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Mutations in the fourth EGF-like domain affect thrombomodulin-induced changes in the active site of thrombin. [1]

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[2]

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Abstract	A number of alanine and more conservative mutants of residues in the fourth domain of thrombomodulin (TM) were prepared and assayed for protein C activation and for thrombin binding. Several of the alanine mutations appeared to cause misfolding or structural defects as assessed by poor expression and/or NMR HSQC experiments, while more conservative mutations at the same site appeared to allow correct folding and preserved activity. Several of the conservative mutants bound more weakly to thrombin despite the fact that the fourth domain does not directly contact thrombin in the crystal structure of the thrombin-TM complex. A few of the mutant TM fragments bound thrombin with an affinity similar to that of the wild type but exhibited decreases in k cat for protein C activation. These mutants were also less able to cause a change in the steady state fluorescence of fluorescein-EGR-chloromethylketone bound to the active site of thrombin. These results suggest that some residues within the fourth domain of TM may primarily interact with protein C but others are functionally important for altering the way TM interacts with thrombin. Residues in the fourth domain that primarily affect k cat for protein C activation may do this by changing the active site of thrombin.
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