Zinc finger proteins of *Plasmodium falciparum*

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**Abstract**

Zinc finger proteins (ZFPs) are a large diverse family of proteins with one or more zinc finger domains in which zinc is important in stabilising the domain. ZFPs can interact with DNA, RNA, lipids or even other proteins and therefore contribute to diverse cellular processes including transcriptional regulation, ubiquitin-mediated protein degradation, mRNA decay and stability. In this review, we provide the first comprehensive classification of ZFPs of the malaria parasite *Plasmodium falciparum* and provide a state of knowledge on the main ZFPs in the parasite, which include the C2H2, CCCH, RING finger and the PHD finger proteins.

**Take aways**

- The *Plasmodium falciparum* genome encodes 170 putative Zinc finger proteins (ZFPs).
- The C2H2, CCCH, RING finger and PHD finger subfamilies of ZFPs are most represented.
- Known ZFP functions include the regulation of mRNA metabolism and proteostasis.

**KEYWORDS**

epigentic regulator, gene expression, malaria, *Plasmodium*, transcription factor, zinc finger protein

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**INTRODUCTION**

Zinc finger proteins (ZFPs) are a large family of regulatory proteins with zinc ion-binding finger-like (ZnF) domains that enable the interaction with RNA, DNA, poly-ADP-ribose, proteins and lipids. Currently, more than 30 different types of ZFPs are described, which are implicated in various cellular processes including transcriptional regulation, chromatin remodelling, proteostasis, signal transduction, as well as cell proliferation and differentiation (reviewed in Cassandri et al., 2017; Singh & van Attikum, 2021). Generally, a ZnF motif is composed of a ~30 amino acid sequence with conserved arrangements of cysteines (C) and histidines (H) (Figure 1a,b). The cysteine and histidine residues are coordinated by a central zinc ion, resulting in a finger-like structure. Instead of zinc, other metals such as cobalt, copper, nickel or cadmium are able to coordinate the loop.

ZFPs are categorised in nine subfamilies based on the cysteine and histidine arrangements within the ZnF motifs, that is, C2H2, CCCH, C3HC4 (the really interesting new gene [RING] finger subfamily), C2HC5, C4HC3 (the plant homeodomain [PHD] finger subfamily), C2HC, C4, C6 and C8 subfamilies. In C2H2 motifs, which were the first ones identified back in the 1980s, two cysteines followed by two histidines are arranged around the central zinc ion (Figure 1a). In addition to the C2H2-type, the CCCH-type, the RING-type and the PHD-type are the most common subfamilies in eukaryotes (Figure 1b; reviewed in Klug, 2010; Jen & Wang, 2016; Cassandri et al., 2017). While C2H2-ZFPs include a large number of transcription factors, which mediate direct interactions with DNA, RING finger proteins...
(RFPs) include numerous E3-ubiquitin ligases, and PHD finger proteins often act as epigenetic regulators during chromatin remodelling. Many ZFPs contain multiple and different types of ZnF domains.

In humans, ZFPs have been linked to a wide variety of diseases including cancer, Parkinson’s disease, psoriasis, diabetes and congenital heart disease (reviewed in Cassandri et al., 2017), making them potential drug targets. A series of compounds from metals like gold, platinum, cobalt, antimony and selenium are currently being tested as ZFP inhibitors (Abbehausen, 2019).

In recent years, ZFPs have gained increasing attention in the protozoan Plasmodium, the causative agent of the tropical disease malaria. Approximately 229 million people suffered from malaria in 2019, leading to 409,000 deaths particularly in African children (WHO World Malaria Report, 2020). The disease is transmitted from human to human by blood-feeding mosquitoes. In both hosts, human and mosquito, the parasite passes through various life cycle stages, including the clinically relevant blood stages (Figure 2). To ensure successful replication in both hosts, Plasmodium parasites require a sophisticated molecular machinery facilitating cell growth and proliferation as well as environmental adaptation and stage conversion.

