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The role of IL-10 in Infected Mice Due to Visceral Leishmaniasis

Amal kamil Abdulsada
College of Health and Medical Technologies, Middle Technical University, Baghdad, Iraq

Email: amalar7070@gmail.com

Abstract. In this study, 30 Balb mice were inoculated with Leishmania donovani amastigote which was taken from a farm for growing visceral leishmaniasis, and 20 healthy Balb mice were taken as a control group. The mice ages ranged between (4-11) months. The study was conducted at the Veterinary Research Center in Diyala province during the period from March 2024 to January 2025. The results showed that the mean age of mice infected with visceral Leishmaniasis was (4-7) months 11 (22.0%) compared to the controls 8 (16.0%), and the mean age (8-11) was 18 (36.0%) compared to the controls 31 (62.0%) with no significant differences (P= 0.99). The prevalence of Leishmania donovani infection in male mice was 20 (40.0%) compared to the controls 36 (72.0%), which was more than females 9 (18.0%) compared to the controls with no significant variations (p=0.57). The mean level of anti Leishmania donovani IgG mice antibodies was (2.49±2.67) compared to the controls (0.83±0.57) with a highly significant variation (P= 0.003), and the mean level of IL-10 was (22.09±8.12) with a highly significant difference (P≤0.0001). The mean level of anti-leishmania donovani mice IgG antibodies in males was (2.74±3.18) compared to the controls (0.75±0.26) and the mean level of anti-leishmania donovani mice IgG antibodies in females was (20.55±0.67) compared to the controls (1.10±1.13) with no significant differences (P=0.52). While the mean level of IL-10 in males was (22.79±8.97) compared to the controls (4.81±1.91) and mean level of IL-10 in females was (20.55±6.00) compared to the controls (10.12±11.57) with no significant differences (P=0.36). The mean level of anti-leishmania donovani antibodies in mice age (4-7) months was (1.99±0.83) compared to the controls (0.68±0.26) and the mean level of anti-leishmania donovani antibodies in mice age (8-11) months was (2.79±3.33) compared to the controls (0.70±0.19) with no significant differences (P=0.26). While the mean level of IL-10 in age (4-7) months was (21.97±8.30) compared to the controls (1.70±0.60) and mean level of IL-10 in age (8-11) months was (22.16±8.25) compared to the controls (7.33±2.03) with no significant differences (P=0.24). There were a direct correlations between Leishmania donovani mice IgG antibody levels and IL-10 levels with (r=. 337*,. 337*) respectively. The correlations were highly significant (P=0.05), while our findings also showed negative correlations between Leishmania donovani mice IgG antibody level and ages at (r=-.-.001) and sex at (r=-.042) with (P= .994) and (P=.775) respectively. A mutation happened in IL-10 genes at rs1800876 SNPs, and wild TT was altered to CC & TC respectively in comparison to the control group with visceral leishmanial mice infection.

Highlights:

1. No age or sex impact – Infection prevalence showed no significant differences.
2. Strong immune response – Higher IgG and IL-10 levels in infected mice.
3. Genetic mutation detected – IL-10 gene mutation linked to infection.

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Keywords: IL-10, mice, visceral Leishmaniasis

