Parasite aspartic peptidases and their relevance as therapeutic targets

Sojka Daniel, Hartmann David, Dvořák Jan

Parazitologický ústav BC AVČR České Budějovice, Czech Republic; School of Biological Sciences, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom

E-mail: sojkadan@gmail.com

Parasitic organisms live at the expense of other organisms - their hosts. Interestingly, virtually all known animal species serve as hosts and more than 50% of all animal species are parasitic at some stage in their life history. In humans, parasites cause some of the most troublesome diseases including malaria, leishmaniasis, sleeping sickness, Chagas disease and schistosomiasis. It has been estimated that 3/4 of world's human population is infected by parasites, many people carry multiple infections and the prevalence is extremely high among poor and illiterate people.

Peptidases (proteases, proteolytic enzymes) secreted by parasitic organisms are involved in various adaptive functions such as tissue penetration, larval migration, molting, immune evasion, retardation of blood coagulation, digestion of host blood proteins, and degradation of the cellular matrix. According to the MEROPS database aspartic peptidases (EC 3.4.23.X) are classified into several clans, families and subfamilies. Vertebrate cathepsin D (EC 3.4.23.5) is a member of the clan AA, which also includes Saccharomyces cerevisiae proteinase A, HIV protease, pepsin, chymosin, renin, cathepsin E and several other peptidases. The 3D structure of these enzymes mainly consists of two homologous lobes (A1, pepsin family). Each lobe contains a catalytic dyad of aspartate residues that activate a nucleophilic water molecule in between them and hydrolyze the substrate protein bond in the active site pocket. The primordial aspartic peptidases might have been homodimers as they appear in retroviruses (A2, retropepsin) and the bilobal structure has been proposed to have arisen from an unequal meiotic cross-over of two direct repeats of the ancestral gene.

Inhibition of aspartic cathepsin D-type peptidases (APDs) has been a regularly discussed anti-parasite intervention strategy since APDs have been considered as virulence factors of *Trypanosoma cruzi* and *Leishmania sp*. and have been demonstrated to have important roles in protein trafficking mechanisms of apicomplexan parasites. APDs also initiate blood digestion as components of multienzyme proteolytic complexes in malaria, platyhelminths, nematodes and ticks. Keeping in mind that years of great research performed in this field since its last broad revision, this contribution is meant as a novel look at very specific endopeptidases of the aspartic peptidase family in the genomic and post-genomic era of selected parasites. We would like also to specifically point out novel trends for future research and for the application of novel anti-parasitic compounds and vaccines based on constraint activity of cathepsin D-like molecules crucial for parasite survival and reproduction. Increasing amount of DNA and RNA sequencing data indicate that parasites express multiple APD isoenzymes of various functions that could now be specifically evaluated using revolutionary functional-genomic and biochemical tools, from which we can further exploit the potential of APDs as targets for novel effective intervention strategies against parasitic diseases that still pose an alarming threat to mankind.