Systemic Review: The Pathogenicity of *Plasmodium berghei* in The Liver and Spleen of the Experimental Mice

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**Authors’ contributions**

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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**ABSTRACT**

Malaria is still one of the most prevalent tropical and parasitic diseases throughout the world, representing a global health concern. Even with all efforts to restrict disease transmission and national malaria control programs, malaria infection continues to cause considerable morbidity and mortality in resource-poor countries. Malaria infection occurs in two stages, the Exoerythrocytic and Erythrocytic stage. The exact biology of malaria parasite in human hosts is likely relatively similar, with the main differences being attributable to the human immune response, the number of previous infections and the exposure profile. The disease severity can be determined by the balance between the pro-inflammatory and anti-inflammatory cytokines. Although, research about the clinical characterization and histology of malaria has shown some information regarding the pathogenesis, the actual mechanisms by which malaria parasites produce severe disease, the immunity defends against infection is remained unknown. Studies in animal models can reveal details about the processes of severe malaria infection and human defense mechanisms. Because of its similarities to the Plasmodium species that cause human malaria, *Plasmodium berghei* is used as a model organism for the experimental research. In addition, of affecting the central nervous system, *Plasmodium berghei* infection in the Swiss Webster mouse causes systemic...
damage, and affects numerous organs including the liver and lymphoid organs. The infected spleen demonstrations include the splenomegaly, re-modelling and other basic changes consist of the red pulp's expansion, marginal zone's slight damage, enlarged vasculature and the barrier cells activities. Moreover, the liver shows hyperplastic Kupffer cells, fatty change, portal tract inflammation, cholestasis, liver cell necrosis, sequestration of Parasitized Red Blood Cells (PRBCs) and deposition of hemozoin pigments.

Keywords: Plasmodium berghei; Malaria; Splenomegaly; Rodent strains.

1. INTRODUCTION

The most important protozoal disease, Malaria is happened by the Plasmodium sp. which is involved by the Anopheles mosquito in its life cycle and cause a threatening disease in most countries that concern the worldwide attention [1]. The human malaria is caused by five species which are P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi [2]. The most common species of malaria in Africa is P. falciparum which is also the most virulent one and causes the highest number of malaria-related mortality worldwide [3]. On the other hand, P. vivax, P. ovale, and P. malariae generally cause a milder form of malaria with lower mortality rates [2] as well as few human cases are caused by P. knowlesi. It is well documented that malaria is common diseases in poor countries with a significant negative effect on the economic development [4-5].

2. EPIDEMIOLOGY

Although strict control and elimination measures are applied through the international and national malaria control programs throughout the world, malaria is still one of the most important parasitic disease worldwide representing a global health concern [6]. Plasmodium infection continues to cause high rates of morbidity and mortality with 229 million cases and an estimated of 409,000 deaths in 2019 in 87 malaria-endemic countries [7]. About 67% of all malaria deaths were in young aged children less than five years old [6]. In the WHO’s African Region (AFR), almost 94% of cases were reported as malaria cases, and in the WHO’s Southeast Asia Region (SEAR) and Eastern Mediterranean Region (EMR) almost 3.0 and 2.2% of cases were reported as malaria cases respectively [8]. Moreover, in non-endemic regions and malaria-free countries, imported malaria cases are now increasingly reported and represent an emerging public health problem for these countries.

In endemic countries, risk of vector borne diseases including malaria are currently increasing due to changes in the ecosystem and global warming [9]. On the other hand, in non-endemic and malaria free countries, imported malaria is now a public health issue because of the increasing travel and/or migratory movements for employment or due to the geopolitical conflicts [10-13].

3. LIFE CYCLE, CLINICAL PICTURE AND PATHOPHYSIOLOGY

Malaria infection develops via two phases, the Exo-erythrocytic (liver-related phase) and the Erythrocytic (red blood cell or erythrocyte) phase. As a result of a mosquito bite, the Sporozoites in the mosquito's saliva penetrate the skin and enter the bloodstream, then travel to the liver where they infect hepatocytes, multiplying asexually for 8-30 days without causing any symptoms [14].

