

**A14** How serpins change their shape for better and for worse

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The serpins are unique amongst the many families of serine protease inhibitors in having an action that is dependent on a change not only in their shape but also in their topology. We have now completed a series of crystallographic structures that provide a video depiction of this conformational change and show how it is utilised to give irreversible protease inhibition. This potential for irreversible inhibition makes the serpins the evolutionary choice as inhibitors of the key proteolytic pathways of both cells and tissues. The mobile mechanism also has an additional selective advantage, as it can be readily adapted to give subtle modulations of inhibitory activity. Thus the spontaneous occurrence of the conformational change ensures a short half-life for the inhibitor of fibrinolysis PAI-1. This is counteracted by the binding to PAI-1 of vitronectin, which in turn has consequences for cell migration and angiogenesis. The elegance of the modulating mechanisms is seen with the changes in antithrombin on its binding to heparin and even more so with recent structures showing the multistep allosteric mechanism of heparin cofactor II. The downside is the vulnerability of this conformational mechanism to mutations, which we can now see in detail as the cause of a range of familial diseases from thrombosis to dementia.