The Role of Aryl Hydrocarbon Receptor in Malaria Immunity During Adulthood, Childhood and Pregnancy: A review article

Abstract

Malaria is most prevalent parasitic disease , it caused by coccidian parasite of the genus plasmodium , four species are usually infect human beings, P. falciparum, P. vivax, P. malriae and P. ovale, Most of malaria cases resulted from P. falciparum and P. vivax. Aryl hydrocarbon receptor (AHR) is an environmental sensor exists in many parts of human body such as lung , spleen , gut and breast . In this review we discussed the functions of it as regulator for proinflammatory and anti-inflammatory cytokines , the possible role of diet during pregnancy and breastfeeding in boosting immunity against malaria during pregnancy and childhood by triggering AHR. Also we hypothesize that probable role of it in synchronizing erythrocytic schizogongy. Experimental studies recommended to know more about the biological protective functions of AHR.

Keywords: Malaria parasite, Aryl hydrocarbon receptor , Breastfeeding, Circadian rhythm of erythrocytic schizogongy, Immunity

Background:

Malaria is a protozoan parasitic infection caused by one or more of the identified species of plasmodium which infect humanbeings (Plasmodium vivax, Plasmodium ovale , Plasmodium ovale curtisi, Plasmodium malariae, and Plasmodium knowlesi).

It stills a disturbing worldwide health disaster. Internationally, an expected 300-500 million people infected with malaria annually, resulting in 1.5-2.7 million deaths every year. Because of the increase in the global move to and immigration of people from malaria endemic areas, the rate of imported cases of malaria in developed countries has raised. Approximately 10,000-30,000 travellers from industrial countries are likely to contract malaria yearly. Also, drug-resistant Plasmodium falciparum malaria exists to expand and now involves about all regions of the globe. An increasing number of travellers exposed to drug-resistant plasmodia .Malaria presents a wide range of systemic clinical consequences and many life threatening organ pathologies, including the fatal cerebral malaria. Comparable to other infectious diseases, it is an inflammatory reaction-induced disease, and positive results to

infection depend on fine tuned regulation of immune responses that capably eliminate plasmodia and allow protective immunity build up[1].

Aryl hydrocarbon receptor (AHR) is a member of the periodic circadian protein (PER)–AHR nuclear translocator (ARNT)–single-minded protein (SIM) superfamily of transcription factors, where the PER–ARNT–SIM (PAS) domain senses evenly endogenous factors and exogenous factors . It , and other members of the PAS superfamily that alarmed in monitoring oxygen concentrations, redox potential and alterations in the circadian rhythm, regulate adaptation to the cellular setting. It, for adjusts biological activities that are extremely related to tissue homeostasis and to the progress of pathological states ranging as inflammation [2]. It is widely expressed in the body and in particular in the immune system. It is greatly signified in spleen , lymph nodes, lung , gut skin and breast to face pathogens at the these vital organs ,in keeping with its main role as an environmental sensor [**figure:1**]. It is greatly expressed in Th17 cells, not noticeable in Th1 and Th2 cells, and slightly expressed in regulatory T cells (Tregs) [3].
The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that activated by small molecules provided by the diet, microorganisms, metabolism and pollutants [4]. Moreover, it reported that the AHR pathway involved in maintaining a balance between promoting and preventing oxidative stress [5].

Discussion:

Study done by Brant F et al showed that AhR-knockout (KO) mice infected with *P. berghei* Anka displayed augmented parasitemia, earlier death, promoted leukocyte-endothelial cell interactions in the brain microvasculature, and raised inflammation in brain (interleukin-17 [IL-17] and IL-6) and liver (gamma interferon [IFN-γ] and tumor necrosis factor alpha [TNF-α]) in comparison to infected wild-type (WT) mice [6].
AHR-ligation did not just reduce the number of Th17 cells but moreover prepared naïve CD4(+) T cells to release IL-22 without IL-17 and IFN-gamma [7].
Th17 mainly take part to inflammation by recruitment of neutrophils and induction of secretion of many pro-inflammatory mediators, counting IL-6, IL-1,), chemokines, tumor necrosis factor α (TNF-α) and metalloproteinases .It produces IL-17, IL-17F, and IL-22, so inducing a massive tissue reaction due to the wide allocation of the IL-17 and IL-22 receptors [8].
Study done by Bueno LL et al showed that malaria-infected people present a noteworthy raise of IL-17-producing $CD4^+$ T cells in peripheral blood, which accompanied with creation of IFN-γ, IL-10 and TGF-β [9]. IL-22 is a member of the IL-10 cytokine family, which recognized highly significant in immune regulation.
A firm regulation between the pro– and anti–inflammatory immune responses throughout plasmodial infection is of critical significance, as a disturbance guides to severe malaria pathology [10].