Introduction

The transmission of the dimorphic intracellular haemoflagellate protozoa parasite of genus Leishmania to a vertebrate occurs via phlebotomine sandfly's bite, which is a vector that can cause Leishmaniasis [1]. The majority of infected animals and humans show no clinical signs and symptoms, but if they do, they may be presented in a form of cutaneous leishmaniasis (CL) [1]. Translation of host T cell-mediated immune responses into feasible treatment forms is becoming a sought-after treatment goal in leishmanial infections, which are intracellular protozoal infections that target host's tissue macrophage [2]. In visceral disseminated leishmanial infection, three interrelated approaches were used to pursue this aim experimentally and/or clinically: (i) to identify specific constituents of T cell-dependent, and macrophage-activating pathways that may function alone as an immunotherapy [3] (ii) to understand how the same Th1-cell-related mechanisms regulate in vivo response to chemotherapies [4] and (iii) to blend chemo- and immune-therapy for optimizing intracellular Leishmanial killing inside host tissues. The effective defenses against visceral zing strains, such as Leishmania donovani, relies mainly on Th-1 lymphocytes, and acquired resistances are directed by T cells and macrophage-activating cytokine [5]. Interleukin-12 and gamma interferon gamma-γ, among the latter, play chiefly experimentally basic roles. Such cytokines start and/or drive the basic responses of anti-leishmania Th-1 cell and administrate tissue granuloma assembly, which are components where the IFN-γ activated mononuclear phagocytes kill the intracellular parasite [6]. Furthermore, the endogenous IFN-γ and IL-12 along with host T-cell, are also necessary to express the leishmanicidal effects of conventional chemotherapies and pentavalent antimonies [7]. Unsurprisingly, then, using the cytokines of pro-host defenses in exogenous forms, whether alone or with antimonies, represents main immunotherapeutic approaches thereby far testing clinically and or/experimentally visceral infections [8].

In both human and experimental kala-azar (visceral leishmaniasis). Downregulation mechanism was also recognized which include Th-2 cell-related responses. This evidence along with immunopathogenetics instructions taken from cutaneous Leishmaniasis major infection's models pointed in separate

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immunotherapeutic directions, which targeted (inhibited) the impacts of simultaneously-induced and suppressive cytokines [9]. Whereas transforming growth factor beta and may be Th2 cell-derived IL-4 and/or IL-13 might exert those impacts on visceral infections significant evidences that support central, deactivating roles of the endogenous IL-10 [10].

The induction of IL-10 occurs in both human and experimental infections, and its wide effects support the costimulatory mechanism and proliferation and secretion of antigen-presenting cell and T-cells, as well as macrophage responsiveness to activate Th-1 cell-related cytokine. Though not devoid of pro-inflammatory impacts, it is clear that IL-10 possesses the ability for disabling the host anti-leishmania defenses and fostering visceral infections as well as impairing responsiveness to chemotherapies (antimony).

For characterizing the role of IL-10, we aimed to study the behaviors of L. donovani in modified mice that overexpress or lack the endogenous IL-10 and also to test the blockade of receptor of IL-10 (IL-10R) that is used alone or with antimony, as an immunotherapy in established infections [11].

Methods

Thirty Balb mice were inoculated with Leishmania donovani amastigote which was taken from a farm for growing visceral leishmaniasis, and twenty healthy Balb mice were taken as a control group. The mice ages ranged between (4-11) months. The study was conducted at the Veterinary Research Center in Diyala province during the period from March 2024 to January 2025. The mice have been inoculated with amastigotes of L. donovani through intracardial route on the day zero. In 100 µl of RPMI media, all animals received 2×107 parasites. On the days 10, 20, 30, 45, 60 and 120 after infection, the mice were sacrificed and weight of their liver/spleen were estimated. In the sacrificed animal's spleens and livers, the parasite loads were estimated as: Number of amastigotes/number of nucleated cells X organ weight (in mg)×2×105 [21]. In certain experiments, animals in which infections were progressing intracardiall, the calculationit was followed by measuring the total parasite's loads in the infected organs. It was shown that the load of liver's parasites began to increase first after infections reaching the maximum around 60 days post-infections. Then, it began to decline severely via retaining

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significant amounts of parasite's loads even at 120 days following infections. 5 ml of whole blood were taken from infected mice by intracardiac injection after anesthetizing the mice.

Anti IgG antibodies and IL-10 were measured using the sandwich ELISA (Enzyme-Linked Immunosorbent Assay) kits.

