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**MGUS: not so benign after all**

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In this issue of Blood, Kristinsson and colleagues provide evidence that MGUS is a risk factor for the development of DVT.

It is well appreciated that persons with multiple myeloma have an increased risk of venous thrombosis. More recently, this relative risk has been shown to be increased further in these patients while on therapy with thalidomide and its derivatives. The mechanism of this increased risk for thrombosis has traditionally been attributed to traditional neoplasia risks for thrombosis, such as decreased mobility, surgical procedures, use of chemotherapy, and/or indwelling catheters. In this study, Kristinsson et al reviewed 4,196,197 veterans who were hospitalized at least once at Veteran Affairs hospitals in the United States and identified a total of 2,374 patients with monoclonal gammopathy of undetermined significance (MGUS) and 6,192 multiple myeloma patients. In the whole study population, there were 39,272 persons with a deep vein thrombosis (DVT) with totals of 31 and 151 occurring among MGUS and multiple myeloma patients, respectively. Compared with the whole study population, the relative risk of DVT following a diagnosis of MGUS and multiple myeloma was 3.3 (2.3-4.7) and 9.2 (7.9-10.8), respectively. As the authors point out, it is important to realize that these data were gathered prior to the current prevalent use of thalidomide in myeloma patients.

These results have important implications. The fact that patients with MGUS have an increased risk of DVT together with the known risk of transformation to multiple myeloma suggests there may be a common underlying mechanism or etiology to the 2 conditions that is independent of cancer treatment.

Limitations of this study include the obvious facts that it is retrospective and the diagnoses are determined only by the discharge diagnostic codes. Due to the difficulty of separating patients with pulmonary embolism from other respiratory conditions, patients with isolated pulmonary embolism were not identified and so we don’t know if there is an increased risk for that. Nonetheless, this study should point the way to identifying the underlying pathogenesis of DVT in patients with plasma cell dysplasia and may ultimately help to identify those patients who should have thromboprophylaxis.

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

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**Shear activates platelet-derived latent TGF-β**

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Although platelets are a rich source of latent TGF-β, it has not been determined how platelet-derived latent TGF-β is activated in vivo. In this issue of Blood, Ahamed and colleagues report that shear and stirring efficiently activate the latent TGF-β.

Platelets release various bioactive substances upon blood clotting, including platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β. Of the 3 TGF-β isoforms, TGF-β1 is the major isoform in human platelets. PDGF stimulates the growth of mesenchymal cells, including smooth muscle cells and fibroblasts, whereas TGF-β is a potent growth inhibitor for most cell types and induces production of extracellular matrix (ECM) proteins. However, in contrast to other growth factors, bioactivity of TGF-β is shielded by the latency-associated peptide (LAP).1 TGF-β is secreted in latent high-molecular-weight complexes, which require an activation step for exhibiting their functions. Latent TGF-β complexes contain 3 components: the active (mature) TGF-β dimer, LAP, and the latent TGF-β binding protein (LTBP).

LAP is a disulfide-bonded dimer derived from the N-terminal part of the TGF-β precursor, whereas the mature TGF-β is the C-terminal part of the TGF-β precursor. After proteolytic processing from the mature part of TGF-β, LAP remains associated with it by noncovalent interaction, and thereby LAP confers latency to TGF-β. In vitro, latent TGF-β is activated by various treatments which alter the structure of LAPs, including extremely low or high pH, heating at 100°C and treatment by SDS. Under physiological conditions, plasmin and certain proteases activate latent TGF-β through proteolytic digestion of LAP. Thrombospondin-1 (TSP-1) has also been shown to activate latent TGF-β. In this case, TSP-1 interacts with LAP and disrupts the complex between TGF-β and LAPs.2

In addition to LAP and TGF-β, the latent TGF-β complex in human platelets contains a single copy of LTBP, which is disulfide-bonded to LAP. Latent TGF-β without LTBP is called the small latent complex (SLC) while that with LTBP is called the large latent complex (LLC). Out of the 4 isoforms of LTBPs, LTBP-1 is the major form in human platelets. As described above, LAP is sufficient to confer latency to TGF-β. But, then what are the functions of LTBP-1? Since LTBP-1 binds to ECM, it may function for proper localization of the latent TGF-β complex in vivo. In addition, recent findings revealed that LTBP-1 plays an important role in activation of latent TGF-β in vivo.

Annes et al1 reported that LLC, not SLC, is activated by a traction-mediated mechanism in vivo. The TGF-β1 (and TGF-β3) LAPs contain a RGD sequence and bind to certain integrins, including αvβ6 and αvβ3.3 LTBP-1, on the other hand, interacts with the
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