

Oligopeptidase B of trypanosomes: drug and vaccine target

¹Coetzer, T.H.T. and ²Morty, R.E.

¹Biochemistry, School of Molecular and Cellular Biosciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa; ²Current address: Zentrum Fr Innere Medizin, Medizinische Klinik Und Poliklinik II, Justus Liebig Universitt, Giessen, Germany.

Oligopeptidase B (EC 3.4.21.83) has been isolated from *Trypanosoma brucei*¹, *T. congolense*² and *T. cruzi*³. The oligopeptidase B subfamily belongs to one of two branches of the S9 prolyl oligopeptidase family of serine peptidases. Whereas the archetypical member of this family, prolyl oligopeptidase (EC 3.4.21.26), exclusively hydrolyses substrates with proline in P1, oligopeptidase B has trypsin-like activity, preferring basic residues in P1 of small (<3.5 kDa) peptides. These trypanosomal peptidases have the prolyl oligopeptidase family GXSXGGZZ consensus sequence and show considerable sequence homology in the catalytic domain, but greater homology to each other than to post-prolyl-cleaving peptidases⁴.

Oligopeptidase B is inhibited by irreversible serine peptidase inhibitors, peptide aldehydes and peptidyl chloromethylketones, but not by serpins and α_2 -macroglobulin. Inhibition by thiol-reactive reagents, suggests the presence of a cysteine residue that must be reduced and available for activity. There is no inactive precursor form of oligopeptidase B and its activity may be controlled in vivo by the polyamines spermine and spermidine and intracellular reducing agents e.g. trypanothione.

Catalytically active oligopeptidase B (80 kDa) is released from dying *T. b. brucei* parasites into the host circulation thus potentially contributing to the pathogenesis of trypanosomiasis⁵. The cytosolic *T. cruzi* oligopeptidase B mediates Ca_{2+} -signalling in host cells that is required for trypomastigote invasion. The ability of oligopeptidase B null mutants of *T. cruzi* to invade mammalian cells and infect mice was markedly impaired. Trypanosomal oligopeptidase B is therefore an attractive target for drug and vaccine design.

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²Morty, R.E., Authi, E., Troeberg, L., Lonsdale-Eccles, J.D. and Coetzer, T.H.T. (1999) Purification and characterisation of a trypsin-like serine oligopeptidase from *Trypanosoma congolense*. *Mol. Biochem. Parasitol.* 102, 145-155.

³Burleigh, B.A., Caler, E.V., Webster, P. and Andrews, N.W. (1997) A cytosolic serine endopeptidase from *Trypanosoma cruzi* is required for the generation of Ca_{2+} -signalling in mammalian cells. *J. Cell Biol* 136, 609-620.

⁴Morty, R.E., Lonsdale-Eccles, J. D., Morehead, J. , Caler, E. V., Mentele, R., Auerswald, E.A., Coetzer, T.H.T , Andrews, N. W. and Burleigh, B. A. (1999) Oligopeptidase B from *Trypanosoma brucei*. A new member of an emerging subgroup of serine oligopeptidases. *J. Biol. Chem.* 274, 26149-26156.

⁵Morty, R.E., Lonsdale-Eccles, J. D., Mentele,R., Auerswald,E.A. and Coetzer, T.H.T (2001) Trypanosome-derived oligopeptidase B is released into the plasma of infected rodents, where it persists and retains full catalytic activity. *Infect. Immun.* 69, 2757-2761.