*International Journal of Biomedical Research*

ISSN: 0976-9633 (Online)
Journal DOI:10.7439/ijbr
CODEN:IJBRFA

## Review Article

# Protective Function of Intermediate T Cells against Malaria Infection in Mice with Different Genetic Background

**Hanaa Y. Bakir*** and Amal M. Elmatary

*Department of Parasitology, Faculty of Medicine, Assiut University, Egypt*

***Correspondence Info:**
Dr. Hanaa Bakir,
Department of Parasitology,
Faculty of Medicine, Assiut University, Egypt
E-mail:hanaabakeer@yahoo.com

**Abstract**

This review proposed the possibility that malaria protection might be achieved through intermediate T cells, which is one of the constituents of innate immunity. Intermediate T cells here in have been assessed to represent the flexibility of the immune system with the alteration of genetic background in different mice groups during malaria infection. Intermediate T cells are unique subset of unconventional lymphocytes that express an intermediate (int) density of T Cell Receptor-CD3 (TCR-CD3) complex on its surface (i.e. $TCR^{int}$ cells), which distinguishes them from conventional T cells (thymus-derived T cells or $TCR^{high}$ cells). $TCR^{int}$ cells comprise from two subsets with a distinct phenotype Natural killer (NK) $1.1^{+}$ subset (NKT cells) and $NK1.1^{-}$ subset. The protective function of $TCR^{int}$ cells was challenged by infecting mice from different genetic background with malaria. There was a prominent expansion of intermediate T cells in the liver of the mice even the genetically deficient one, which is characteristic of an innate immune response. In parallel with such expansion, no expansion is seen in conventional T cells due to severe thymic atrophy. Thus, intermediate T cells are emerging as an important subset of lymphocytes; with a protective role that is modulated according to the genetic background of the mice. Added to that establishment of an effective immune defense network to modulate the reciprocal regulation between conventional and unconventional T cells.
**Keywords:** Malaria, Mice, and Intermediate T cells

## 1. Introduction

Malaria remains an important cause of morbidity and mortality. Approximately 207 million malaria cases and 627 000 malaria-related deaths were reported globally in 2012. The greatest toll is exacted in sub-Saharan Africa, where over 80% of all malaria episodes and 90% of all malaria-related deaths occur. The huge malaria burden in sub-Saharan Africa has been partly attributed to the presence of efficient vectors that maintain high levels of transmission[1, 2]. Malaria life cycle involves two hosts, the insect vector and the intermediate mammalian host. During its complex, multi-stage life cycle, the malaria parasite not only expresses a great variety of proteins at different stages, but these proteins also keep changing. As a result, a natural infection with malaria parasites leads only to a partial and short-lived immunity that is unable to protect the individual against a new infection[3].

Although the advent of DDT and chloroquine led to the belief that eradication was possible, the spread of parasites and insects resistant to the drugs and insecticides has led to a resurgence of the parasite in economically disadvantaged countries[4]. This worsening situation has called for the development of new control measures, of which vaccines have been a priority since the late 1970s. However, the complex interplay of parasite proteins with the immune system of the host has also made it difficult or even impossible to develop an effective vaccine against the disease. Up to now, no vaccine formulation with sufficient efficacy against malaria parasite has been developed[5]. Reasons for these failures are mostly due to the complexity of the malaria parasite.

## 2. Natural or innate immunity against malaria

Innateimmunity against malaria is an inherent refractoriness of the host that prevents the establishment of the infection or an immediate inhibitory response against the introduction of the parasite. The innate immunity is naturally present in the host and is not dependent on any previous infection[6, 7]. Acute malarial infection induces immediate, non-specific immune response that tends to limit the progression of disease. The humoral and cellular mechanisms of this 'nonspecific' defense are poorly defined. Extrathymic T Cells and autoantibody producing B-1 cells have been considered as the prime movers of this response. Natural killer (NK) cells are found in blood, in secondary lymphoid organs as well as in peripheral non-lymphoid tissues. Related cell types, probably playing a role in innate malaria immunity, are the Natural killer T (NKT) cells in the mice carry both the NK1.1 surface marker and T cell receptors (TCR)[8]. NK cells have been shown to increase in numbers and to be able to lyse *P. falciparum*-infected erythrocytes in vitro. NK cells in peripheral blood produce interferon-gamma in response to *Plasmodium* infected erythrocytes, leading to parasiticidal macrophage activation. This may be of greater importance for innate malaria immunity than their potential to lyse infected host erythrocytes[8, 9].

