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Dynamin-like proteins in *plasmodium falciparum*: Molecular characterisation

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Abstract
Members of the dynamin superfamily are big GTPases that have remained mostly unchanged throughout evolution and are primarily characterised as mechanochemical enzymes engaged in membrane scission processes. Due to its large GTPase domain, conserved dynamin M and GED domains, and dynamin-like protein subgroup membership, PfDYN2 is a member of the dynamin superfamily. PfDYN2 partially co-localized with markers for the parasite endoplasmic reticulum, Golgi apparatus, and apicoplast, indicating that it may be involved in vesicular trafficking and/or organelle fission events that have been associated with the final stages of the parasite's development in erythrocytes. The P. falciparum genome only contains two members of the dynamin superfamily, PfDYN2 and PfDYN1.

Keywords: Dynamin superfamily, *plasmodium falciparum*, PfDYN2 and PfDYN1

Introduction
Since ancient times, the human species has been aware of malaria. It is well-known that these infectious diseases are widespread throughout the world, with 500 million cases and 1-3 million fatalities annually [1]. The protozoan parasite Plasmodium, which is carried by arthropods and is a member of the phylum Apicomplexa, is what causes malaria. The parasite Plasmodium can infect over 100 different species. The severity of the sickness and how quickly the symptoms worsen are determined by how quickly they replicate. According to the most recent WHO estimates, which were published in December 2016, there were 429 000 fatalities from malaria in 2015 and 212 million infections. Malaria poses a threat to about half of the world's population. Since 2010, there has been a 29 percent decrease in malaria mortality rates worldwide due to improved prevention and control techniques. The last ten years have seen a significant improvement in malaria control due to better diagnosis, novel artemisinin combination therapy (ACT) treatment approaches, and widespread use of insecticide-treated mosquito nets.

There is only one mitochondria in the entire Plasmodium, and its fission and segregation are carefully synchronised with nuclear division and cytokinesis. However, little is understood about the parasite's mitochondrial fission machinery. All eukaryotic cells, including those of Plasmodium, engage in the ubiquitous process of endocytosis, which involves the internalisation of substances from the external environment into membrane-bound vesicles that are created by invaginating and pinching off portions of the plasma membrane. Vesicular trafficking is often used to transport the endocytosed material through a succession of endocytic compartments and deliver it to hydrolytic, acidic compartments for digestion [2]. The erythrocytic cytosol is consumed by intraerythrocytic malarial parasites of the genus Plasmodium by endocytosis, and it is then transported to the parasite feeding vacuole via cytosomal vesicles. The cytostome's neck pinches off following endocytosis to release a double-membrane endocytic vesicle containing erythrocyte cytoplasm [3, 4].

Large GTPases called dynamins and dynamin-related proteins (DRPs) participate actively in endocytosis and carry out vesicle fission by GTP hydrolysis. These GTPases proteins play a variety of roles in protein transport as well as cell and organelle division in eukaryotic cells ranging from yeast to mammals. These proteins are crucial for the production of vesicles during receptor-mediated endocytosis, recycling of synaptic vesicles, internalisation of caveolae, division of organelles, protein trafficking, and cytokinesis [5-7]. A large GTPase domain, followed by the dynamin M domain and a C-terminal region containing a GTPase effector domain (GED), are shared by dynamins and dynamin-like proteins.

The dynamin M and GED domains are involved in enzyme oligomerization and the regulation of the GTPase activity. Dynamins have a variety of biochemical characteristics and cellular localizations that are conferred by different domains, which could account for the heterogeneity of their biological roles.

Protein Identification
Eps15 homology domain (EHD) proteins are among those proteins that have been shown to include structural and functional domains that like those of dynamin. EHDs are adenosine triphosphatases (ATPases) that have seen little change throughout evolution. They have been connected to endocytosis and vesicular transport mechanisms that are mediated by clathrin coats and other unknown coats involved in endosomal trafficking routes. Additionally, it has been suggested that EHD, in combination with other essential proteins of the pathways during parasite growth, may have a role in intracellular sorting through protein-protein interactions and/or calcium storage [8, 9].

Malaria Distribution
The disease of malaria is still a major public health concern in tropical areas of the world. The epidemiology and transmission of malaria have significantly changed as a result of increasing worldwide efforts and financing over the past ten years from both WHO and local authorities for the cause of malaria. Malaria-eliminating (lower malaria burden) and high burden

(greater spread and frequency of malaria) countries were established within the areas impacted by the disease in order to focus efforts. Malaria-free nations including Armenia, Morocco, and the United Arab Emirates have been regarded to have totally eradicated the disease, while high burden nations have made less progress in this regard [10]. The type of malarial protozoan that gets infected determines how often malaria spreads. While *P vivax* is more common in cooler, more temperate, and polar zones, *P. falciparum* predominates in tropical and warm areas close to the equator. The climax of this can be seen in the expansion of *P. vivax*, which caused more than 3000 deaths in 2015, more than 86% of which occurred outside of Africa. Compared to cooler zones, where transmission is typically slow and seasonal, malaria transmission is more widespread and common [11].

