of 50-90 kDa, such as HR1B, jarahagin, and Ht-a[69,70] which are mosaic proteins consisting of a metalloproteinase domain similar to that of small hemorrhagin at the N-terminus, an additional disintegrin-like domain in the middle portion, and a cysteine-rich domain at the C-terminus (Fig. 2). However, it is noted that the conserved RGD sequence of disintegrin is replaced by an SECD sequence (HR-1B, jararhagin, Table 1). Au et al. showed that rhodostomin may share a common precursor with a hemorrhagic protein, suggesting that disintegrin and the hemorrhagin protein may share a common gene sequence.[71] Furthermore, the predicted N-terminal sequence of jararhagin is preceded by 150 amino acids of a proprotein sequence with a striking homology to the proprotein sequence found in the coding genes of trigramin[72] and rhodostomin.[73] In a snakebite victim, snake venom metalloproteinases and disintegrins synergically cause bleeding, since metalloproteinases degrade the capillary basement membrane and disintegrins inhibit platelet aggregation by inhibiting fibrinogen binding to platelet $\alpha_{IIb}\beta_3$ of activated platelets. Recently, Jia et al. expressed the disintegrin-like/cysteine-rich domain of atrolysin A and demonstrated that this recombinant protein inhibited collagen- and ADP-induced platelet aggregation. The sequence, CRASMSECDPAEHC, which occurrs in jararhagin and catrocollastatin (corresponding to the RGD loop of disintegrins) may be responsible for the inhibitory effect on collagen-induced platelet aggregation.[74,75] Adhesion of platelets to newly exposed endothelial collagen is an early event in arterial thrombosis. Integrin $\alpha_2\beta_1$ is the adhesion receptor for collagen. Venom metalloproteinases such as jararhagin, catrocollastatin, and crovidisin[76] have been reported to specifically inhibit platelet aggregation and the adhesion of collagen to platelets. Jararhagin has been referred to as a collagen receptor antagonists while catrocollastatin and crovidisin bind to collagen rather than to $\alpha_2\beta_1$. Jararhagin binds to a platelet α_2 subunit via the disintegrin-like domain, followed by proteolysis of a β1 subunit.[77] Therefore, the reason why the striking difference exists in their mechanism of action is still awaiting further investigations since they all share a high degree of sequence homology.

Several non-coagulant, nonenzymatic snake venom components, such as aggretin and trimucytin, cause platelet aggregation and release reactions by acting as an $\alpha_2\beta_1$ agonist.[78,79] Both $\alpha_2\beta_1$ agonists induce platelet activation through the activation of endogonous phospholipase C and tyrosine kinases. ^{125}I-aggretin binds to platelets with a high affinity (Kd, 4.0 ± 1.1 nM), and the number of binding sites is estimated to be 2119 ± 203 per platelet.[79] On the other hand, a collagen-like protein convulxin is thought to activate platelets through the binding of platelet GPVI, the activation receptor of collagen, leading to platelet activation.[80]

Disintegrins and Membrane-anchored ADAMs

In contrast to hemorrhagins, ADAMs are cell membrane-anchored proteins, containing metalloproteinase, disintegrin-like, cysteine-rich, epidermal growth factor-like, transmembrane and cytoplasmic domains[81] (Fig. 2). AMDMs have been identified in human, monkey, rabbit, rat, guinea pig, and bovine tissues as well as in *Xenopus* and *Caenorhabditis elegans* tissues. Two ADAMs, fertilin and cyritestin, occur in mammalian testis and are thought to participate in the egg-sperm fusion process. Fertilin (previously named PH-30) is composed of α and β subunits.[81] The precursor of fertilin α (ADAM1) has a metalloproteinase domain with a catalytic site consensus sequence. Blobel and others proposed a model for the sperm-egg fusion.[5] The metalloproteinase domain of profertilin α has most likely been removed by the time the protein appears on the cell surface. Profertilin β is processed by releasing the pro- and metalloproteinase domains. Finally, the mature fertilin α/β heterodimers on the sperm surface bind to the integrin $\alpha_6\beta_1$ expressed on the egg surface thereby initiating sperm-egg binding and fusion. Using echistatin to study human sperm adherence and penetration of hamster qolemma, Broson et al.[82] found significantly decreased adherence of sperm pretreated with this disintegrin, whereas echistatin did not inhibit oocyte penetration of sperm.

In contrast to mature fertilin, most ADAMs represent membrane-anchored proteins with metalloproteinase and disintegrin domains. Metalloproteinase disintegrins participate in cleaving at least a substrate, the