The Plasmodium genome comprises roughly 5,500 genes. Each life cycle stage requires approximately two-thirds of genes for optimal growth as a consequence of functional optimization caused by genomic

**FIGURE 1** Zinc finger motifs and proteins in *P. falciparum*. (a) Schematic of the C2H2-type ZnF motif. (b) Structures of the most common ZnF motifs. C, cysteine; H, histidine; Zn$^{2+}$, zinc ion. (c) Schematic of selected ZFPs of *P. falciparum*.
reductions during the evolution of Plasmodium (Bozdech et al., 2003; Bushell et al., 2017). Because only a small proportion of gene products is truly specific to a particular developmental stage of the parasite's life cycle, an extensive network of regulatory proteins needs to adjust gene expression on the transcriptional and post-transcriptional levels (reviewed in, for example, Bennink & Pradel, 2019; Hollin & Le Roch, 2020). A number of ZFPs have meanwhile been suggested to contribute to this regulatory protein network (Bischoff & Vaquero, 2010; Coulson, Hall, & Ouzounis, 2004; Reddy et al., 2015).

In this review, we performed a genome-wide search for putative ZFPs in *P. falciparum*, revealing 170 ZFP-encoding genes, which corresponds to 4% of all genes (Table S1; PlasmoDB database; Aurrecoechea et al., 2009). Approximately 90 ZFPs are considered essential for blood stage proliferation (Zhang et al., 2018). The majority of the ZFPs have orthologues in *P. berghei, P. yoelii, P. vivax* and *P. knowlesi*, most of which are also classified as essential proteins (Table S1; PlasmoGEM database; Schwach et al., 2015). Of the 170 putative *P. falciparum* ZFPs, C2H2 (9), CCCH (27), RING (48) and PHD-type (11) subfamilies are the most represented, which are hereby discussed.

### 2 H2-TYPE ZFPs

C2H2-type ZnF motifs share the consensus sequence C-X_{2-4}-C-X_{3-5}-C-X_{3-4}-C-X_{3-5}-H. The two cysteine and two histidine residues of the motif fold into a finger-like structure of a two-stranded antiparallel β-sheet and an α-helix after interacting with zinc ions (Figure 1a,b). C2H2 motifs particularly interact with DNA. A single C2H2 motif can span a DNA sequence of three consecutive base pairs, and the contact is usually established by distinct amino acids within the α-helix. In ZFPs, C2H2-type ZnF motifs with different triplet binding features are often combined to provide recognition specificity of longer DNA sequences (reviewed in Wolfe, Nekludova, & Pabo, 2000; Klug, 2010). Originally described as transcription factors, C2H2-type ZFPs often also interact with RNA, and DNA and RNA binding involves different zinc finger loops.

So far, we identified nine C2H2-type ZFPs in *P. falciparum*, which exhibit peak expression in the asexual and sexual blood stages (Table S1; Aurrecoechea et al., 2009; Lopez-Barragan et al., 2011). Of these, seven have only one C2H2-type ZnF motif, and the impact of such a single motif on DNA specificity is yet unclear. Of the two ZFPs

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**FIGURE 2** Known ZFPs of the *P. falciparum* blood stages. The known ZFPs of the asexual blood stages (blue box) and the gametocytes (orange box) are listed according to their ZnF motifs. ERAD, endoplasmic reticulum-associated degradation; PTM, post-translational modification; UPS, ubiquitin-proteasome system.
with two C2H2-type ZnF motifs, for one (the DnaJ protein PF3D7_1005600), a DNA sequence specificity could be predicted (Table S1).