Cell Cycle and Division of Plasmodium

A single *P. falciparum* parasite first invades the host red blood cell (RBC) and then, 48 hours later, around 30 additional daughter parasites egress from the host RBC [12]. The parasite develops throughout this life cycle, reaching a point where schizogony, a special type of cell division, starts. In this process, the parasite replicates its DNA and then divides into two nuclei inside of a healthy nuclear membrane [13-16]. A multi-nucleated cell is formed as a result of this process being repeated numerous times asynchronously. A single cytokinesis event marks the end of schizogony, during which the multi-nucleated cell divides into about 30 daughter cells known as merozoites that will extrude and infiltrate fresh host RBCs. The inner membrane complex, a membranous structure, is involved in this specific type of segmentation (IMC) [17]. It has been demonstrated that the IMC in *P. falciparum* controls the shape and rigidity of developing merozoites and is connected with proteins inside the parasite, but its biogenesis and mechanisms of action are still poorly known [18]. Notably, it is still unclear how segmentation, where sub-cellular content must be evenly distributed within daughter cells, may occur concurrently with asynchronous nuclear replication. Segmentation works in tandem with the division and distribution of organelles such the endoplasmic reticulum, the Golgi apparatus, and secretory organelles that are particular to parasites.

Diagnosis

Early and timely detection of malaria is essential for keeping the disease under control and preventing the rapid infestation of illness in the local community. The prognosis of the disease depends heavily on the clinical diagnosis because the majority of the early symptoms of the illness (fever, chills, sweats, headaches, muscle pains, nausea, and vomiting) are difficult to identify from other infections. The standard microscopy and recombinant DNA technology-based diagnostic techniques are still used today. To aid in early detection, there is a critical need for the development of low-cost, highly sensitive diagnostic tools that can identify numerous, tiny, and different strains of the Plasmodium parasite.

Dynamin superfamily

Proteins that are active players in membrane transport and can enable the targeted movement of vesicles between compartments are necessary for eukaryotic cells. The eukaryotic cells have different dynamin family members, such as conserved NTPase or GTPase, which are involved in protein transport, cell and organelle division. Dynamin is a term derived from the Greek word dynamis, which denotes force and strength. They are hence known as mechanochemical enzymes. Dynamin was first identified as a microtubule association protein in the drosophila [19].

Initially, it was thought that dynamin's function was limited to microtubule sliding, where it prevented synaptic vesicle release and caused paralysis in drosophila. The ensuing paralysis suggests that the buildup of "seized" endocytic pits at the presynaptic plasma membran is what causes the depletion of vesicles. Recent research on the movement of clathrin-coated vesicles across the membrane, however, suggests that dynamin proteins are involved in the action. As a result, the discovery of dynamin revealed a new dynamin superfamily of GTPases that play a variety of roles in membrane remodelling processes in eukaryotic cells [20]. The members of the dynamin family fall into two categories: one category includes classical dynamins that are engaged in pinching off and moving Golgi-derived vesicles to endocytosis machinery the other category contains dynamins that are involved in mitochondrial division. The structural characteristics of GTPase activity and some of the common roles played by proteins from the Dynamin superfamily in membrane remodelling include highly conserved N-terminal, middle, and C-terminal GTPase domains. Additionally, classical dynamins feature a pleckstrin homology (PH) domain that may be able to bind to membrane phospholipids as well as a PRD that may let it interact with specific actin cytoskeleton proteins [21, 22].

The dynamin GTPase is a member of a vast protein superfamily whose members are all typically engaged in membrane remodelling processes such vesicle and organelle transfer via fission/fusion-based mechanisms and cytokinesis. The primary members of the protein superfamily include dynamin 1, dynamin-1 like protein, dynamin-2, dynamin-like 120kDa protein, mitochondrial protein, dynamin-containing protein 2, and dynamin-containing protein 4. Classical dynamins, dynamin-like proteins, OPA1, Mx proteins, Mitofusins, and gyanylate binding proteins/atlastins are additional members of the superfamily [23].

Dynamin in *P. falciparum*

Dynamin-like protein 1 (PfDYN1) and dynamin-like protein 2 are two dynamin-like proteins that are encoded by the P. falciparum parasite (PfDYN2). Additionally, proteins having dynamin-like characteristics have been found, and these proteins include Eps15 homology domain (EHD) proteins. EHDs were evolutionarily conserved adenosine triphosphatases (ATPases) which have been connected to processes of endocytosis and vesicular transport carried out by the clathrin coats and additional as-yet-unidentified coats engaged in endosomal trafficking processes [24]. PfDYN1 is referred to as a "classical dynamin" since it shares all five functional domains with other eukaryotic cells and is recognised to be involved in vesicle-mediated trafficking. Due to the small number of research that have been done so far, this protein's exact function in haemoglobin absorption is not well understood. The phylogenetic analysis and molecular architecture of PfDYN2 definitely positioned it in the dynamin-like proteins (Dlps) subgroup, which may be implicated in organelle partitioning and/or vesicular trafficking. The fact that P. falciparum only has one homolog of the EHD protein and that it contains all of its functional domains raises the possibility that it plays a part in organelle segregation or endocytosis. The ATP-binding G domain, an additional helical domain, a linker region, and an Eps15 homology (EH) domain are all parts of the structure of EHD proteins. EHDs are proposed to be a member of the dynamin-like superfamily since they share a structural and functional domain with dynamin/DRPs.

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