Following a dormant period in the liver, Sporozoites differentiate into hundreds of Merozoites, which escape into the bloodstream and infect the red blood cells, kicking off the Erythrocytic stage of the life cycle [15]. In order to evade the immune system and escape from the liver, the parasite wraps itself in the membrane of the infected liver cell [16].

Within the red blood cells, Plasmodium multiply asexually again, and periodically break the cells to infect new red blood cells to complete the life cycle of Plasmodium; some of the Merozoites in the infected erythrocytes undergo sexual multiplication and develop into sexual forms (Gametocytes), which are ingested by the female mosquitoes. Inside the mosquito, all the Gametocytes mature to Gametes that grow to Ookinetes followed by Oocysts that produce many lively Sporozoites. When the Oocyst eruptions, it releases the Sporozoites that can be move to the Mosquito's salivary glands. Next the infection in the human body will begin and then the mosquito fly looking for another victim [17].
The Malaria symptoms include anemia, illness, thrombopenia, anxieties, headache, nausea, muscle ache, anorexia, rigor, looseness, abdominal distress, coughing, annexations, respiratory pain, hypoglycemia, metabolic acidosis, hyperlactemia, coma related the high intracranial pressure (cerebral malaria) and finally the retinopathy. Fetal Growth Restriction (FGR) is one of the complications of malaria in pregnancy, which can result in preterm birth and low birth weight. As reported, the malaria symptoms are related to the infected erythrocytes rupture and the malaria toxins releasing, and that will stimulate the peripheral blood mononuclear cells and the cytokines releasing [18].

The exact biology of malaria parasite in human hosts is likely relatively similar, with the main differences being attributable to the human immune response, the number of previous infections, and the exposure profile [19-24]. The symptoms of malaria infection coincide with the first erythrocyte Schizont rupture and release of Merozoites into the peripheral circulation. As the parasites proceed through their asexual life cycle stages the level of parasitemia correlates to the level of human response which include fever, C-reactive protein, and tumor necrosis factor α (TNF-α) [25].

During the early infection, release of TNF-α is triggered by macrophages phagocytosing Merozoites, ruptured Schizonts, or antigen-presenting trophozoites in the blood or spleen [2-27]. This cytokine, together with others in a cascade, are responsible for fever during malaria infection. Interleukin 10 (IL-10) and interferon γ (IFN-γ) are confirmed that have the dangerous role in the primary malaria pathogenicity [28-33]. Previous reports documented that the disease severity depends upon the balance between the pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors, and effector molecules [34-35]. The high levels of IL-1B, IL-6, IL-8, and TNF-alpha, also the low IL-10: TNF-alpha ratio have been stated in late-onset severe illness. However, the cytokinesis role is still not completely understood [17].

In successive infections, part of the antibody created by the earlier immune system’s macrophage–T-cell–B-cell axis grants increased macrophage activity, resulting in more efficient parasite clearance and the creation of new antibodies [30,24,36]. Additional antibodies form as the human host immune system works its way through the constantly presented parasite protein repertoire, providing additional protection [37].

The parasite can evade the immune system of human host because for most of its human life cycle it inhabits the liver and blood cells and is relatively invisible to the immune surveillance. The spleen, on the other hand, destroys circulating infected blood cells. To avoid this fate, the P. falciparum parasite produces adhesives proteins on the surface of the infected blood cells, which cause the blood cells adhering to the walls of small blood arteries, effectively blocking the parasite’s passage through the general circulation and spleen [38-39]. Sequestered of infected erythrocytes cross the blood–brain barrier with immune cells infiltration causing cerebral malaria [40-41].

4. THE SPLEEN IN MALARIA INFECTION

The splenic mononuclear phagocytic system is highly phagocytic and capable of removing parasitized red blood cells (pRBC), are one of the first lines of defense against the blood-stage malaria infection [42-43]. Splenic marginal zones also include innate immune cells including marginal zone macrophages (MZM), marginal metalphilic macrophages (MMM), and migrating dendritic cells (DC), which are specially positioned to destroy (PRBCs). The marginal zone macrophages (MZM) and the marginal metalphilic macrophages (MMM), also are important for the blood-borne particles and certain infections clearance [44-46]. The marginal zones’ position also makes them a favorable habitat for malaria antigens to be captured by antigen-presenting DC, which then migrate into the T-cell regions [47-49].

