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contexts protects against GVHD.[6] However, Treg percentage did not change in JES6-1–treated recipients. Although Tregs might be necessary for protection (which was not tested), Song et al showed that other pathways are involved. In particular, recipient expression of the immune regulatory receptor PD-L1 is required for GVHD protection because PD-L1$^{-/-}$ recipient mice die from GVHD when treated with JES6-1. Likewise, the group shows that PD-L1 is required for the local colon and liver propagation of CD4^{+} TR1 cells, which make IL-10. CD4^{+} TR1 cells are known to regulate and prevent GVHD.[7] Song et al elegantly shows that IL-10 produced by donor-derived TR1 cells is needed for GVHD protection by the adoptive transfer of IL-10$^{-/-}$ donor cells. They also show increased PD-1:PDL-1–dependent Eomes expression by colon and liver infiltrating donor effector T cells. Higher Eomes expression correlates with anergic and exhausted donor T cells likely incapable of mediating GHVD. One consideration is that Eomes expression in T cells after transplantation can reduce GVL.[8]

In a series of elegant experiments evaluating GVL, Song et al showed that JES6-1 treatment does not prevent immune clearance of the BCL-1 and BC-CML cancer cell lines, whereas treatment with tacrolimus does. Song at al used single cell RNA-Seq and confirmatory flow cytometric of splenic T cells and showed that JES6-1–treated mice have different T-cell immune reconstitution of CD4 and CD8 populations in the spleen that do not appear anergic vs what is seen in GVHD target tissue. This may promote GVL. Song et al present some evidence that NK cells are not responsible for GVL, but further mechanistic studies are needed to understand the preservation of GVL in this model, including evaluating alternative hypotheses such as the increase in TR1 cells that may be responsible for increased GVL.

Overall, the study by Song et al reinforces the concept that IL-2 and donor CD4^{+} T cells in the local tissue microenvironment play a major role in GVHD pathophysiology through the PD-L1 pathway and the complex interplay of cell populations such as Treg, TR1, and effector T-cell subsets. The authors also make the fundamental observation that targeting the IL-2 pathway more precisely may promote GVL immunity.

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VASCULAR BIOLOGY

Comment on Zirka et al, page 2256

VT duets: inflammation/coagulation—wall/flow

Jose Antonio Diaz | Vanderbilt University Medical Center

In this issue of *Blood*, Zirka et al[1] investigated the role of Slc44a2 in thrombosis. Specifically, they focused on determining how Slc44a2 expressing either the human neutrophil antigen (HNA)-3a or HNA-3b on neutrophils could modulate their adhesion and activation of von Willebrand factor (VWF) under certain flow conditions. Prior genome-wide association studies linked expression of HNA-3b on the Slc44a2 protein with a decreased risk of venous thrombosis (VT) in humans. Slc44a2 is a ubiquitous transmembrane protein and a receptor for VWF. The authors examined how neutrophil Slc44a2 expressing either HNA-3a or HNA-3b modulated adhesion and activation on VWF under flow. Transfected HEK293T cells or neutrophils homozygous for the HNA-3a– or the HNA-3b–coding allele were perfused in flow chambers coated with VWF, mimicking venous shear rates. HNA-3a expression was required for Slc44a2-mediated neutrophil adhesion to VWF at those shear rates. Adhesion was enhanced when neutrophils were activated with lipopolysaccharide. Specific shear conditions with high neutrophil concentrations worked like a "second hit," inducing the formation of neutrophil extracellular traps. Neutrophil mobilization was also measured by intravital microscopy in venules. Mice lacking Slc44a2 showed a massive reduction in neutrophil recruitment in inflamed mesenteric venules.

