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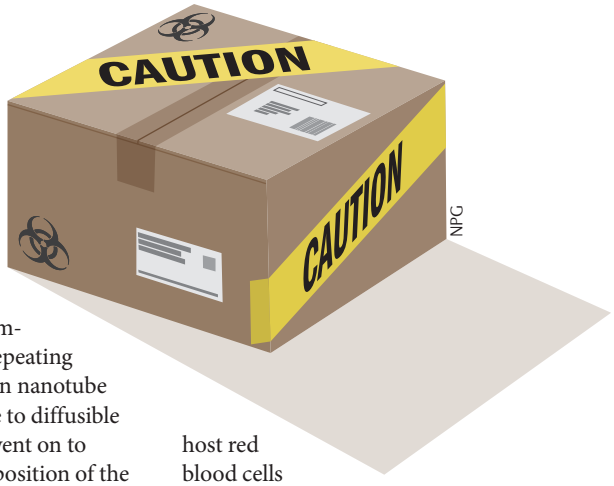
PARASITE BIOLOGY

Virulence packages



Several microorganisms produce extracellular membrane vesicles (EMVs), which mediate interactions with the environment, with other microorganisms and with host cells. Now, a new study shows that the parasite *Trypanosoma brucei* also produces EMVs, which transfer virulence factors between different trypanosomes and interact with host erythrocytes, causing anaemia.

African trypanosomes are vector-borne flagellate parasites that, following transmission by infected tsetse flies, grow in the bloodstream of their mammalian hosts. Humans are immune to most African trypanosomes owing to the expression of trypanosome lytic factors (TLF), which are complexes of lipids and proteins that include the pore-forming toxin apolipoprotein L-1 (ApoL-1). However, *T. b. rhodesiense* expresses the virulence factor serum-resistance associated protein (SRA), which binds to and neutralizes ApoL-1, enabling this parasite to escape immunity and establish human infection. Furthermore, trypanosome infection causes anaemia, although how the parasite induces this is unclear.

To investigate the mechanisms of pathogenesis of *T. brucei*, Szempruch, Sykes *et al.* visualized bloodstream parasites using differential interference contrast (DIC) video microscopy and observed highly dynamic nanotubes that protruded from the cell posterior. Transmission electron microscopy (TEM) revealed that these nanotubes budded from the flagellar membrane and enclosed repeating spherical units that, on nanotube dissociation, gave rise to diffusible EMVs. The authors went on to characterize the composition of the EMVs and found that they contained multiple membrane proteins and proteins associated with the flagellar matrix, which supports budding from the flagellar membrane as their mechanism of biogenesis. In addition, EMVs contained several virulence factors, including SRA.

As EMVs can mediate cell–cell communication, and as humans can sometimes be infected by trypanosomes that do not encode SRA, the authors investigated whether EMVs could transfer resistance against TLF to parasites that do not produce SRA. Indeed, adding EMVs produced by *T. b. rhodesiense* (which produces SRA) conferred resistance against TLF to *T. b. brucei* (which does not produce SRA), in a dose-dependent manner. Furthermore, the authors showed that EMVs interact with the recipient cell at the flagellar pocket and directly fuse with the plasma membrane, with EMV lipids then diffusing rapidly throughout the trypanosome membrane.

The fusogenic capacity of EMVs and their production in the bloodstream led the authors to investigate whether the vesicles interact with host red blood cells (RBCs). Indeed, *T. brucei* EMVs fused with RBCs, which led to the incorporation of parasite proteins into the host cell plasma membrane and increased membrane rigidity. Furthermore, the injection of EMVs into mice resulted in a decrease in the number of RBCs, suggesting that the fusion of the vesicles with RBCs modifies their physical properties and causes anaemia.

> “fusion of the vesicles to RBCs … causes anaemia”

Collectively, these data demonstrate that trypanosomes can produce EMVs that package multiple virulence factors and mediate interactions with other parasites and with host cells. Furthermore, although additional studies are needed to characterize the exact mechanism that results in anaemia, these findings suggest that EMVs may act as novel therapeutic targets during human infection with African trypanosomes.

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ORIGINAL ARTICLE Szempruch, A. J., Sykes, S.E., *et al.* Extracellular vesicles from Trypanosoma brucei mediate virulence factor transfer and cause host anemia. *Cell* **164**, 246–257 (2016)
FURTHER READING Pays, E. *et al.* The molecular arms race between African trypanosomes and humans. *Nat. Rev. Microbiol.* **12**, 575–584 (2014)