Malaria parasite infections cause a dramatic, variable, splenic response, which is primarily defined by Splenomegaly (Fig. 1). In fact, the size of spleen has been used to estimate the severity of malaria transmission in endemic areas [50-51], studies on animal also showed the association between spleen enlargement and the severity of anemia complicating malaria [52]. The spleen is the key organ involved in the establishment of the immune response and the clearance of pRBCs during the erythrocytic phases of malaria infection [53]. Parasites, on the other hand, counterattack by creating persistent infections by evading and modulating the immune response as well as remodeling the spleen, resulting in occasionally unbalanced
immunological responses that can lead to serious disease [54].

Erythrocyte deformability was discovered to be crucial for their elimination in sinusoidal spleen, such as human and rat spleen. Early studies on Plasmodium berghei-infected rats revealed that splenic trapping of infected and heat-induced abnormal erythrocytes was impaired during precrisis, a period marked by splenomegaly, decreased cordal blood flow, and extramedullary erythropoiesis, but that was restored before the onset of crisis, a period marked by massive destruction of PRBCs [46, 43].

During precrisis, two defense mechanisms might work together: The constriction of the cords by erythroid precursors may cause the circulation to close, and the production of soluble substances by cordal macrophages may slow the parasite's intracellular development [56]. The changed characteristics of erythrocytes are a primary determinant of their entrapment and evacuation by the spleen during the crisis phase [57]. Research on microcirculation and splenic function during acute falciparum malaria indicated that patients with splenomegaly expedited clearance of radioactively labelled erythrocytes more than malaria patients with normal spleen sizes [58-59] [57]. Patients with normal spleen sizes, on the other hand, had a faster clearance of radio-labelled erythrocytes after antimalarial treatment. These findings indicated that splenomegaly in sinusual spleens impacts blood microcirculation and, as a result, the organ's filtering function. It's still unclear whether improved splenic function has any clinical benefits for people with Plasmodium falciparum or other parasites [46].

![Fig. 1. Malaria Splenomegaly, the parasite spread within blood encourages the RBC lysis and the gathering of the toxic by-products. The greater haemolysis, the RBC clearance, the red pulp macrophage activation, the inflammation and oxidative damages lead to the splenomegaly in the malaria infected human body [55]](image)

5. THE LIVER IN MALARIA INFECTION

The liver is well-known as the organ that is absolutely necessary for the intra-hepatocyte development of the Plasmodium pre-erythrocytic stages. Furthermore, it has an important role in the host's defense against the malaria parasite's blood stages, which cause morbidity and
mortality [60]. The liver does, in fact, have its own immune system that operates locally but has a systemic impact. It recognizes and generates effective immune-reactivity against infections, while on the other hand, it generates tolerance to prevent the immune-reactivity with “self” and harmless substances such as food components [61].

Malaria Sporozoites are transferred to the liver via the circulation, where they infect hepatic stellate cells (HCs) and multiply asexually [62]. Although the parasites’ pre-erythrocytic development in the liver is clinically asymptomatic, it is not avoidable by the liver’s intrinsic immune system [63]. Merozoites are then released from HCs and penetrate erythrocytes, for asexual multiplication, which is linked to malaria morbidity and mortality [60].

The formation of autoimmunity in humans is linked to the acquisition of natural immunity against blood-stage malaria [64]. Previous research has revealed that autoimmunity plays a significant regulatory function in malaria protection [65-66]. Accordingly, autoantibodies and sera from patients with a variety of autoimmune diseases, but not malaria, have been observed to suppress the growth of P. falciparum in human RBCs in vitro [67-68]. Then noticed autoimmunity, which is apparently focused on the auto-antigens and on the parasite-induced neo-auto-antigens that found on the Plasmodium-infected RBCs surface, is seemingly important for the protection against the malaria blood-stage [69].

Abo et al. [70] stated that the autoimmunity development in the liver and the low-level of autoimmune improvement may be the most important factor of the protective immunity against the malaria stages in the blood.

