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Title of thesis: Structure function study of different conformations of serine protease inhibitor for its antiangiogenic function.

ABSTRACT

Serpins are a class of more than 400 proteins that are structurally and mechanistically similar but functionally distinct. Identifying molecular basis of antithrombin antiangiogenic and antitumor activity holds a great promise for other serpins due to their ability to bind cofactor and adopt wide range of conformation. Antiangiogenic antithrombin conformations are RCL (reactive center loop) inserted conformations (latent, cleaved and polymeric) with weak affinity for heparin whereas the RCL exposed (native) has high heparin affinity and is also non-antiangiogenic. Antithrombin can be modified in the presence of H_2O_2 to give a weak heparin affinity conformation that probably has its reactive center loop exposed. This conformation can act as an appropriate control to assess the role of RCL insertion in antiangiogenic role of heparin. Further a comparative analysis of all the conformation of antithrombin is needed to assess their relative potential as an antiangiogenic protein in comparison with already known anti-tumor drugs. A comparative assessment of antithrombin conformation using CAM, wound healing and circular dichroism analysis in the presence and the absence of heparin have been studied.

Main conclusions of the thesis are as follows:

(1) Oxidised antithrombin was for the first time shown to have potent antiangiogenic and wound healing activities. (2) Latent and oxidised conformations of antithrombin showed antiangiogenic activities which were better than the thalidomide control. (3) Reactive center loop inserted conformations are capable of significant conformation change on account of heparin binding. (4) Antithrombin's weak affinity for heparin probably interferes with the physiological growth factors binding to endothelial cell and acts synergistically with unfractionated heparin to completely retard angiogenesis.