Abstract

Schistosomiasis is a serious infectious disease that afflicts over 200 million people in tropical and subtropical regions. It is caused by *Schistosoma* blood flukes that live in human blood vessels and obtain nutrients from host hemoglobin, which is degraded by digestive proteases. Current therapy relies on a single drug and concern over resistance necessitates new drug development. In *Schistosoma mansoni*, cathepsin B1 (SmCB1) is a critical digestive protease that is a target molecule for therapeutic interventions. This thesis provides a comprehensive characterization of SmCB1 focused on structure-activity relationships and inhibitory regulation based on six crystal structures solved for SmCB1 molecular forms and complexes.

SmCB1 is biosynthesized as an inactive zymogen in which the N-terminal propeptide operates as a natural intra-molecular inhibitor by blocking the active site. Detailed biochemical and structural analyses have identified a new and, so far, unique mechanism of SmCB1 zymogen activation through which the propeptide is proteolytically removed and the regulatory role of glycosaminoglycans in this process has been described. A study of SmCB1 proteolytic activity has revealed that the enzyme acts in two modes, as endopeptidase and exopeptidase, which makes it an efficient tool for host hemoglobin digestion. A major part of the thesis focused on the identification of new molecules for SmCB1 inhibition using two different approaches. First, reversible peptide inhibitors derived from the structure of the SmCB1 propeptide were designed and synthesized that are effective *in vitro* in the micromolar concentration range. Second, peptidomimetic inhibitors with a vinyl sulfone reactive group were identified that are effective *in vitro* in the nanomolar concentration range. The mechanism of the interaction between SmCB1 and the vinyl sulfone inhibitors was studied in detail using crystallographic structures of SmCB1 in complexes with the inhibitors and by computational chemistry methods. Finally, the *ex vivo* efficiency of the vinyl sulfone inhibitors was demonstrated by the suppression of live schistosoma parasites in culture.

To conclude, this thesis has defined SmCB1 as a target molecule for the suppression of *S. mansoni* and has identified new types of inhibitors for the development of potential anti-schistosomal drugs.