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IMMUNE EVASION

A new role for rhomboid proteases

Rhomboids are transmembrane serine proteases with an intramembrane active site, and they are unusual among membrane proteins in that they have been conserved throughout evolution in all kingdoms of life. Despite this conservation, little is known about their cellular roles. Previous work has shown that rhomboids are involved in host-cell invasion by malaria and related intracellular parasites, but it has been unclear what role they have in pathogens, which maintain an extracellular existence. A potential role for rhomboids in immune evasion has now been uncovered by Baxt and colleagues, who report their findings in *Genes & Development*.

The authors studied rhomboid function in the extracellular parasitic amoeba *Entamoeba histolytica*. This amoeba causes the intestinal infection amoebiasis, which, among parasitic diseases, ranks second only to malaria in terms of global morbidity. The authors focused on *E. histolytica* because, unusually among eukaryotes, it encodes only one rhomboid protein (EhROM1) with the residues that are required for catalysis.

To assess its proteolytic activity, Baxt *et al.* expressed EhROM1 in mammalian cells together with the canonical rhomboid substrate Spitz, a signalling molecule from *Drosophila melanogaster*. They obtained high expression levels of EhROM1 by recoding its open reading frame, but, despite this, Spitz remained uncleaved.

Baker *et al.* recently discovered that, unlike canonical rhomboids, a rhomboid from *Plasmodium falciparum* exhibits atypical substrate specificity — it cannot cleave Spitz, but can cleave several classes of adhesin. They therefore tested whether EhROM1 has a similar atypical specificity and found that it can indeed cleave *P. falciparum* adhesins.

But what is the native substrate of EhROM1? A candidate substrate search identified an *E. histolytica* cell-surface galactose/*N*-acetylgalactosamine-binding (Gal/GalNAc) lectin. This lectin is crucial for amoebic virulence, and the authors showed that EhROM1 can specifically cleave it.

To confirm that this cleavage event is physiologically relevant, Baxt *et al.* analysed the localization of EhROM1 and the Gal/GalNAc lectin in the invasive form of *E. histolytica*. They found that these proteins become colocalized in vesicles during phagocytosis (*E. histolytica* is proficiently phagocytic, which contributes to its virulence). They also become colocalized at the base of the cap structure during surface-receptor shedding for immune evasion. This work therefore implicates rhomboid proteases in immune evasion for the first time and, in doing so, has identified a potential therapeutic target for combating amoebiasis.

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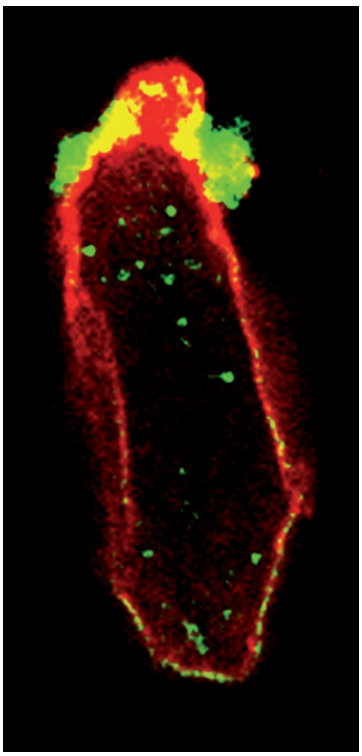

In the invasive form of *Entamoeba histolytica*, the rhomboid protease EhROM1 (green) and the galactose/N-acetylgalactosamine-binding (Gal/GalNAc) lectin (red) become colocalized at the base of the cap structure during surface-receptor shedding for immune evasion. Figure kindly provided by Sin Urban, Harvard Medical School, Boston, USA.

ORIGINAL RESEARCH PAPER Baxt, L. A., Baker, R. P., Singh, U. & Urban, S. An *Entamoeba histolytica* rhomboid protease with atypical specificity cleaves a surface lectin involved in phagocytosis and immune evasion. *Genes Dev.* **22**, 1636–1646 (2008)

FURTHER READING Baker, R. P., Wijetilaka, R. & Urban, S. Two *Plasmodium* rhomboid proteases preferentially cleave different adhesins implicated in all invasive stages of the malaria lifecycle. *PLoS Pathog.* **2**, e113 (2006)