They concluded that Slc44a2/HNA-3a is important for the adhesion and activation of neutrophils in veins during inflammation and when submitted to specific shears similar to those in veins. The authors included blood flow as part of their methodology, which is a critical component in the thrombosis process in blood vessels. Although the flow devices available have limitations, these types of tools bring blood flow into the equation. Blood flow could be even more critical

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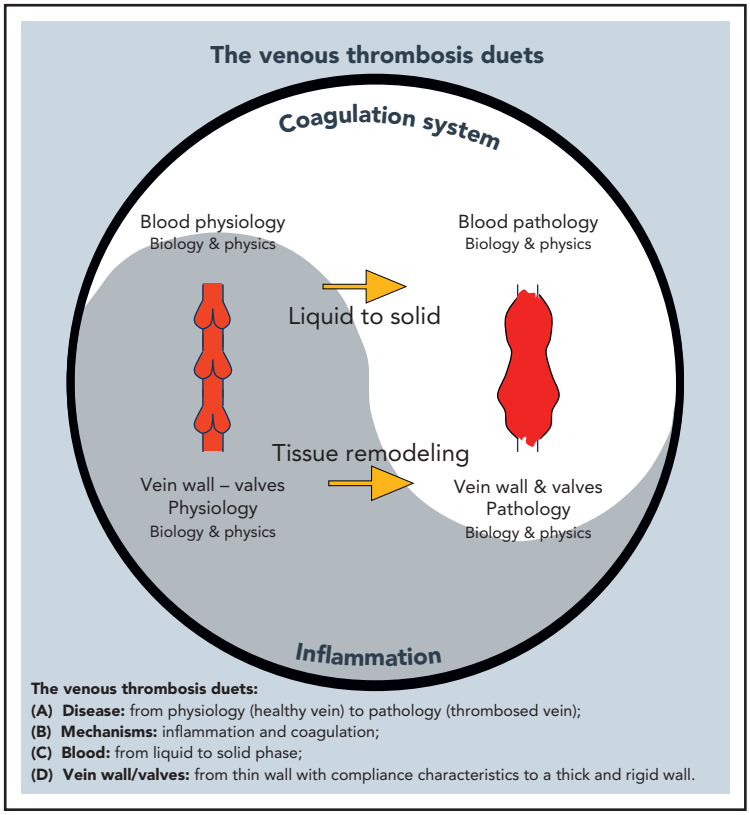

Venous thrombosis duets. Inflammation and coagulation interact closely transforming a healthy vein with normal circulating venous flow into a pathologic thrombosed environment, involving bio-physical changes. Far from being only the coagulation system, other system, particularly inflammation play critical role. Inflammation in the VT process deserves to be investigated and therapeutically considered.

as we advance in our understanding of the VT process. Investigating VT is and should be a multidisciplinary effort.[2] The authors combined biology and physics, which captures a more complete picture of the disease and needs to be encouraged in basic science investigations (see figure). As part of this multidisciplinary effort, I want to encourage engineers to continue their efforts to develop tools that allow researchers to investigate the vein wall and flow conditions together. These tools are needed.

Inflammation was introduced to experimental VT in 1973.[3] Since then, studies have investigated different ways to understand how inflammation is part of the VT process, from the role of P-selectin[4] and other adhesion molecules to the recent discovery of the galectin-3.[5] Also, inflammatory cytokines such as interleukin 6 (IL-6) were shown to have a clear role in VT,[6] a concept unfortunately now highlighted and reinforced by the studies on COVID-19–associated thrombotic events. Several studies are confirming the role of inflammation on the COVID-19 association with VT, including the therapeutic use of anti–IL-6.[7]

Today, it is clear that inflammation is part of the VT process. Although it is believed that inflammation participates in all stages during the VT process (initiation, amplification, resolution), multiple questions remain unanswered. The question of whether 1 pathway can be safely targeted, or the most likely scenario that several mechanisms will be responsible for the thrombosis-inflammation intersection, needs more effort. However, this work moves the field 1 step closer on our way to map the intersection of inflammation and VT, providing evidence that could ultimately be used to improve the current outcome of our VT patients.

Last, the lesson learned is the fact that VT should not be seen as a "clotting process inside the veins" but more as a multifactorial condition that includes inflammation as a critical component of the VT process. Of course, the coagulation system's participation in VT is critical, but investigators are demonstrating a dualism, and the coagulation partner is the inflammation. VT epidemiologic data clearly show that tagging the coagulation system is essential, but it seems to be not enough. This emerging message should be spread among research and development, students, and professionals at all levels. Thinking outside the box guides us further from the coagulation system alone, and the efforts of this group lead our future research. Congratulations to the authors.

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