Cells of innate immunity are also important in the initiation and development of adaptive immune responses. NK cells induce the production of the pro-inflammatory chemokine Interleukin-8, which in turn plays its role in the recruitment and the activation of other cells during malaria infection. Dendritic cells, macrophages, gamma delta T cells and NKT cells also sense the presence of the parasite and participate in the immune response[10]. NKT cells are potent inhibitors of liver stage parasite replication in mouse malaria systems in vitro. Malaria infection gives rise to strongly elevated blood concentrations of non-malaria-specific immunoglobulin, but the importance of the underlying polyclonal B-cell activation for innate immunity is not known[10-12].

## 3. Generation and differentiation of intermediate T Cell Receptor ($TCR^{int}$) cells

It is well established that the thymus is an essential organ for the support of T-cell differentiation. However, some T cells termed extrathymic T cells have been found to differentiate without such support by the thymus. The major sites of these T cells are the liver and intestine. The liver has been found to be one of the important hematopoietic organs even after birth[13]. Namely, adult liver still comprises c-$kit^{+}$ stem cells and gives rise to extrathymic T cells, NK cells, and even granulocytes. Extrathymic T cells generated in the liver of mice are $TCR^{int}$ cells. Abo et al[14]have revealed that the subsets of $TCR^{int}$ cells comprise cells with a distinct phenotype. The interleukin 2 Receptor(IL-2$\beta^{+}$ $NK1.1^{+}$ subset consists mainly of double- negative (DN)$CD4^{-}8^{-}$ cells and

$CD4^+$ cells, whereas the IL-$2R\beta^+NK1.1^-$ subset consists mainly of $CD8^+$ cells[15]. All T cells in congenitally athymic nude mice (mice without thymus) are $TCR^{int}$ cells; it is obvious that $TCR^{int}$ cells are generated extrathymically[16,17].

In parallel with the extrathymic pathway in the liver, $TCR^{int}$ cells are also generated through an alternative intrathymic pathway[14]. Although a few $TCR^{int}$ cells are dispersely present in the cortex region, the majority of these T cells exist in the medullary region[18]. In contrast, the mainstream of T-cell differentiation for the generation of conventional T cells occurs in the cortex region. Similar to the case of extrathymic T cells in the liver, $TCR^{int}$ cells in thymus are generated into three subsets, i.e. (DN) $CD4^-8^-$, $CD4^+$, and $CD8^+$.[19]

Although intermediate T cells are few in number in youth, they gradually increase in number with aging. Even in youth, the number and function of intermediate T cells are elevated under conditions of stress, infection, malignancy, pregnancy, autoimmune disease, chronic graft-versus-host diseases, etc. Under these conditions, the mainstream of T-cell differentiation in the thymus, which produces conventional T cells, is rather suppressed. Therefore, reciprocal regulation between extrathymic T cells and thymus-derived T cells might be present[8,14].

**3.1 Characteristics of intermediate T cells**

Intermediate T cells are intimately associated with innate immunity. Although intermediate T cells have slightly distinct properties depending on the sites, they consistently express IL-2R β chain on the surface[16]. Similar to the case of NK cells, intermediate T cells have the IL-$2R\alpha^-\beta^+$ phenotype i.e. an intermediate affinity IL-2R. In contrast, conventional T cells have the IL-$2R\alpha^-\beta^-$phenotype under resting conditions but have the IL-$2R\alpha^+\beta^+$ phenotype i.e. a high affinity IL-2R under activated conditions. In other words, NK cells and extrathymic T cells consistently express intermediate affinity IL-2R under usual conditions[15]. Reflecting this situation, NK cells and extrathymic T cells respond quickly to corresponding antigens. It is speculated that conventional T cells acquired a resting state in phylogenic development but NK cells and extrathymic T cells did not yet. This situation indicated that more primitive lymphocytes respond more quickly (NK cells > $TCR^{int}$ cells > $TCR^{high}$ cells) [20]. Among these, however, the magnitude of response is the greatest in $TCR^{high}$ cells.