The best-studied C2H2-type ZFP of *P. falciparum* is the transcription factor TFIIIA homologue PfTRZ (telomere repeat-binding ZFP), which was originally discovered by a quantitative trait loci analysis of the cycling times of two *P. falciparum* clones and hence assigned a role in cell cycle progression (Figures 1c and 2; Reilly Ayala, Wacker, Siwo, & Ferdig, 2010). A subsequent in-depth analysis identified PfTRZ as a telomere-binding protein. Depletion of PfTRZ resulted in a delayed cell cycle of the intraerythrocytic stages and impaired telomere length homeostasis (Bertschi et al., 2017). PfTRZ further binds to 5S rDNA telomere-binding protein. Depletion of PfTRZ resulted in a delayed cell cycle of the intraerythrocytic stages and impaired telomere length homeostasis (Bertschi et al., 2017). PfTRZ further binds to 5S rDNA genes to regulate 5S rRNA synthesis. A similar loss-of-function analysis of the *P. berghei* homologue PbZfp did not reveal any defect during intraerythrocytic development, while the transmission to the mosquito was reduced (Gopalakrishnan, Aly, Aravind, & Kumar, 2017). Furthermore, PbZfp was assigned to function in epigenetic regulation, since lack of PbZfp reduced histone methylation levels.

Another *Plasmodium* C2H2-type ZFP, PfZNF2, was investigated during a study of the homologous protein in *Toxoplasma gondii*, termed TgZNF2 (Gissot et al., 2017). Depletion of TgZNF2 impaired proliferation of *T. gondii* while the complementation with the homologous PfZNF2 rescued the knockout-phenotype, suggesting similar functions of both proteins. *T. gondii* lacking TgZNF2 were arrested in the G1 cell cycle phase and unable to transport polyA+ mRNA out of the nucleus, indicating that the ZFP is involved in mRNA nuclear export (Figures 1c and 2). In line with the loss-of-function data, TgZNF2 interacts with various nuclear proteins of mRNA export and cell cycle regulation (Gissot et al., 2017).

## 3 CCCH-TYPE ZFPs

CCCH-type (also termed C3H1-type) ZFPs have the zinc ion coordinated by three cysteines and a single histidine (Figure 1b). They commonly function as RNA-binding proteins (RBPs) with important roles in the RNA metabolism, including pre-mRNA splicing, polyadenylation, mRNA export, translation, but also ubiquitination and transcriptional repression (reviewed in Fu & Blackshear, 2017; Maeda & Akira, 2017; Hajikhezri, Darweesh, Akusjarvi, & Punga, 2020). The best-studied CCCH-type ZFPs in humans are the tristetraprolin (TTP) proteins such as roquin 1 and regnase 1, which are characterised by a tandem repeat of CCCH-ZnF motifs important for the regulation of immune-related genes and the modulation of signalling pathways. TTPs mainly execute their function by binding to AU-rich elements in mRNAs, resulting in the removal of the poly-A tail from the mRNA, thereby marking it for decay (reviewed in Fu & Blackshear, 2017). Our genome-wide search identified 27 CCCH-type ZFPs in *P. falciparum* (Table S1). The function of most of them is not known, and mainly bioinformatics analyses have been used to predict their molecular roles. For example, the putative ZFPs PRBMR22 and PICWCC2 share significant homologies with human HsRBM22 and yeast ScCWC2, respectively (Reddy et al., 2015). Both ScCWC2 and HsRBM22 are involved in an active conformation of the spliceosome catalytic center (Rasche et al., 2012). The plasmodial homologues PFPRBM22 and PFPCWC2 possess RNA recognition motifs and are anticipated to be involved in pre-mRNA splicing (Reddy et al., 2015).

PFU2AF1 is a putative splicing factor U2AF small subunit with significant homology to AtU2AF35b of *Arabidopsis thaliana* (Reddy et al., 2015). This protein is described as splicing factor U2AF small subunit B and is important in splicing of pre-mRNA (Kralovicova, Knut, Cross & Vorechovsky, 2015; Park et al., 2017; Wang & Brendel, 2004). Based on sequence similarity, PFU2AF1 is predicted to be involved in mRNA splicing (Reddy et al., 2015).

Another identified CCCH-type ZFP in *P. falciparum* is PFNAB2, a putative nuclear RBP with homologies to human HsZC3H14 (Reddy et al., 2015; Tuteja & Mehta, 2010). HsZC3H14 is involved in poly-A tail length control in neuronal cells and binds polyadenosine RNA oligonucleotides (Kelly et al., 2007, 2014). In addition to the CCCH motif, PFNAB2 also possesses a PW1-type nucleic acid binding domain, having a key role in transcription, splicing, polyadenylation and translation (Szymczyna et al., 2003).

