The role of ADAMTS13 in the new pathogenesis of TTP

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Thrombotic Thrombocytopenic Purpura (TTP) is a severe microvascular occlusive microangiopathy characterized by thrombocytopenia, Coombs-negative hemolytic anemia and ischemic symptoms localized mainly but not exclusively in central nervous system and resulting from diffuse platelet thrombi in microcirculation [1]. To understand the broad clinical spectrum of TTP it is important to read the original case report prior to effective treatment, when the full natural history of this fatal illness was appreciated. In 1924 Dr. Moschowitz [2] described the first case in a previously healthy 16-year-old girl who died with multiple organ failure and post-mortem examination showed widespread thrombi in the terminal circulation of several organs, composed mainly by platelets. These thrombi remain the hallmark of pathologic diagnosis.

The current era in our knowledge began with the observation by Moake and his colleagues in 1982 [3] of unusually large multimers of von Willebrand factor (ULVWF) in the plasma of patients with chronic relapsing TTP. They are similar to those normally contained in vascular endothelial cells and platelets but absent in plasma. These ULVWF multimers promote platelet-dependent microvascular thrombosis, suggesting that patients lacked a VWF protease able to reduce the size of VWF multimers by cleavage. The next key step was the discovery made 14 years later, when Furlan, Tsai et al. [4,5] isolated a VWF-cleaving protease that had properties consistent with the activity that had been postulated to be absent in patients with TTP. These two groups subsequently published evidence that patients lacked a VWF protease able to reduce the size of VWF multimers by cleavage. The ULVWF strings are anchored to the endothelial cell membrane via P-selectin molecules that are secreted concurrently with the ULVWF multimers [15]. Specifically, ADAMTS13 enzyme binds under flow conditions to accessible A3 domains in the monomeric subunit of ULVWF multimers and then cleaves Tyr 1605-Met 1606 residues located within the A2 domain as they are secreted in long “strings” from stimulated endothelial cells [13,14]. The ULVWF strings are anchored to the endothelial cell membrane via P-selectin molecules that are secreted concurrently with the ULVWF multimers [15]. Specifically, ADAMTS13 enzyme binds under flow conditions to accessible A3 domains in the monomeric subunit of ULVWF multimers and then cleaves Tyr 1605-Met 1606 peptide bonds in adjacent A2 domain. Majerus et al. [16] have shown that the spacer and TSP1-1 like domains are required for ADAMTS13 binding to VWF, that may be modu-
lated by CUB and TSP1-2/8 like domains. As a consequence of ADAMTS13 deficiency, ULVWF multimers are not cleaved after their secretion from endothelial cells, but remain anchored to the cells. Passing platelets adhere via their GpIb and GpIIb/IIIa to the A1 and the A3 domains of the monomeric subunits of ULVWF strings anchored to P-selectin to form large, potentially occlusive, platelet thrombi.

Moreover, considering that severely deficient ADAMTS13 activity may not always be sufficient to cause TTP, in the last two years some researchers have started to investigate other proteins that might be involved in the mechanisms underlying TTP. Pimanda and their colleagues have been demonstrated that the multimeric size of VWF can be controlled by disulfide bonds-reduction by thrombospondin-1 (TSP-1) [17]. VWF reductase activity was centered around Cys974 in the C-terminal sequence of TSP-1 but the role of TSP-1 in the aetiology of TTP is under investigation. Many other aspects of ULVWF processing are now rapidly coming into focus, such as the involvement in ULVWF secretion of such cytokines as IL-8, TNF-α and IL-6 in complex with its receptor. This might be explain the role of inflammation as triggering agent in TTP [18]. Furthermore different authors are studying the regulation of ADAMTS13 activity by different factors as thrombin and plasmin, that cleave ADAMTS13 at specific sites, resulting in the loss of ADAMTS13 activity [19]; or chloride ions which, binding to VWF and causing its conformational change, have specific inhibitory effect on ADAMTS13 activity [20]. Finally it has been demonstrated that the VWF A1 domain inhibits the cleavage of A2 domain by ADAMTS13 and this inhibition can be relieved by interaction of A1 domain with platelet GpIb or certain glycosaminoglycans (heparin) [21].

Until now it has been paved the way to understand the exact role of ADAMTS13 and the other modulators in developing TTP but many unresolved issues still remain.

References