Both NK cells and intermediate T cells are granular lymphocytes in morphology[21]. In case of intermediate T cells in the liver, they have an intermediate density of TCR-CD3 complex on the surface. On the other hand, conventional T cells are estimated to be $TCR^{high}$ cells[22]. Watanabe et al[15] identified $TCR^{int}$ cells in mice by applying two-color staining for CD3 and IL-2Rβ, they demonstrated that NK cells were identified as IL-$2R\beta^+CD3^-$, $TCR^{int}$cells as IL-2Rβ+$CD3^{int}$, and conventional T cells as IL-$2R\beta^-CD3^{high}$. In other words, both NK cells and $TCR^{int}$cells consistently express IL-2Rβ, while conventional T cells lack the expression of IL-2Rβ.

**3.2 Role of intermediate T cells in protecting the body from plasmodium**

The body seems to be protected against malaria by innate immunity. This concept supported by the fact that malarial infection induces a prominent expansion of intermediate T cells (IL-$2R\beta^+TCR^{int}$cells) in the liver. No expansion is seen in conventional T cells (IL-2R $\beta^-TCR^{high}$cells) [8]. When $TCR^{int}$ cells isolated from the liver of mice that had recovered from malarial infection were injected into irradiated recipient mice, these mice could survive malaria without parasitemia[23]. Malaria infection is accompanied by severe thymic atrophy and the proportion of $TCR^{high}$ cells rather decreases in the periphery. Indeed, there is no protective effect of $TCR^{high}$ cells when these T cells isolated from mice recovered from malaria are injected into irradiated mice[23, 24].In addition to the activation of intermediate T cells in the liver of mice with malarial infection, we found that the production of autoantibodies such as anti-DNA antibody is seen in the sera of these mice[8,25]. In other words, many signs during malarial infection mimic those seen in autoimmune diseases. These results also support our observation that the body is protected against malaria by innate immunity. Since severe inflammation associated with expansion of intermediate cells occurred in the liver during malarial infection, therefore production of cytokine was examined in the sera of the mice in terms of IL-4 and Interferon γ (IFNγ[8, 26]. Both IL-4 and IFNγ were detected in the acute phase, but only IL-4 was detected thereafter. This profile indicated a Th0 type in the early phase of malarial infection and a Th2 type in the late phase.

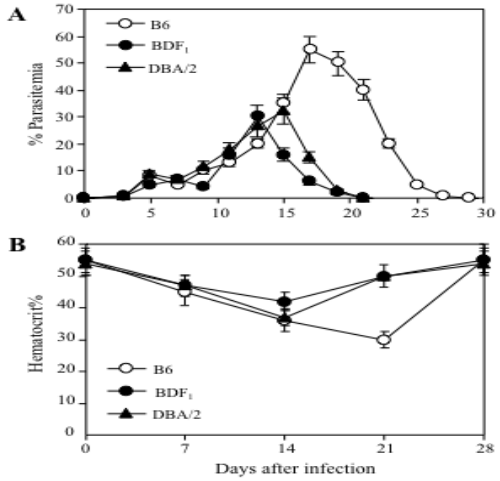
## 4. Immune response of mice with different genetic background to malaria infection

Resistance and susceptibility to malarial infection and other infections are known to be modulated by genetic background[27-29].

