

Dynamic protein ubiquitination by USP1 is essential for malaria transmission

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Transmission of malaria parasites from the vertebrate host to mosquito vector requires specialised precursor cells also known as gametocytes. Gametocytes are sexually dimorphic where both male and female cells have unique properties to initiate the sexual life cycle in the mosquito. Within seconds of experiencing the mosquito environment male gametocytes commence a complex signalling cascade resulting in three rounds of DNA replication, endomitosis and axoneme assembly to release eight flagellated gametes in 10-15 minutes, which will fertilise with female gametes to form diploid zygotes. How the male gametocyte is capable of such astonishing speed of mitosis is an intriguing question. Light and electron microscopy have revealed, in comparison to the female, the male contains a significantly larger nucleus, understandably to accommodate the 8n genome. Moreover, the male nucleus appears to have an unusual chromatin organisation which is large and loosely stained. We have discovered this unique chromatin topology is regulated by a key post-translation modification, ubiquitination. Ubiquitination of proteins acts as signals that have multiple effects from targeting substrate proteins for degradation to modulating their function, localisation and activity. Reversible ubiquitination is catalysed by the action of both writers (E3-ligases) and erasers (deubiquitinases). We have found an essential role for a deubiquitinase, USP1 during two crucial stages of sexual development, resulting in a complete block in parasite transmission to the mosquito. In the absence of USP1, male gametocytes show abnormal chromatin compaction and, in response to the mosquito environment, fail to replicate their DNA. Curiously, the activity of USP1 is not restricted to male gametocyte DNA or nuclear homeostasis. Although USP1 deficient females are capable of fertilization, the fertilized cells do not undergo subsequent meiotic DNA replication implying USP1 activity orchestrates DNA replication dynamics in both sexes. Our proteomic studies reveal that USP1 interacts with the DNA replication and chromatin modification machinery and we are now in the process of identifying the molecular effectors of USP1. Currently we are building a clearer picture of how USP1-mediated dynamic protein ubiquitination regulates the unique biology of *Plasmodium* gametocytes, which could lead to new transmission blocking strategies.