domains contribute to the binding and proteolytic processing of VWF under physiologic conditions.

Previous studies have shown that the metalloprotease domain of ADAMTS13 alone is ineffective in cleaving VWF,6,7 but if the various noncatalytic domains are incrementally added back, proteolytic activity is gradually restored.6,7 These results suggest a linear relationship between the domains of ADAMTS13 and VWF proteolysis. Gao et al8 have identified several potential sites on the VWF-A2 domain that may make direct contacts with various proximal noncatalytic domains of ADAMTS13 under static conditions. This result is in agreement with that reported previously by Ai et al,4 in which ADAMTS13 variants truncated after the spacer domain with an additional internal deletion of either disintegrin domain or disintegrin plus TSP1-1 repeat have markedly reduced proteolytic activity toward VWF fragment and exhibit no proteolytic activity toward full-length VWF. Collectively, these data support the hypothesis that all the proximal noncatalytic domains of ADAMTS13 are required for productive engagement with VWF-A2 domain at least under static/denaturing conditions.

In this issue of Blood, de Groot et al9 focus on the involvement of the disintegrin domain of ADAMTS13 in VWF processing in more detail. They use molecular modeling (panel B in the figure) and site-directed mutagenesis to identify the amino acid residues within this domain that are essential for successful cleavage of VWF. They show that 3 out of 8 ADAMTS13 disintegrin mutants they have produced exhibit dramatically reduced activity toward VWF fragment, namely VWF115 (amino acid residues 1554–1668 of VWF), and full-length VWF polymers under static/denaturing conditions.2 Kinetic analyses show a 5- to 20-fold reduction in the catalytic efficiency in cleavage of VWF115 by these mutants.9 Further experiments have identified that the positively charged Arg349 in ADAMTS13 appears to directly interact with the negatively charged Asp1614 on the VWF-A2 domain (figure panel B).9 The authors hypothesize that this seemingly weak interaction between the disintegrin and VWF-A2 appears to be essential for efficient catalysis of VWF under static/denaturing conditions. This task may be achieved in collaboration with other proximal noncatalytic domains. Indeed, the first TSP1 repeat, the Cys-rich domain, and the spacer domains bind VWF-A2 fragment with higher affinity than the disintegrin domain.6 These results suggest that binding of all the proximal noncatalytic domains of ADAMTS13 to VWF is necessary to position the active site of ADAMTS13 to the scissile bond (Tyr1605–Met1606) on VWF, resulting in productive cleavage.

It remains to be seen how this domain functions in concert with the other domains of ADAMTS13 in the presence of shear stress that alters VWF conformation in a more physiologic way. Could it be that the other domains of ADAMTS13 are more important than the disintegrin domain in binding VWF in order to align it with the scissile bond for cleavage in vivo? For instance, the recent report by Zhang et al10 suggests a role of the middle and distal parts of the noncatalytic region in participating in binding and proteolytic processing of VWF under fluid shear stress. Therefore, further investigation of the precise interactions between each of ADAMTS13 domains and VWF may shed light on understanding the pathogenesis of thrombotic thrombocytopenic purpura, a potentially fatal illness caused primarily by the absence of plasma ADAMTS13 proteolytic activity, as a result of ADAMTS13 mutations or acquired autoantibodies against ADAMTS13 enzyme.

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Comment on Opiela et al, page 5635

RTEs: lazy T-cell teenagers

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In this issue of Blood, Opiela and colleagues analyze the phenotype and function of the lymphoid periphery’s youngest T cells, RTEs.

Recent thymic emigrants (RTEs) are T cells that have just exited from the thymus, having completed an approximately 2-week journey that takes them from stem cell to committed T cell. Only 1% to 5% of thymocytes survive this complex maturation process that begins with T-cell receptor gene rearrangement and ends with a select population of lineage committed T cells that are both self-major histocompatibility complex (MHC)–restricted and self-tolerant.1 Throughout the lifetime of the individual, RTEs are essential for the maintenance of a diverse population of naive peripheral T cells, ready to further differentiate into appropriate effector T cells upon encounter with foreign antigen.

It has long been of interest to identify and analyze RTEs as a population distinct from the bulk of peripheral T cells, in order to quantify thymic output and to assess whether T-cell maturation continues after thymic egress. Understanding RTE biology is of particular importance for predicting recovery of the immune system following lymphoablative therapy or viral infection, and for the study of immunity in neonates (in which the bulk of the lymphoid periphery consists of RTEs) and in aged individuals (in which RTEs represent a small minority of peripheral T cells). Previous methods for tagging RTEs have included intrathymic injection of fluorochromes, transplantation of congenically marked thymus

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The functional defects allow the individual to purge self-reactive T-cells by permitting new emigrants to scan the periphery for tissue-specific antigens without the danger of eliciting autoimmune reactions. Neotopes must uniquely cope with lymphopenia and the absence of mature peripheral T-cells. Given that T-cells undergoing homeostatic proliferation adopt a memory cell phenotype and heightened function, the IL-7-driven proliferation of neonatal RTEs may both help fill up empty space and provide a population of memory-like T-cells. Clearly, much remains to be learned about how the youngest peripheral T-cells cope with their adolescence and successfully transition into adulthood.

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