**4.1C57BL/6 (B6), $BDF_1$, and DBA/2 mice**

DBA/2 mice ($H\text{-}2^d$) are resistant to non-lethal *Plasmodium (P.) yoelii17XNL* infection and lethal strain *P. yoelii17XL*, but inversely sensitive to a lethal strain of *P. yoelii YM*[30, 31].However, this is a very strange phenomenon because many functions of conventional T cells, especially $CD8^+$ cytotoxic T-cell in DBA/2 mice are rather defective as compared with the case of other strains of mice[24,32].In our previous study[25,33], we investigated how intermediate T cells in the liver are modulated by malarial infection in mice with different genetic background. To precisely determine the genetic background, we used three types of mice C57BL/6 (B6) mice ($H\text{-}2^b$), (B6×DBA/2) $F_1$ ($BDF_1$,$H\text{-}2^{b/d}$) and DBA/2 mice ($H\text{-}2^d$). These mice groups were infected with a non-lethal strain of *P. yoelii* and compared in terms of parasitaemia (Fig. 1a). DBA/2, $BDF_1$ mice recovered from malaria more quickly than B6 mice, and showing a low degree and short duration of parasitaemia ($P < 0.05$). The hematocrit percentage was also compared among the three strains (Fig. 1b). The decrease in hematocrit percentage was smaller in DBA/2 and $BDF_1$ mice than in B6 mice ($P < 0.05$).

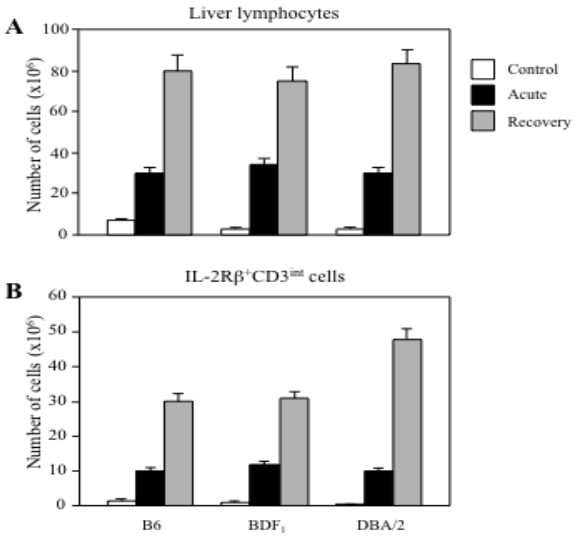
**Fig 1: Resistance of DBA/2 and $BDF_1$ mice to malarial infection.**
**A. Parasitemia, B. Hematocrit.**




The number of lymphocytes yielded by the liver during malarial infection was compared among the three strains (Fig. 2a). As expected, the number of lymphocytes in the liver greatly increased, especially during the recovery phase, in all tested mice ($P < 0.05$). As shown in (Fig. 2a), the acute phase occurred on day 7 in all mice, but the recovery phase occurred on day 20 in DBA/2 and $BDF_1$ mice and on day 28 in B6 mice. Although the recovery phase

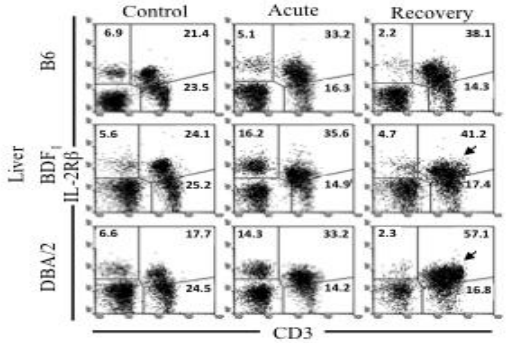
was retarded in B6 mice, the number of lymphocytes was comparable to that found in the other strains of mice. The absolute numbers of IL-2Rβ$^{+}$CD3$^{int}$cells were calculated(Fig. 2b), there were also marked increases in the numbers of IL-2Rβ$^{+}$CD3$^{int}$cells in DBA/2 and BDF$_1$ mice during recovery phase ($P < 0.05$).