Liver injury can be induced by direct parasite effect. Moreover, indirect liver injury may be induced through the infection-induced overreactions of the liver-innate immune system as, e.g., oxidative stress increasing that is induced by ROS/RNS and happened during the phagocytic the kupffer cells activity, the production of pro-inflammatory cytokines, the perforin release, the large granular lymphocytes granzymes, and lysosomal enzymes, the autoreactive cytotoxic T cells and the “bystander killing” of liver cells due to cell-mediated cytotoxicity are increased [71]. Furthermore, the hepatic natural killer T cells (NKT) that stimulated during the malaria erythrocytic stage through the IL-12 produced from the KCs and can encourage the hepatotoxicity [72-73].

Even apparent “non-immune” mechanism causing liver destruction, such as the nearly doubling of ammonia level in blood plasma reported at peak parasitemia during deadly P. chabaudi malaria, is very certainly immune-mediated [74]. The presence of elevated systemic ammonia indicates serious local hepatic impairment. Indeed, the liver’s metabolism, particularly its detoxification ability, is disrupted, as demonstrated by large down-regulations of genes encoding enzymes involved in phase I–III metabolism [74].

During the liver stage, The hepatocytes are generally secured from the apoptotic development, permitting the merozoites to be free in the blood circulation, that suggests the malaria sporozoites can stop the pro-apoptotic pathways [75-76].

On other point, the malaria’s blood stages cause severe damage in the liver. When the humans are infected with Plasmodium falciparum or Plasmodium vivax, it was proven that the hepatic dysfunctions and malarial hepatitis are demonstrated [77]. Malaria patients had elevated liver transaminases, alkaline phosphatase, and hyperbilirubinemia [78]. Clinical jaundice in malaria patients infection can be induced by several causes i.e. intravascular hemolysis from (PRBCs), Glucose-6-phosphate dehydrogenase deficiency-related hemolysis or anti-malarial medications, disseminated intravascular coagulation (DIC) or co-existing septicemia-induced hepatitis [79].

The liver histology in severe malaria has previously been studied. Among the most common features was hyperplastic Kupffer cells [80-82,78] fatty change [83,78] portal tract inflammation [84-85] cholestasis [86-87,78, 88], liver cell necrosis [80,89], sequestration of PRBCs and the deposition of haemozoin pigments [80,81,82,900]. Moreover, Viriyavejakul et al confirmed that the existence of profuse chronic inflammatory cell infiltration in the liver tissue and the absence of liver cell necrosis [78]. Cellular infiltration of the portal tract consists mainly of lymphocytes and a few plasma cells [81]. Sequestration of PRBCs is a common feature and depends on malaria parasite load [78]. All these complications can lead significantly to hepatic failure [88].
6. USING ANIMAL MODELS AND RODENT STRAINS TO STUDY PLASMODIUM PATHOGENESIS

Plasmodium species, due to their complicated life cycles, have evolved diverse and redundant mechanisms to deflect and dodge the host immune response, therefore protection is unlikely to be linked to the ability to recognize and neutralize a particular antigen [91].

While research into the clinical characterization and histology of malaria has shown some information regarding the pathogenesis, the actual mechanisms by which malaria parasites produce severe disease and how immunity defends against infection remain unknown. Studies in animal models can reveal details about the processes of severe malaria infection and human defense mechanisms, and there are good examples of how they've revealed details about the characteristics of human malaria infection. Although no one model will be able to reproduce the complexity and spectrum of disease and immunity seen in the human malaria infections, there are some similarities between the human and animal malaria infections and disease [92].

Overall, experimental animals are valuable to study mechanisms of disease and possible development of infection, since clinical studies include limitations like ethical issues and the need of invasion systems, animal models have to be considered as a further strength to bring developments in our understanding knowledge of human infection [93-94].

The high similarities in the Plasmodium species that responsible of causing human malaria, the Plasmodium berghei is considered as the best model species for the researches inhuman's malaria. P. berghei has a life cycle that is extremely similar to that of the species that infect humans, and it infects mice with symptoms that are comparable to those seen in human malaria. Importantly, P. berghei is easier to genetically alter than the Plasmodium species that infect humans, making it a good model for Plasmodium genetics study [93-95].