While investigating the role of RBPs during the process of translation, two other CCCH-type ZFPs, encoded by genes PF3D7_0525000 and PF3D7_0906600, were identified and predicted to be RBPs. Experimental evidence revealed the existence of these proteins in polysomal fractions extracted from intra-erythrocytic stages of the parasite (Bunnik et al., 2016), suggesting potential roles in mRNA homeostasis.

An in-depth analysis of mRNA N6-methyladenosine (m^6^A) modifications in *P. falciparum* revealed a protein exhibiting a YTH domain-like CCCH-type ZnF domain, named PFYTH.1 (Figures 1c and 2; Baumgarten et al., 2019). Generally, proteins possessing YTH domains are specified as m^6^A reader proteins in eukaryotes, involved in facilitating mRNA degradation and translational activation (reviewed in Patil, Pickering, & Jaffrey, 2018). However, PFYTH.1 was formerly known as cleavage and polyadenylation specificity factor subunit 4, PICPSF4 (Stevens, Howe, & Hunt, 2018). Interestingly, the C-terminal YTH domain and the disordered low-complex N-terminal sequence arrangement of PFYTH.1 share homology with human protein YTH domain-containing family protein 1 (HsYTHDF1) and *Saccharomyces cerevisiae* methylated RNA-binding protein 1 (ScMRB1) (Baumgarten et al., 2019; Patil et al., 2018). The protein HsYTHDF1 plays a crucial role in mRNA stability by interacting with the CCR4–NOT complex to promote degradation of m^6^A-modified mRNA (Zaccara & Jaffrey, 2020), while yeast ScMRB1 is involved in regulating the phosphate metabolism by decreasing the stability of mRNA of a transcription factor of the phosphate pathway (PHO) and, thus, was also named ScPho92 (Kang et al., 2014). A direct role of ScMRB1 in regulating m^6^A-specific mRNA modification is not known (Luo & Tong, 2014). The plasmodial PFYTH.1 has a peak expression in the early intraerythrocytic stages and reduced transcript levels in the late blood stages, thereby signifying the decline in m^6^A-modified mRNA (Baumgarten et al., 2019).

The CCCH-type ZFP PFDF13 was identified as an essential blood stage-specific protein in *P. falciparum*, since anti-PFDF13 antibodies inhibited intraerythrocytic growth (Daubenberger et al., 2003). The
protein is unique to *Plasmodium*, with a highly conserved N-terminal ZnF motif suspected to be involved in protein–protein interaction.

## 4 | RING FINGER PROTEINS

RFPs are a large diverse group of ZFPs characterised by cysteine-rich domains of 40–60 amino acids coordinated by two zinc ions. The RING motif has a consensus sequence of C–X7–C–X9–39–C–X1–3–H–X12–3–C–X2–C–X4–48–C–X7–C (Figure 1b). RFPs have been discovered in many organisms where they play diverse functions, including transcription, RNA transport, signal transduction, DNA repair, organelle transport and ubiquitination (reviewed in Saurin, Borden, Boddy, & Freemont, 1996; Borden, 2000). In contrast to other ZFPs, RFPs mainly execute their function through protein–protein interactions. The best-studied RFPs are those that act as E3 ligases, which mediate the transfer of ubiquitin to target proteins, thereby initiating their degradation by the ubiquitin-proteasome system (UPS) (reviewed in Deshaies & Joazeiro, 2009).

In *P. falciparum*, we found 48 putative RFPs, most of which have not been studied so far. Plasmodial RFPs that have been functionally investigated either act as E3 ligases or interact with other proteins to regulate various physiological processes. RING finger E3 ligases identified in *P. falciparum* include PFRNF5 and PHRD1, which were first discovered by bioinformatic analysis and assigned to the endoplasmic reticulum (ER)-associated degradation (ERAD) pathway (Figures 1c and 2; Chung, Ponts, Prudhomme, Rodrigues, & Le Roch, 2012; Harbut et al., 2012). The ERAD pathway is a well-coordinated and extensive monitoring system, which ensures that misfolded proteins are rapidly extracted from the ER and then degraded by the UPS.