**Figure 2.A: Number of lymphocytes yielded by the liver. B6, BDF$_1$ and DBA/2 mice were used for malarial infection. The acute phase was day 7 in all strains, whereas the recovery phase was day 28 in B6 mice and day 20 in DBA/2 and BDF$_1$ mice.*P< 0.05**
**B: Identification of the absolute number of IL-2Rβ$^{+}$CD3$^{int}$ cells. *P< 0.05**



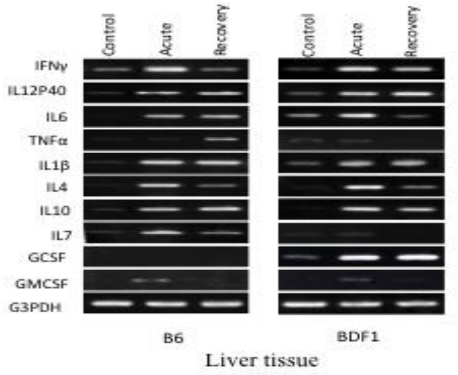

To identify lymphocyte subsets, two-color staining for CD3 and IL-2Rβ was carried out;TCR$^{int}$IL-2Rβ$^{+}$ cells expanded more prominently in DBA/2 and BDF$_1$ mice (H-2$^{d}$ carrying strain) than in control B6 mice (H-2$^{b}$) (indicated by arrows Fig 3).

**Figure 3: Identification of IL-2R□$^{+}$CD3$^{int}$ cells. Two-color staining for CD3 and IL-2Rβ were conducted in the liver. Arrows indicate the expansion of IL-2Rβ$^{+}$CD3$^{int}$ cells. Numbers in the figure represent the percentages of fluorescence-positive cells in the corresponding areas. Representative results of three experiments are depicted.**




The production of various cytokine mRNA during malarial infection was compared between B6 mice and BDF$_1$ mice by Reverse transcription polymerase chain reaction (RT-PCR) (Fig. 4). In addition to IFN-γ and IL-4 mRNAs, the levels of inflammatory cytokine (i.e. IL- 12p40, IL-6, TNF-α, IL-1β and IL-10) mRNAs increased in both B6 mice and BDF$_1$ mice. The most marked difference was in the decrease of TNF-α and IL-7 mRNAs during the recovery phase in BDF$_1$ mice. In contrast, G-CSF mRNA increased in BDF$_1$mice. The level of GM-CSF mRNA was low in both strains of mice.

**Figure 4.Signs of cytokine mRNAs in the liver tissue of B6 and BDF$_1$ mice during malarial infection. Integrity of RNA was confirmed by the sign of G3PDH. Representative results of three experiments are depicted.**




These results suggest that DBA/2 mice, which have poor functions of conventional T cells, show rather strong functions of unconventional T cells. This genetic defect seems to induce a compensatory function of primitive lymphocytes that is important for the acquisition of resistance against malarial infection [25].

**4.2 Athymic nude mice**

Mannoor et al[24] using congenitally athymic nude mice B6-*nu*/*nu* mice carry only $TCR^{int}IL\text{-}2R\beta^{+}$ cells but lack $TCR^{high}IL\text{-}2R\beta^{-}$ cells. The major expanding T cells were $NK1.1^{-}IL\text{-}2R\beta^{+}CD3^{int}$cells when athymic nude mice were infected with malaria and subsequently recovered from it. Moreover, by cell transfer experiments, these $NK1.1^{-}IL\text{-}2R\beta^{+}CD3^{int}$cells were found to have the ability to protect the mice from malaria if such lymphocytes were isolated from the liver of mice that had recovered from malaria. These results suggest that the protection from malarial infection might be consequent of immunological events achieved by intermediate T cells.

**4.3$\beta_2$-microglobulin-deficient ($\beta_2$m (–/–)) mice**

Another study, conducted by Taniguchi et al[34] using $\beta_2$-microglobulin-deficient ($\beta_2$m (–/–)) mice, which lack $CD8^{+}$ cytotoxic T cells and NKT cells. Deficiency of NKT cellsoccur due to the absence of both MHC class I antigens and CD1d antigens (MHC class I-like molecule with $\beta_2$-microglobulin component)[35]. The results showed that $\beta_2$m (–/–) mice showed a level of parasitaemia similar to that of B6 mice and were able to recover from malaria infection. In other words, mice were found to recover from malaria in the absence of $CD8^{+}$T cells and NKT cells. A major expansion of IL-2R□$^{+}TCR^{int}$cells was common in B6 and $\beta_2$m (–/–) mice. These results suggest that there is a compensatory phenomenon in the immunity of $\beta_2$m (–/–) mice.