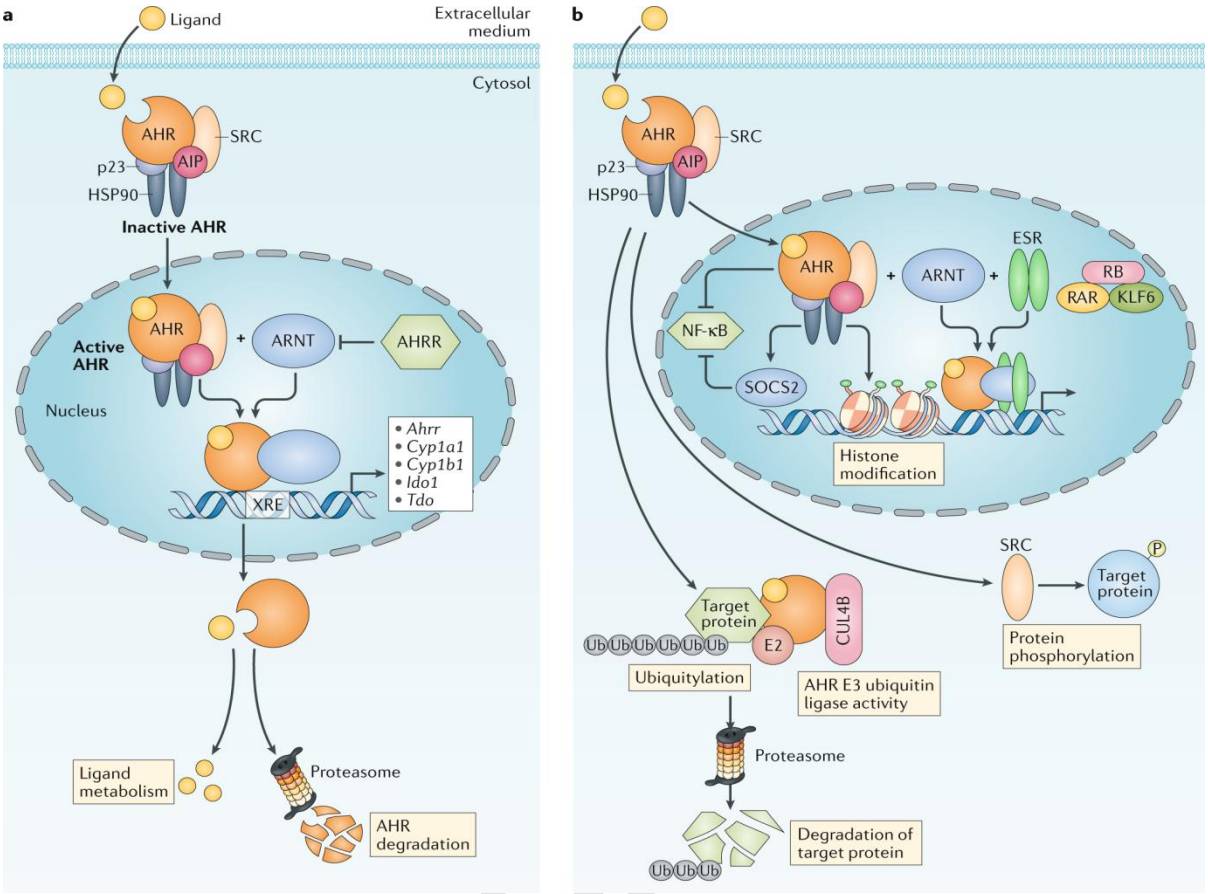

Figure (1): Shows Environmental sensor , Aryl hydrocarbon receptor.

Current work demonstrates that daily rhythms also allow parasites to maximise fitness in the context of environmental interactions with their hosts [11]. Genetic depletion of AhR promoted behavioural responses to alterations in the light-dark cycle, raised rhythmic amplitude of circadian clock genes in the liver, and distorted rhythms of glucose and insulin [12].

The functional human hematopoietic progenitor cells express the aryl hydrocarbon receptor, and that stimulation of this receptor in hematopoietic progenitor cells forces extension of the progenitor cells, along with megakaryocyte- and erythroid-lineage cells, proposes that [aryl hydrocarbon receptor] has a very significant biological role in how blood cells form in the human body [13].

Study done by Brazeau NF et al showed that exclusive breastfeeding (EBF) accompanied with a low risk of clinical malaria between 6 months aged children in Congo republic , signifying a defensive influence of EBF against malaria [14]. Study done by showed taking a diet rich in the aryl hydrocarbon receptor (AHR) ligand indole-3-carbinole (I3C), or of breast milk, triggers AHR [15] and we hypothesized that activation of aryl hydrocarbon receptors decrease malaria mortality among infants.

Conclusion:

We conclude that aryl hydrocarbon receptor play important role in malaria immunity during adulthood and childhood periods. It decreases level of proinflammatory

cytokines by influencing number of Th17 cells and maintenance of tight balance between proinflammatory and anti-inflammatory cytokines . Diet throughout the pregnancy and breastfeeding after delivery activate aryl hydrocarbon receptors and offer protection against malaria infection to the pregnant women, foetuses and infants. Furthermore we hypothesized that synchronized erythrocytic schizogongy controlled by aryl hydrocarbon receptor(AHR). Experimental studies required to know more about the biological roles of ARH in malaria immunity.

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