Nature Reviews Microbiology | AOP, published online 9 February 2015; doi:10.1038/nrmicro3444

PARASITE BIOLOGY

PINning down *Theileria*

> TaPIN1 promotes oncogenesis by binding to and destabilizing FBW7

Theileria spp. parasites are transmitted by ticks and cause a lymphoproliferative disease in animals, particularly cattle. A unique feature of these intracellular apicomplexans is their ability to transform leukocytes into an oncogenic state; however, the mechanistic basis of this was previously unknown. Now, Marsolier *et al.* identify a secreted peptidyl-prolyl isomerase (PPIase) of *Theileria annulata* as a key factor underlying host cell transformation, owing to its ability to manipulate oncogenic signalling in the host.

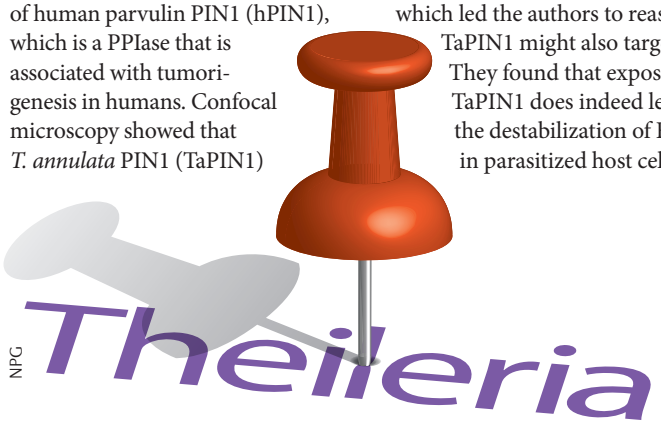
To identify proteins secreted by *Theileria* spp. that could contribute to host cell transformation, the authors carried out an *in silico* screen of parasite genomes to search for genes encoding signal peptides that are specific to the *Theileria* genus. This screen identified 33 candidate genes, one of which encoded a homologue of human parvulin PIN1 (hPIN1), which is a PPIase that is associated with tumorigenesis in humans. Confocal microscopy showed that *T. annulata* PIN1 (TaPIN1) is secreted into the cytoplasm and nucleus of host cells, and a combination of *in vitro* and *in vivo* assays confirmed that it is an active PPIase with an ability to transform bovine leukocytes.

The oncogenic phenotype induced by *Theileria* spp. is known to be associated with the c-Jun N-terminal kinase (JNK) and activator protein 1 (AP-1) signalling pathways. AP-1 is a heterodimeric transcription factor, composed of c-Jun and c-Fos proteins, that is activated by JNK-mediated phosphorylation of c-Jun. Activation of c-Jun is crucial for *Theileria*-induced transformation and host cell proliferation, however the ubiquitin ligase FBW7 targets oncoproteins (such as c-Jun) for degradation. Interestingly, hPIN1 was previously shown to promote auto-ubiquitylation of FBW7, resulting in its destabilization, which led the authors to reason that TaPIN1 might also target FBW7. They found that exposure to TaPIN1 does indeed lead to the destabilization of FBW7 in parasitized host cells, and immunoprecipitation experiments showed that TaPIN1 interacts directly with FBW7. Together, these data indicate that TaPIN1 promotes oncogenesis by binding to and destabilizing FBW7, which indirectly elevates the cellular levels of c-Jun as FBW7-mediated degradation of c-Jun is inhibited. As no other FBW7 substrate was perturbed by TaPIN1 inhibition or FBW7 knockdown, the authors concluded that increased levels of c-Jun is the main outcome of the TaPIN1–FBW7 pathway.

Finally, the authors also went on to show that TaPIN1 is directly inhibited by the anti-parasite drug buparvaquone, and that buparvaquone-resistant strains have mutations in the Ta*pin1* gene. As buparvaquone-resistant *Theileria* spp. strains are an emerging clinical concern, the authors propose that new anti-TaPIN1 compounds have the potential to be effective against drug-resistant theileriosis.

Collectively, these data establish the mechanism by which *Theileria* spp. induces transformation of its host cells and highlight the ability of pathogens to hijack host cell signalling for their own benefit.

Naomi Attar



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ORIGINAL RESEARCH PAPER Marsolier, J. *et al.* *Theileria* parasites secrete a prolyl isomerase to maintain host leukocyte transformation. *Nature* http://dx.doi.org/10.1038/nature14044 (2015)