TABLE 1. Main biological functions and molecular properties of microbial metalo-aminopeptidases that support their essentiality or involvement in virulence.

Protease family	Metalo-aminopeptidase (source)	Molecular activity or property that determines their main functions	Main functions	Essentiality or involvement in virulence	Experimental evidences that support their relevance
M1	PfA-M1 (*P. falciparum* parasite)	Alanyl-aminopeptidase activity	Hemoglobin degradation	Essential	- Bestatin and specific inhibitors block parasite growth - Their toxicity is reduced in parasites overexpressing PfA-M1 - Knockout is lethal
M17	*Mt*LAP (*M. tuberculosis* bacterium)	Leucyl-aminopeptidase activity	Unknown	Essentiality not demonstrated	Bestatin inhibits bacterial growth *in vitro* and during macrophage infection
	PfA-M17 (*P. falciparum* parasite)	Leucyl-aminopeptidase activity	- Hemoglobin degradation - Erythrocyte invasion (probably) - Other housekeeping functions	Essential	- Bestatin and a specific inhibitor block parasite growth - Knockout is lethal
	*Tb*LAP-B (*T. brucei* parasite)	Leucyl-aminopeptidase activity (probably)	Kinetoplast DNA segregation	Not essential, involved in virulence	Down-regulation induces a delay in cytokinesis
	LAP-B (*Leishmania* spp. parasite)	Leucyl-aminopeptidase activity (probably)	- Leucine supply during host infection - Intracellular protein degradation and turnover - Host cell invasion (all probably)	Essentiality not demonstrated	Selective inhibition may interfere with parasite viability
	*Ac*LAP (*A. castellanii* parasite)	Leucyl-aminopeptidase activity	Encystation	Not essential, involved in virulence	Knockdown and bestatin produce encystation inhibition
	*Tg*LAP (*T. gondii* parasite)	Leucyl-aminopeptidase activity (probably)	Hydrolysis of dipeptides produced by cathepsin Cs and proteasoma (probably)	Not essential, involved in virulence	Knockout inhibits the parasite ability to attach and/or invade cultured cells, attenuating virulence in a mouse model
	*Sa*M17-LAP (*S. aureus* bacterium)	Cysteinyl-glycinase activity (probably)	- Bioactivates / inactivates key cellular proteins involved in metabolism, cell wall biosynthesis or signaling - Sulfur metabolism (all probably)	Not essential, involved in virulence	- Required *in vitro* for bacterial survival inside human macrophages - Knockout attenuates virulence in *in vivo* mouse models

TABLE 1 (continued). Main biological functions and molecular properties of microbial metalo-aminopeptidases that support their essentiality or involvement in virulence.

Protease family	Metalo-aminopeptidase (source)	Molecular activity or property that determines their main functions	Main functions	Essentiality or involvement in virulence	Experimental evidences that support their relevance
M17	*Td*M17-LAP (*T. denticola* bacterium)	Cysteinyl-glycinase activity	Glutathione catabolic pathway	Essentiality not demonstrated	Glutathione and Cys-Gly protect the cellular components from oxidative damage
	*Hp*M17AP (*H. pylori* bacterium)	Cysteinyl-glycinase and arginyl-aminopeptidase activities	- Defense in human macrophages - Drug resistance mechanisms - Housekeeping role - Maintains an adequate cytoplasmic pool of free arginine (all probably)	Essentiality not demonstrated	- Upregulated in response to the anti-*H. pylori* agent, NE-2001, and oxidative stress caused by nitric oxide and metronidazole - Bestatin inhibits bacterial growth
	PhpA (*P. aeruginosa* bacterium)	Quaternary structure	Regulates transcription of the virulence-associated *algD* gene	Not essential, involved in virulence	Mutation in a metal-binding residue increases transcription of *algD* gene and produces a slow growth phenotype *in vivo*
	*Vc*PepA (*V. cholera* bacterium)	Quaternary structure	Modulates transcription of the cholera toxin gene under different environmental conditions	Not essential, involved in virulence	Knockout increases levels of cholera toxin in non-inducing conditions
M18	PfA-M18 (*P. falciparum* parasite)	Aspartyl-aminopeptidase activity	- Hemoglobin degradation - Erythrocyte membrane rupture (all probably)	Essential	Knockdown inhibits parasite growth
M24	*Mt*MetAP1a (*M. tuberculosis* bacterium)	Methionyl-aminopeptidase activity	Removal of N-terminal methionine from newly synthesized peptides	Essential	- Knockdown inhibits bacterial growth - Overexpression confers resistance to the antibacterial effect of enzymatic inhibitors
	*Mt*MetAP1c (*M. tuberculosis* bacterium)	Methionyl-aminopeptidase activity	- Removal of N-terminal methionine from newly synthesized peptides - A major role in the host macrophage phagosome	Not essential, involved in virulence	Overexpression confers resistance to the antibacterial effect of enzymatic inhibitors
	*Ld*MetAP2 (*L. donovani* parasite)	Methionyl-aminopeptidase activity	- Apoptosis - Removal of N-terminal methionine from newly synthesized peptides	Essentiality not demonstrated	- Overexpression and apoptosis are associated - Inhibitors prevent the induction of apoptosis, but do not prevent parasite death