**4.4 AIM (Apoptosis Inhibitor expressed by Macrophages) deficient mice**

In a recent study, Li *et al*[36] used AIM (Apoptosis Inhibitor expressed by Macrophages) deficient ($AIM^{-/-}$) mice. The AIM is exclusively secreted by tissue macrophages[37]. Endogenous AIM rapidly increases in response to inflammatory stimuli, inhibits apoptosis of thymocytes and induces resistance to apoptosis in various immunocytes such as macrophages (including Kupffer cells) [37,38], natural killer T (NKT) cells, and conventional T cells[39]. In this study, although the peaks of parasitemia in the $AIM^{-/-}$mice were a little higher than in the B6 mice, parasitemia in the $AIM^{-/-}$mice disappeared earlier than in the B6 mice. The expression of $\gamma\delta TCR^{int}$ cells, especially the $V\gamma7^{+}\gamma\delta$ T cells increased in the liver and spleen of the $AIM^{-/-}$ mice, but not in the B6 mice during the late stage of malaria infection. In addition, the recovery from malaria-induced tissue damage was more rapid in the $AIM^{-/-}$ mice than in the B6 mice. These results suggest that the $\gamma\delta TCR^{int}$ cells, which are an unconventional subset, play an important multi-faceted role in protection against malaria infection.

## 5. Conclusions

The obvious conclusion from the data discussed here is that the intermediate T-cells are emerging as an important subset of unconventional lymphocytes, which modulate themselves to play an active protective role in host defense. In this respect, these results indicate that primitive T cells, namely intermediate T cells may be much more activated in some groups of mice than the others and therefore resistance to malaria infection occur in mice which may have defective function in some immune cells. Because of this situation, the immune system has to be switched from the usual system associated with conventional T cells to the emergency system associated with NK cells and unconventional T cells. Based on the data discussed above, it is clear that a better knowledge of the mechanisms governing innate immunity based on genetic background will provide new clues for understanding how the emergency immune system works in malaria infection and helps in designing therapeutic strategies.