IL10-F TGTAAAACGACGGCCAGTAAGTAAGGGACCTCCTATCC

IL10-R CAGGAAACAGCTATGACAGAGCTCCTCCTTCTCTAAC

Statistical analysis

The SPSS version 20 program was applied involving (Mean±SD) as well as the t-test for analyzing the data. $P < 0.05$ value was regarded as significant

Result and Discussion

The results showed that the mean age of mice infected with visceral Leishmaniasis was (4-7) months 11 (22.0%) compared to the controls 8 (16.0%), and the mean age (8-11) was 18 (36.0%) compared to the controls 31 (62.0%) with non-significant differences (P= 0.99). The prevalence of Leishmania donovani infection in male mice was 20 (40.0%) compared to the controls 36 (72.0%), which was more than females 9 (18.0%) compared to the controls with non-significant variations (p=0.57) as shown in table 1.

Table (1): Age and sex ratios among infected mice

Groups		**Case**	**Control**	**Total**	**P-value**
Age range (Months)	(4-7)	11 (22.0%)	8 (16.0%)	19 (38.0%)	0.99 (N.S)
	(8-11)	18 (36.0%)	13 (26.0%)	31 (62.0%)	
Total		29 (58.0%)	21 (42.0%)	50 (100.0%)	
Sex	Male	20 (40.0%)	16 (32.0%)	36 (72.0%)	0.57 (N.S)
	Female	**9 (18.0%)**	**5 (10.0%)**	**14 (28.0%)**	
Total		**29 (58.0%)**	**21 (42.0%)**	**50 (100%)**	

The results showed that non-significant variation was seen in incidence between ages. Veronika, et al. (2024) reported that the age between 8 months to 2 years is the

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best age of experimental mice [12]. While according to sex, Rodríguez, et al, (2017) demonstrated that the Leishmania infantum distribution according to gender caused visceral leishmaniasis to mice in Brazil. They formerly noticed that visceral leishmaniasis is more commonly found in males compared to females which live in endemic areas, although they are similarly exposed. With the use of a larger sample, we showed that visceral leishmaniasis is more commonly observed in males compared to females, but only following puberty. The models of BALB/c and C57BL/6 mice affirmed the presence of biological basis for male's susceptibility to symptomatic visceral leishmaniasis [13]. The difference between male and female hormones may be the reason why males are more susceptible to visceral leishmaniasis [13].

The mean level of anti Leishmania donovani IgG mice antibodies was (2.49±2.67) in comparison with the controls (0.83±0.57) with higher significant variations P= 0.003 and the mean level of IL-10 was (22.09±8.12) with highly significant change (P≤0.0001) as illustrated in table (2).

Table (2): The mean level of IgG and IL-10 between cases and control

Parameters	**Groups**	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**P-value**
IgG	Case	30	2.49	2.67	0.49	0.003
	Control	20	0.83	0.57	0.12	H.s
IL-10	Case	30	22.09	8.12	1.50	≤0.0001
	Control	20	6.07	5.90	1.28	H.S

The results in table 2 revealed an increase in the levels of IgG antibodies in the mice compared to the control group. These findings agreed with (Hussein, 2020) who showed a significant elevation (P<0.05) in IgA. IgG and IgM levels in infected mice in comparison with the controls and in treated groups with aqueous extracts of studied plants, which indicates the effectiveness of such extracts in treating leishmaniasis [14]. Also, Lima, et al, (2022) expound that the IgG neutralization and production was enhanced by adjuvants. DDA/Sap is involved in the elevation of IgG1, IgG2a, IgG2b and IgG3 isotype. The total avidity of IgG is regarded high in addition of the avidity of IgG1, IgG2a and IgG2b. IgG antibodies, particularly IgG2a, IgG2b and IgG3 are efficiently transferred to offsprings [15]. Furthermore, Gupta, et al, (2024) demonstrated that the