The P. berghei pathology in mice varies from that happened by P. falciparum in people in many parts, while the red blood corpuscles accumulation in the brain blood arteries is the greatest cause of human's mortality with P. falciparum, although this is still unknown to what extent that occurs in the infected mice with P. berghei. Instead, mice infected with P. berghei have an accumulation of immune cells in their cerebral blood vessels. This raised a question about the use of P. berghei infections in mice as a good model of cerebral malaria in humans or not [92].

There are different factors affect the malaria development in the animal model, the greatest important in them is the strain of mice used under study. However, little is known about the performance of different mouse strains when they are utilized to generate malaria rodent models. The inbred C57BL/6 and BALB/c mouse strains, as well as the outbred KM and ICR mouse strains, are commonly used in malaria research [96,43]. Furthermore, detailed characterization of P. berghei infection in the Swiss Webster mouse was done by Jerusalem and Desowitz in their early studies [97-98].

Plasmodium bergheiANKA (pbA) strain represents the well-characterised animal model to investigate cerebral malaria (CM) [99] the infected mice developed a lethal neurological syndrome 6–12 days after infection in 50–100% of all infected mice [99-100]. Despite the significant progress has been achieved regarding the use of animal models in malaria in the study of different aspect, there is still a long way to go before a thorough knowledge of cerebral malaria pathogenesis is achieved and potentially transferred to the human situation, allowing the development of more efficient preventative, curative, or adjunctive therapies. A significant challenge resides in that the ultimate outcome being affected by factors related to the host, the parasite and the environment [101-104].

Wang et al. studied four types of mice strains after infection with P. berghei K173. He used the ICR, BALB/c, KM and C57BL/6 mice strains. The survival time of the mice strains after infection with P. berghei K173 was investigated. Although infection was always fatal, mice infected with P. berghei K173 had a wide range of survival times. While the onset time of BALB/c mice was earlier than that of KM mice, the survival time of BALB/c mice was slightly similar to that of KM mice. The lethal parasitaemia of KM mice was 65%, while the lethal parasitaemia of other strains was over 80%. The growth rate of C57BL/6 mice was slower than that of other strains, and the survival period was longer than that of other strains [43].
Histopathological changes in mice with cerebral malaria (CM) includes micro-hemorrhages and vessel obstruction mostly by activated monocytes [100] and less prominently, *Plasmodium* infected RBCs [105-106], supported these results and he also confirmed that the brain in the malaria infected Swiss Webster mice with clinical CM presented the alterations characteristic of CM, particularly micro- and perivascular hemorrhages particularly in the cerebellum cerebral malaria. Moreover, large subarachnoid and cerebellar hemorrhages were also recognized. Both pigmented and non-pigmented mononuclear cells were recognized in brain vessels contained. The majority of these mononuclear cells were monocytes containing malaria pigment in their cytoplasm. These monocytes were stimulated and demonstrated adhesion to each other, the endothelium, and erythrocytes. Lymphocytes, including activated and proliferating cells, were identified in the brain arteries [107].

7. PATHOGENICITY OF *PLASMODIUM BERGHEI* IN MICE LIVER AND SPLEEN

In addition to affecting the central nervous system, *Plasmodium berghei* infection in the Swiss Webster mouse causes systemic damage, affecting numerous organs including the liver and lymphoid organs, same as it does in humans [108,107].

Mice with clinical CM showed enlarged liver loaded with malaria pigment. In infected Swiss Webster mice, the sinusoids showed adhesion of activated monocytes to the endothelium, lymphocytes and erythroid cells forming cell clusters. The activated monocytes were loaded with pigment. The large liver vessels presented similar finding where it contained many clusters of adherent pigment-containing mononuclear cells. Kupffer cells were hypertrophic and saturated with malarial pigment. Hepatocyte vacuolization, which was more intense in Swiss Webster mouse, was a common finding, particularly near the central-lobular vein, the radial arrangement of hepatocytes disrupted and loos normal characteristic. In the sinusoids, megakaryocytes were occasionally identified [109-111]. Late in the course of PbA infection in Balb/c mice that did not develop conventional CM, metabolic alterations suggestive of hepatic encephalopathy were also observed [112]. Infected liver of Swiss albino mice showed hepatic centrilobular vacuolation and vascular congestion indicative of hepatic necrosis [13].

