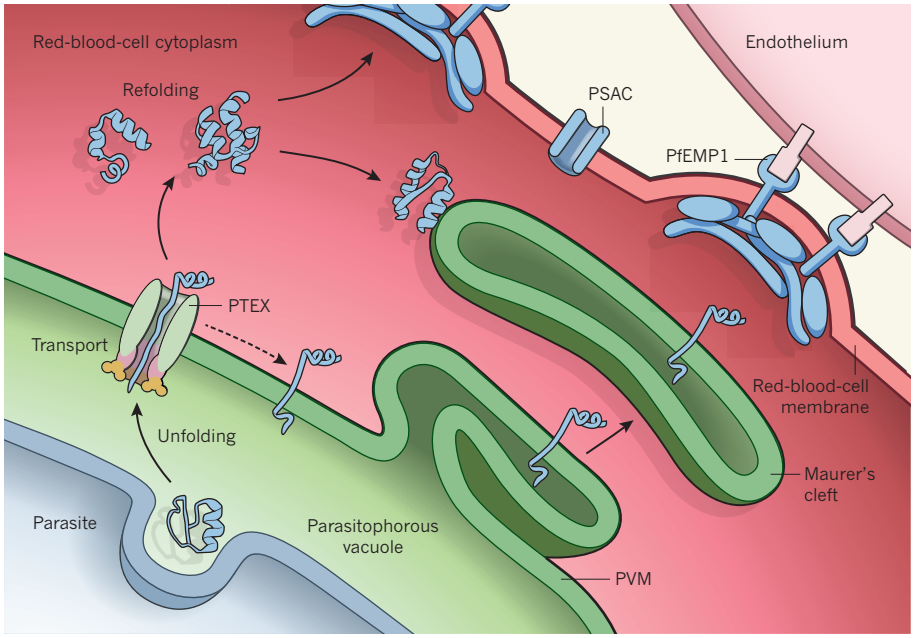

Figure 1 | Transport of parasite proteins into the host red blood cell. The protein complex PTEX mediates export of malaria-parasite proteins across the parasitophorous vacuolar membrane (PVM), which separates the cytoplasm of an infected cell from the vacuole in which the parasite resides. Parasite proteins are first secreted into the vacuolar space, in which they are unfolded before transport through PTEX; they are then refolded in the host-cell cytoplasm. Some membrane proteins might undergo lateral transfer (dashed arrow) from PTEX into the PVM, a process that would allow movement within membranes to reach vesicles known as Maurer's clefts. Exported proteins then localize to specific sites in the cell or on the red-cell membrane, at which they serve functions that are crucial to intracellular parasite growth. Examples include nutrient uptake through PSAC and PfEMP1-mediated binding of infected cells to endothelial cells that line blood vessels.

unclear are if EXP2 indeed defines the pore and what roles the other PTEX components might serve. Could membrane proteins passing through PTEX undergo lateral transfer into the parasitophorous vacuolar membrane to allow migration along membranous extensions (Fig. 1), as established for translocons in other organisms[9]? Finally, proteins that pass into the host-cell cytoplasm will require refolding, presumably by parasite chaperones that are also exported and must somehow be refolded themselves[10].

Another fundamental finding of these studies is that suppression of protein export interferes with intracellular parasite growth, indicating that exported proteins have essential roles in parasite survival. The authors observed adverse effects on parasite development *in vitro* and *in vivo*, with immature ring-stage parasites unable to mature to the trophozoite stage. By contrast, inhibiting PTEX after maturation to the trophozoite stage was well tolerated, with no effect on parasite egress from the cell or invasion of new red blood cells, suggesting that these latter processes do not depend on proteins exported late in the cycle. But development of early-stage gametocytes, the sexual stage of the parasite life cycle required for malaria transmission by mosquitoes, was also severely compromised.

Which activities of the numerous exported proteins account for the parasite growth inhibition seen in these studies? Although binding of infected cells to endothelial receptors is required for parasite survival *in vivo*, it is dispensable for *in vitro* culture. A leading candidate is the uptake of nutrients by the plasmodial surface anion channel (PSAC), an essential activity associated with the parasite protein cytoadherence-linked antigen 3 (CLAG3)[11,12]. Beck and colleagues found that CLAG3 still enters the host-cell cytoplasm when PTEX is suppressed, implying that it is exported by a distinct mechanism, perhaps during invasion. At the same time, solute transport by PSAC was curtailed, suggesting that other exported proteins are required for nutrient-channel formation.

In human malaria, binding of infected cells to the endothelium averts their destruction by the spleen and is primarily mediated by members of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) protein family. Each member has multiple binding domains at its extracellular face and a single transmembrane domain to anchor the protein over parasite-induced knobs on the infected cell[13]. How does PfEMP1 move from the parasite to the red-blood-cell membrane? Although the protein is not cleaved by plasmepsin V, its atypical PEXEL motif and transmembrane domain both seem to contribute to its export[4]. Subsequent refolding of the endothelium-binding domains in the host cytoplasm presumably requires disulphide-isomerase enzymes to bring numerous cysteine amino-acid residues together correctly and may involve a battery of chaperones[14,15]. Specialized sorting organelles known as Maurer's clefts and proteins at the surface knobs also seem to be required for the ultimate insertion of PfEMP1 in the host membrane[16]. In light of the complex folded structure of PfEMP1 and the possible involvement of many chaperones, the compromised export of this protein observed by both Beck *et al.* and Elsworth *et al.* could reflect an indirect effect of PTEX inhibition. Further study will be required to determine the precise mechanisms for trafficking and presentation of this key virulence factor.

The two new articles reveal a remarkably broad range of substrates for the translocon and provide compelling evidence that protein export is essential for the parasite and therefore represents a potential therapeutic target. We foresee that combinations of drugs that target both PTEX and exported parasite activities, such as PSAC-mediated nutrient uptake, may be highly synergistic antimalarial therapies. ■

Sanjay A. Desai *and* **Louis H. Miller** *are in the Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland 20852, USA.*
e-mails: sdesai@niaid.nih.gov; lmiller@niaid.nih.gov

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CORRECTION

The final corrections (to remove mentions of specific chromosomes) to the Retractions (*Nature* **511,** 112; 2014) were accidentally omitted from the print versions. The online versions were correct.