Two putative RING finger E3 ligases are encoded by genes PF3D7_0312100 and PF3D7_0316900. These RFPs were identified as putative apicoplast RING finger E3 ligases. PF3D7_0312100 was shown to localise to the apicoplast and exhibit E3 ligase activity (Agrawal et al., 2013). The authors suggested that the protein is part of the apicoplast ERAD-like pathway capable of mediating ubiquitination important for the import of nuclear-encoded apicoplast proteins.

Another putative RING finger E3 ligase is PRRNF1 (Ngwa et al., 2017). PRRNF1 possesses a C-terminal RING domain, which shows a significant homology with the human E3 ligase Praj-1 known to mediate protein degradation by the UPS (Yu, Chen, Tagle, & Cai, 2002; Lu et al., 2020). PRRNF1 is upregulated in both transcript and protein levels following the treatment of mature *P. falciparum* gametocytes with the histone deacetylase inhibitor Trichostatin A, indicating that it could be regulated by epigenetic mechanisms (Ngwa et al., 2017). It was, therefore, suggested that RNF1 is a potential HDAC-regulated E3 ligase involved in ubiquitin-mediated pathways crucial for gametocyte development (Figures 1c and 2).

PF3D7_1004300 was identified in an ubiquitome screen of *P. falciparum* as an E3 ligase because it binds to ubiquitin covalently before it is subsequently transferred to a substrate (Ponts et al., 2011). PF3D7_1004300 is a homologue of the *A. thaliana* E3 ligase AtCIP8, which has been shown to interact with another RFP named AtCCOP1, a negative regulator of photomorphogenesis involved in the degradation of a positive regulator, AtHY5, via the UPS (Torii et al., 1999).

Two other plasmodial RING finger E3 ligases are PPIAS, a putative E3 Small Ubiquitin-related Modifier (SUMO)-protein ligase predicted to regulate the modification of specific SUMO substrates (Torii et al., 1999), and PNot 4, which possess an N-terminal RING domain and an RNA binding domain. PNot4 was identified as a component of the CCR4/Not complex, which is responsible for mRNA decay (Figures 1c and 2; Shock, Fischer, & DeRisi, 2007). In other eukaryotes, Not4 has been shown to function as an E3 ligase with a specific role in protein quality control via the UPS (Collart, 2013; Panasenko & Collart, 2011; Shock et al., 2007).

PZNF598 is a homologue of the human ubiquitin ligase HsZNF598, which is a component of the NGD/NSD (No-Go decay/Non-Stop decay) mRNA surveillance pathway responsible for translation quality control (reviewed in Juszkiewicz et al., 2018; Erath, Djuranovic, & Djuranovic, 2019). This pathway deals with either damaged, premature adenylated or difficult to translate mRNA sequences that cause the ribosome to stall during the elongation cycle of translation.

*P. falciparum* RFPs involved in functional regulation of other proteins include PfMAT1, which contains an N-terminal RING domain and a MAT1 CDK-activating kinase assembly factor (MAT1) domain. PfMAT1 was identified as an effector protein, which stimulates Pfmrk activity in a cyclin-dependent manner (Figures 1c and 2; Chen et al., 2006). Pfmrk is a putative homologue of the human cyclin-dependent protein kinases 7 (CDK7) (Fesquet et al., 1993; Fisher & Morgan, 1994). In addition to cell cycle regulation, HsCDK7 is involved in transcription and DNA repair (reviewed in Shuttleworth, 1995; Nigg, 1996). The interaction of PfMAT1 with Pfmrk was later validated by demonstrating their co-localization in the nucleus. It was thus suggested that the protein regulates DNA synthesis (Jirage et al., 2010).

