion proteins, and the therapeutic and regulatory effects of clinical preparations of IVIg on autoimmune and inflammatory diseases.
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