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Editorial

Revolutionizing Malaria Research: CRISPR unveils New Frontiers

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The CRISPR mechanism, discovered in bacteria and archaea, operates as an adaptative immune system at the genetic level. By using repetitive sequences, spacers derived from foreign DNA, and CRISPR-associated proteins, CRISPR effectively eradicates foreign genetic material. The mechanism consists of acquisition, expression, and interference stages. In the acquisition stage, Cas's proteins capture stranger DNA, which is then transcribed into RNA in the CRISPR array during the expression stage. In the interference stage, CRISPR RNA (crRNA) combines with Cas's proteins to identify and cut bacterial DNA that matches the crRNA sequences. The precision of CRISPR, particularly with the Cas9 protein, has revolutionized genetic engineering and shows potential for disease treatments like malaria. Additionally, CRISPR provides insights into the evolution of bacterial and archaeal immune systems (Figure 1).

Recent advancements in utilizing Cas9 and linear donor templates have improved the understanding of the genes involved in the growth of the Plasmodium parasite, which causes malaria (Figure 2). These breakthroughs allow for precise cleavage and integration of genetic material, reducing the risk of unintended recombination and off-target mutations. Research studies suggest that these advancements hold promise for more effective treatments against malaria [1, 2, 3]. The introduction of the CRISPR/Cas's system has revolutionized malaria research by providing a versatile tool for genome editing. It enables species-specific diagnosis, investigation of drug resistance, gene drive strategies, and the creation of malaria-resistant mosquitoes (Figure 3). The advancements offer invaluable resources for combating malaria and developing innovative strategies [4, 5].

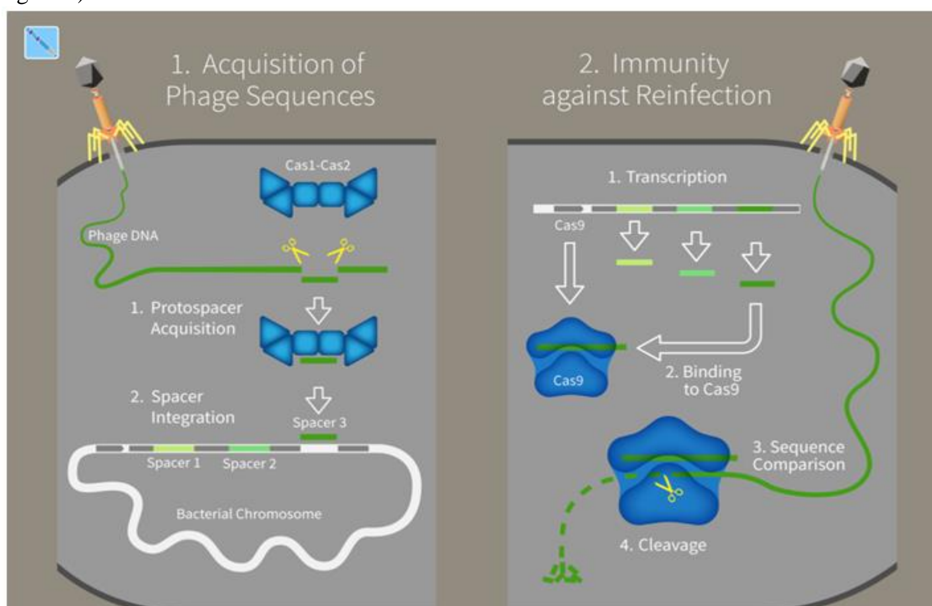

Figure 1: CRISPR-Cas9 Adaptative Immunity. This image is licensed under creative commons attribution.