## References


1. World Health Organization. World Malaria Report 2013. Geneva: *World Health Organization* 2013.
2. Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y, Chareonviriyaphap T, Coetzee M, *et al*. A global map of dominant malaria vectors. *Parasit Vectors* 2012; 5:69.
3. Rénia L. Protective immunity against malaria liver stage after vaccination with live parasites. *Parasite* 2008; 15: 379-383.
4. Molyneux DH. Control of human parasitic diseases: context and overview. *Advances in Parasitology* 2006; 61: 1-45.
5. Rénia L, Gruner A.C, Mauduit M & Snounou G. Vaccination against malaria with live parasites. *Expert Review of Vaccines* 2006; 5: 473-481.
6. Carter R, Mendis K.N. Evolutionary and Historical Aspects of the Burden of Malaria. *Clinical Microbiology Reviews* 2002; 15(4):564-594.
7. Doolan D. L., Dobaño C, Kevin Baird J. Acquired Immunity to Malaria. *Clinical Microbiology Reviews*2009; 22(1):13–36.
8. Mannoor MK, Weerasinghe A, Halder RC, Reza S, Morshed M, Ariyasinghe A, Watanabe H, *et al*. Resistance to malarial infection is achieved by the cooperation of NK1.1(+) and NK1.1(-) subsets of intermediate TCR cells which are constituents of innate immunity. *Cell Immunol*2001; 211(2): 96-104.
9. Perlmann P, Troye-Blomberg M. Malaria and the Immune System in Humans. Malaria Immunology. *Chem Immunol*. Basel, Karger, 2002; 80: 229- 242.
10. Roetynck S, Baratin M, Vivier E, Ugolini S. NK cells and innate immunity to malaria. *Med Sci (Paris)* 2006; 22(8-9): 739-44.
11. Stevenson M M, Riley E M. Innate immunity to malaria. *Nature Reviews Immunology* 2004; 4:169-180.
12. Ariyasinghe A, Morshed SRM, Mannoor M K, Bakir H Y, Kawamura H, Miyaji C, *et al*. Protection against Malaria Due to Innate Immunity Enhanced by Low-Protein Diet. *The Journal of Parasitology* 2006; 92(3): 531-538.
13. Watanabe H, Miyaji C, Seki S, Abo T. c-$kit^{+}$stem cells and thymocyte precursors in the livers of adult mice. *J Exp Med* 1996; 184:687–93.
14. Abo T. Extrathymic pathways of T-cell differentiation and immunomodulation. *International Immunopharmacology* 2001; 1: 1261-1273.
15. Watanabe H, Miyaji C, Kawachi Y, Iiai T, Ohtsuka K, Iwanaga T,*et al*. Relationships between intermediate TCR cells and $NK1.1^{+}$T cells in various immune organs. $NK1.1^{+}$T cells are present within a population of intermediate TCR cells. *J Immunol* 1995; 155:2972–83.
16. Iiai T, Watanabe H, Seki S, Sugiura K,Hirokawa K. Ontogeny and development of extrathymic T cells in mouse liver.*Immunology*1992; 77: 556-563
17. Sato K, Ohtsuka K, Watanabe H, Asakura H, Abo T. Detailed characterization of □ □ T cells withinthe organs in mice: classification into three groups. *Immunology* 1993; 80:380- 387.
18. Kimura M, Watanabe H, Ohtsuka K, Iiai T, Tsuchida M, Sato S, *et al*. Radio-resistance of intermediate TCR cells and their localization in the body of mice revealed by irradiation. *MicrobiolImmunol*1993; 37:641- 652.
19. Maruyama S, Tsukahara A, Suzuki S, Tada T, Minagawa M, Watanabe H,*et al*. Quick recovery in the generation of self-reactive $CD4^{low}$NKT cells by an alternative intrathymic pathway when restored from acute thymic atrophy. *Clin ExpImmunol* 1999;117: 587- 595.
20. Ohtsuka K, Sato K, Watanabe H, Kimura M, Asakura H, Abo T. Unique order of the lymphocyte subset induction in the liver and intestine of mice during *Listeria monocytogenes*infection. *Cell Immunol* 1995; 161:112-124.
21. Bannai M, Oya H, Kawamura T, Shimizu T, Kawamura H, Miyaji C,*et al*. Disparate effect of *beige* mutation on cytotoxic function between NK and NKT cells. *Immunology*2000; 100:165–9.
22. Seki S, Abo T, Ohteki T, Sugiura K, Kumagai K. Unusual αβT cells expanded in autoimmune *lpr*mice are probably a counterpart of normal T cells in the liver. *J Immunol* 1991; 147:1214- 21.
23. Weerasinghe A, Sekikawa H, Watanabe H, Mannoor K, Morshed SR, Halder RC, *et al*. Association of intermediate T cell receptor cells, mainly their $NK1.1^{-}$subset, with protection from malaria. *Cell Immunol* 2001; 207: 28-35.
24. Mannoor MK, Halder RC, Morshed SR, Ariyasinghe A, Bakir HY, Kawamura H, *et al*. Essential role of extrathymic T cells in protection against malaria. *J Immunol* 2002; 169: 301-6.
25. Bakir HY, Tomiyama-Miyaji C, Watanabe H, Nagura T, Kawamura T, Sekikawa H, *et al*. Reasons why DBA/2 mice are resistant to malarial infection. Expansion of $CD3^{int}B220^{+}\alpha\beta$T cells with double-negative $CD4^{-}8^{-}$phenotype in the liver. *Immunology* 2006; 117:127-35.
26. Bakir HY,Tomiyama-Miyaji Cand Abo T. Cytokine Profile of Murine Malaria: Stage-related Production of Inflammatory and Anti-inflammatory Cytokines. *Biomedical Research* 2011; 32 (3): 203-208.
27. Haque A, Echchannaoui H, Seguin R, Schwartzman J, Kasper LH, Haque S. Cerebral malaria in mice. Interleukin-2 treatment induces accumulation of αβT cells in the brain and alters resistant mice to susceptible-like phenotype. *Am J Pathol* 2001; 158:163-72.

