CTL4 controls TEP1-independent melanization of human malaria parasites

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Melanization is one of the most effective innate defense mechanisms in mosquito vectors. Numerous studies have shown that the *Anopheles* TEP1-controlled complement-like system is essential for melanization of the rodent model malaria parasite *Plasmodium berghei*, which evades this defense by recruiting C-type lectins. But the role of TEP1 has not been sufficiently addressed in the context of malaria infection with the clinically relevant human malaria parasite, *Plasmodium falciparum*. Using CRISPR/Cas9 genome editing, we show that the melanization of *P. falciparum* is independent of the TEP1-controlled complement-like system, and a small proportion of *P. falciparum* ookinetes are capable of evading this defense mechanism in the midgut tissue of CTL4^{null} mosquitoes, in contrast to the complete melanization of rodent *P. berghei*. Furthermore, we discovered that the major anti-*Plasmodium* pathway Imd does not influence *Plasmodium* melanization. Our study proves CTL4 as one of the most potent malaria transmission-blocking targets.