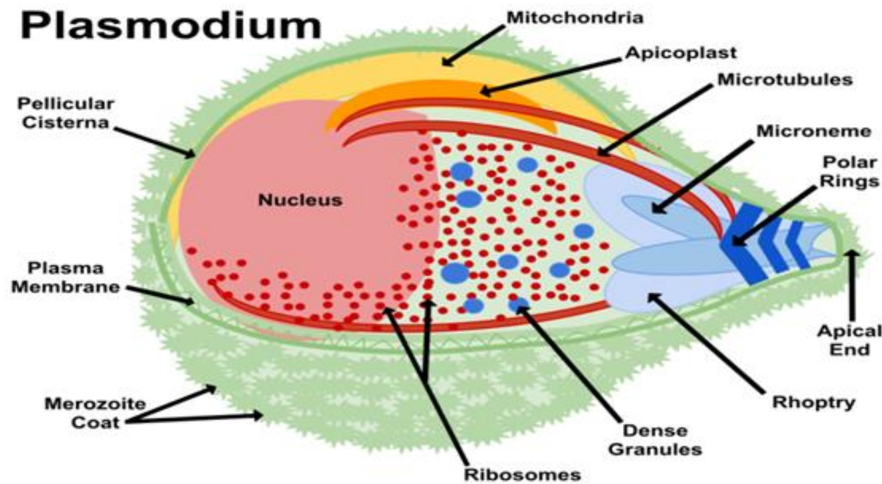

Figure 2: The cell structure of Plasmodium parasite. This image is licensed under creative commons attribution.

Plasmodium parasites causing malaria have a genome of approximately 30 megabases (Mb) with many unknown genes. CRISPR/Cas9 technology enables precise gene editing, unraveling parasite biology, identifying therapeutic targets, and advancing diagnostics [6]. CRISPR-Cas13 allows RNA binding and cleavage without permanent genetic changes [7]. It introduces mutations, tags, and deletions on a larger scale, improving our understanding of parasite biology and potential therapies [8]. Challenges persist in integrating DNA fragments and sequential gene editing, but the suicide-rescue-based system shows promise for large-scale genome editing and developing a live parasite malaria vaccine [9]. Thorough consideration of technical aspects is vital for successful CRISPR-based experiments and gene editing [10].

The application of CRISPR technology in Plasmodium parasite research has led to significant advancements in understanding their biology. Researchers have made noteworthy progress in marker-free gene editing in Plasmodium knowlesi and efficient transfection construct generation. In Plasmodium falciparum, CRISPR/Cas9 has enabled permanent modifications to the parasite's genome, reprogramming gene expression and invasion pathways. Using a Cas9-expressing parasite, scientists achieved site-directed mutagenesis and introduced multiple gene modifications in a single transfection [11, 12]. CRISPR-Cas9 has also been instrumental in unraveling the var gene family's characteristics in Plasmodium falciparum, including antigenic diversity and gene expression switching [13, 14]. CRISPR/Cas-based diagnostic kits facilitate precise species identification and drug resistance marker detection, revolutionizing parasite manipulation for malaria research disease management [15].

Recent research highlights the effectiveness of whole-sporozoite (Wsp) malaria vaccines in generating protective immune responses. A clinical trial focused on a Wsp vaccine composed of genetically attenuated parasites (GAP) that hinder early liver-stage growth. Using CRISPR/Cas9 gene deletion techniques, researchers have developed potential Plasmodium falciparum LA-GAPs. A mutant lacking the mei2-like RNA gene exhibited delayed liver development in human liver-chimeric murine with human erythrocytes. This mutant also showed increased susceptibility to antimalarial drugs, holding promise for future interventions [16]. Addressing asymptomatic carriers is vital for malarial control. A remarkable CRISPR-based diagnostic approach employing the Sherlock platform can detect and differentiate various Plasmodium species with high sensitivity. It can detect infections with an ultra-sensitive threshold of around two parasites by microliter of blood, offering a valuable tool for malaria diagnosis [17, 18, 19].

These editorial highlights the use of CRISPR technology in understanding Plasmodium parasites to help diagnose and treat malaria [20, 21, 22, 23]. Accurate diagnosis and effective treatment of malaria pose significant challenges in the medical field [24, 25, 26].

Abbreviations

Cas's protein: Cascade protein

CRISPR: Clustered regularly interspaced short palindromic repeats

crRNA: CRISPR RNA

Wsp: whole-sporozoite

GAP: genetically attenuated parasite

LA-GAPs: Late arresting genetically attenuated parasites

mei2: Rna-binding protein meiosis

Sherlock: Specific High-Sensitivity Enzymatic Reporter Unlocking

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