28. Boubou MI, Collette A, Voegtle D, Mazier D, Cazenave PA, Pied ST. Cell response in malaria pathogenesis: selective increase in T cells carrying the TCR Vβ8 during experimental cerebral malaria. *IntImmunol* 1999; 11:1553-62.
29. Gorgette O, Existe A, Boubou MI, Bagot S, Gue´net JL, Mazier D, *et al*. Deletion of T cells bearing the Vβ8.1 T-cell receptor following mouse mammary tumor virus 7 integration confers resistance to murine cerebral malaria. *Infect Immun* 2002; 70:3701-6.
30. Ashman RB, Papadimitriou JM, Fulurija A, Drysdale KE, Farah CS, Naidoo O, *et al*. Role of complement C5 and T lymphocytes in pathogenesis of disseminated and mucosal candidiasis in susceptible DBA/2 mice. *MicrobPathog* 2003; 34:103-13.
31. Heiniger HJ, Taylor BA, Hards EJ, Meier H. Heritability of the phytohaemagglutinin responsiveness of lymphocytes and its relationship to leukemogenesis. *Cancer Res*1975; 35:825-31.
32. Halder RC,Abe T, Mannoor MK, Morshed SR, Ariyasinghe A, Watanabe H, *et al*. Onset of hepatic erythropoiesis after malarial infection in mice. *ParasitolInt* 2003; 52:259–68.
33. Bakir HY, Sayed FG, Rahman SA, Hamza AI, Mahmoud AE, GalalLA, *et al*. Comparative Study between Non Lethal and Lethal Strains of Plasmodium yoelii with Reference to Its Immunological Aspect. *J. Egypt. Soc. Parasitol*2009; 39 (2):585-593.
34. Taniguchi T, Tachikawa S, Kanda Y, Kawamura T, Tomiyama-Miyaji C, Li C, *et al*. Malaria protection in beta 2-microglobulin-deficient mice lacking major histocompatibility complex class I antigens: essential role of innate immunity, including gammadelta T cells. *Immunology*. 2007; 122(4):514-21.
35. Adachi Y, Koseki H, Zijlstra M, Taniguchi M. Positive selection of invariant Vα14T cells by non-major histocompatibility complex-encoded class I-like molecules expressed on bone marrow-derived cells. *Proc Natl Acad Sci U S A* 1995; 92:1200- 4.
36. Li C, Mannoor K, Inafuku M, Taniguchi T, Inamine Y, Miyazaki T, *et al*. Protective function of an unconventional γδ T cell subset against malaria infection in apoptosis inhibitor deficient mice. *Cell Immunol* 2012;279(2):151-9.
37. Miyazaki T, Hirokami Y, Matsuhashi N, Takatsuka H, Naito M. Increased susceptibility of thymocytes to apoptosis in mice lacking AIM, a novel murine macrophage-derived soluble factor belonging to the scavenger receptor cysteine-rich domain superfamily. *J. Exp. Med.*1999; 189: 413–422.
38. Haruta I, Kato Y, Hashimoto E, Minjares C, Kennedy S, Uto H, *et al*. Association of AIM, a novel apoptosis inhibitory factor, with hepatitis via supporting macrophage survival and enhancing phagocytotic function of macrophages, *J. Biol. Chem.* 2001;276: 22910- 22914.
39. Kuwata K, Watanabe H, Jiang SY, Yamamoto T, Miyaji CT, Abo T, et al. AIM inhibits apoptosis of T cells and NKT cells in Corynebacterium-induced granuloma formation in mice. *Am. J. Pathol* 2003; 162:837-847.