Further, PfADA2, which contains a transmembrane domain, a RING domain, a Myb-like DNA binding-like domain and a homeodomain, interacts with the *P. falciparum* histone acetyltransferase PIGCN5 (Figures 1c and 2; Fan, An, & Cui, 2004). Recently, PFGCN5 was also shown to associate with genes that are important for the maintenance of parasite cellular homeostasis upon nutrient stress condition, indicating a role in stress regulation (Rawat, Malhotra, Shintre, Pani, & Karmodiya, 2020). It is not known if the RING domain is important for the execution of its function, since, in addition, the Myb-like DNA binding-like domain and the homeodomain can be involved in gene regulation.

Finally, PfUSP39 was identified as a component of the spliceosomal U4/U6.U5 tri-snRNP (small nuclear ribonucleoprotein particle) using a reciprocal best hit analysis of human and yeast splicing factors homologues in *P. falciparum* (Sorber, Dimon, & DeRisi, 2011). The yeast homologue of PfUSP32 named ScSad1p also contains a RING domain, localises to the yeast nucleus and is involved in splicing and the assembly of U4 snRNP to U6 snRNP (reviewed in Massoumi, Marfany, Wu, & Massoumi, 2016). The human homologue HsUSP32 is also important for the recruitment of the tri-snRNP to the prespliceosome, and its depletion causes defect in spindle checkpoint.
function and cytokinesis through regulation of Aurora B mRNA splicing (van Leuken, Luna-Vargas, Sixma, Wolthuis, & Medema, 2008).

5 | PHD FINGER PROTEINS

The PHD finger has a C4HC3 motif and was originally discovered in the plant homeodomain proteins of A. thaliana (Figure 1b). The motif has an average length of 50–80 amino acids and often occurs in clusters or in combination with other domains of chromatin binding. Hence, PHD-type ZNFs often act as epigenetic readers or chromatin modifiers (reviewed in Li & Li, 2012).

In P. falciparum, we identified 11 PHD finger proteins, some of which were discovered in studies aiming at unveiling epigenetic regulators (Table S1; Volz et al., 2010; Oehring et al., 2012; Hoeijmakers et al., 2019). The two recently identified PHD-type ZFPs, PHD1 and PHD2, are members of a novel chromatin-modifying complex of P. falciparum, the SAGA (Spt/Ada/Gcn5 acetyltransferase)-like complex (Hoeijmakers et al., 2019) with functions in H3K9ac acetylation. Because PHD1 was in addition found in a complex associated with the H3K4me3 chromatin mark, a role of PHD1 in cross-talking between both marks was considered. Both H3K4me3 and H3K9ac are known marks of euchromatin and are particularly involved in the activation of virulence (var) gene expression (reviewed in Voss, Bozdech, & Bartfai 2014).

PHD motifs are further present in 3 of the 10 existing SET (Su [var]3-9)–Enhancer of zeste-Trithorax-domain-containing lysine-specific HMTs of Plasmodium, that is, SET1, SET2 and SET10 (Figures 1c and 2; Cui, Fan, Cui, & Miao 2008; Volz et al., 2010). In P. falciparum, the gene coding for SET1 could previously not be knocked out, indicating that the enzyme is indispensable for asexual blood stage growth (Jiang et al., 2013). SET2 has been shown to play an important role in var gene regulation (Jiang et al., 2013; Ukaegbu et al., 2014). SET10 was originally reported to be an H3K4 methyltransferase required to maintain an active var gene in a poised state during blood stage division (Volz et al., 2010). A new study, however, showed that SET10 is neither essential for intraerythrocytic replication nor for the regulation of var genes (Ngwa et al., 2021), while loss-of-function studies suggest a role in transmission to the mosquito (Ngwa, Gross, Musabyimana, Pradel, & Deitsch, 2019).

6 | CONCLUSIONS

ZFPs are involved in diverse cellular processes of eukaryotes. Our genome-wide analysis identified 170 ZFPs in P. falciparum, most of which are in the C2H2, CCCH, RING finger and the PHD finger subfamily. While the role of the majority of these ZFPs is not yet known, recent studies point to the crucial functions of ZFPs in intraerythrocytic growth and gametocyte transmission. Future work is anticipated to unveil the details on ZFP-mediated regulation during life cycle progression and to determine their potential as antimalarial drug targets.

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CONFLICT OF INTEREST

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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