Splenomegaly is one of the characteristic manifestations of malaria during acute attacks, and the severity of splenomegaly often affects the host's capacity to develop a successful response to the parasite [114,43]). The spleen shows structural changes and re-modelling in addition to an increase in organ volume and mass. Expansion of the red pulp, transient loss of the marginal zone (MZ), increased vasculature, and activation of barrier cells may result in the formation of a blood-spleen barrier, altering splenic blood circulation dramatically [115,110,116]. The spleen showed dilatation and cytoadherence in the arteries, primarily of monocytes carrying malaria pigments [117]. CBA mice had previously been shown to have extensive changes in lymphoid organs, such as disturbances in germinal center architecture in the mice’s spleen [118-119].

Furthermore, significant increase in spleen size due to an overall enlargement of the red and white pulp of infected mice. The white pulp of infected mice showed a lack of the usual architecture of germinal centers (GC), resulting in a disordered appearance with no apparent boundaries between dark and light zones. The germinal centers (GCs) that were disorganized showed high centroblast activation and proliferation with limited centrocytic transformation, multiple phagocytic-centres with apoptotic bodies, centripetal penetration of tiny lymphocytes from the periphery, and several perifollicular mitosis. The mantle and MZ disappeared, blurring the lines between the B-cell follicles and the red pulp. According to Lennert's morphological properties, centroblasts and centrocytes were considered [120,46,43].

On days 6–9 after infection, CBA and Swiss Webster mice had an increased number of immunoblasts (activated T cells) and strong plasmacytogenesis in the T-cell region, particularly in the Swiss Webster stock. Malaria pigment was also found in abundance in infected mice's red pulp, primarily within macrophages, and to a lesser level in the MZ. The red pulp was also hypertrophic and contained a wide range of cells, primarily blood cell precursors such as erythroblasts in various stages of maturation, monoblasts, promonocytes, and megakaryocytes, with zones of intense erythropoiesis and foci of monocytopenesis close
to septae distinguishing zones of intense erythropoiesis and foci of monocytopenesis [121].

The spleen contained apoptotic lymphocytes with stained macrophages in the germinal centers. Individual lymphocytes shrink, nuclear chromatin condenses, and apoptotic cells fragment into membrane-bound entities, all of which are signs of apoptosis (apoptotic bodies, which are subsequently phagocytized by macrophages (tangible body macrophages) [121]. All of the infected groups had a lot of megakaryocytes and other haemopoietic precursor cells in their red pulp. During haematopoiesis, a megakaryoblast is a progenitor cell to a megakaryocyte. Extramedullary haemopoiesis, as noticed in the liver, is showed by the occurrence of haemopoietic precursor cells in the spleen. The production and growth of blood cells outside the medullary compartments of the bone marrow is known as extramedullary hematopoiesis [122]. Lymphocytic hyperplasia, hematomas, and thrombosis are the most common degenerative and inflammatory disorders that affect the spleen [123, 89]. Yin et al. [124-126] found that giving dogs Six mg kgartemether intramuscularly for three months caused concurrent extramedullary hematopoiesis in the spleen and suppression of erythropoiesis in the bone marrow. After the healing period, however, remnants of hemozoin pigments were found in the splenic sinusoids [127].

8. CONCLUSION

Malaria remains one of the most serious infectious diseases, it threatens nearly half of the world’s population and led to hundreds of thousands of deaths, predominantly among children in Africa, Plasmodium spp. parasites are the causative agents of malaria in humans and animals, and they are exceptionally diverse in their morphology and life cycles, this diversity provides exceptional adaptability and poses a major assistant for developing effective strategies in pathogenicity in hosts organs including spleen and liver. Because there are parallels between some human and animal presentations of malaria infection and disease, it became clear that animal models allow for more detailed examination of multiple and specific pathophysiological processes caused by malaria infection that is not possible for clinical studies of human malaria through the level and scope of experimental observation and intervention that can be applied to animals. Although there have been of significant pathological effects during malaria in spleen and liver as highlighted in this review, there are still many areas to investigate to further understand pathology associated with malaria during infection and give us the full dynamic view of the role of the spleen and liver in pathological conditions caused by Malaria. In addition, these information in turn should help in the design of novel approaches in malaria drug and vaccine development.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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