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important constituent of adaptive immunity, known as humoral immunity, is known to generate antibodies through plasma and B-cells in response to an antigen. The mostly antibody found in the circulation is IgG, which assists in antigen neutralizations and complement activations [16]. Moreover, there was an increase in IL-10 in Balb mice infected with visceral lieshmaniasis, and these results matched with (Farlane, et al, 2019) who found that in visceral leishmaniasis IL-10 was more significant than IL-4 in parasitic persistence and immunologic suppressions. An evidence tends to indicate that type-2 immunlogic response may really participate in visceral leishmaniasis control rather than being detrimental cytokines for protection of infected hosts. Therefore, our former investigations that utilized gene-deficient mice could identify protective roles of IL-4, IL-4Rα and IL-13 signaling during initial leishmaniasis [17]. Firmino-Cruz, et al, (2018) elucidated that the BALB/Xid mouse showed reduced IL-10 levels in infected footpads, draining lymph node draining to spleen in comparison with WT infected tissues. We could not identify variations in IL-10 numbers that produced CD4+ and CD8+ T-cells between BALB/Xid and WT mice; nevertheless, in BALB/Xid mice, a great decrease in IL-10 produced by follicular B-cells has been observed. Our finding suggested that there was a relationship between B-cells and lesion's pathogenesis via producing IL-10 and antibodies [18]. Interleukin 10 (IL-10) is a cytokine that functions with strong anti-inflammatory characteristics and plays key roles in limitation of host's immune responses to pathogenic agents, thus it prevents host's damage and maintains normal tissues [11].

Table 3 illustrated that mean level of anti-leishmania donovani mice antibodies in males was (2.74±3.18) compared to the control group (0.75±0.26) and the mean level of anti-leishmania donovani mice antibodies in females was (20.55±0.67) compared to the controls (1.10±1.13) with no significant difference (P=0.52). While the mean level of IL-10 in males was (22.79±8.97) compared to the control group (4.81±1.91) and mean level of IL-10 in females was (20.55±6.00) compared to the control group (10.12±11.57) with no significant variation (P=0.36).

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Table (3): The mean level of IgG and IL-10 between cases and control according to Sex

Test	Sex	Case		P-value	Control		P-value
		M	SD		M	SD	
IgG	Male	2.74	3.18	0.46	0.75	0.26	0.52
	Femalale	1.94	0.67		1.10	1.13	
IL-10	Male	22.79	8.97	0.52	4.81	1.91	0.36
	Female	20.55	6.00		10.12	11.57	

These results were consistent with Koloski, et al, (2024) who concluded that infection in male mice was more than in female mice, with a high increase in the levels of IgG antibodies in the mice [19]. In addition, there were monitored by (Casado-Bedmar, et al, 2023) who reported that IL10 deficient mouse (IL-10−/−) up to age of 17 wk with characterization of their fecal and colonic inflammatory phenotypes, in addition to the microbiota alterations. At this time, we originally recognized IL-10−/− females of mice to be more subject to develop intestinal inflammations, with increased fecal miR-21, as well as dysbiosis with more detrimental properties in comparison with male mice [20].

The mean level of anti-leishmania donovani antibodies in mice aged (4-7) months was (1.99±0.83) compared to the control group (0.68±0.26) and the mean level of anti-leishmania donovani antibodies in mice age (8-11) months was (2.79±3.33) in comparison with the controls (0.70±0.19) with non-significant variations (P=0.26). While the mean level of IL-10 in age (4-7) months was (21.97±8.30) compared to the control group (1.70±0.60) and mean level of IL-10 in age (8-11) months was (22.16±8.25) compared to the control group (7.33±2.03) with no significant differences P=0.24, as shown in table (4).

Table (4): The mean level of IgG and IL-10 between cases and control according to age groups (Months)

Test	Age group	Case		P-value	Control		P-value
		M	SD		M	SD	
IgG	(4-7)	1.99	0.83	0.44	0.68	0.26	0.26
	(8-11)	2.79	3.33		0.70	0.19	
IL-10	(4-7)	21.97	8.30	0.95	1.70	0.60	0.24

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	(8-11)	22.16	8.25	7.33	2.03

The prevalence of VL in infected mice was in harmony with Gupta, et al, (2024) who found an age-related but no immune challenge increased total IgG; IgG1 and partly IgG3 were the only immunoglobulin subtypes influenced by immunologic challenges. It is of interest that age and immunologic challenge affect the IgG2b and IgG3 sialylation without further stimulation by immunologic challenge among adult mice, suggesting shift in the IgG to pro-inflammatory and potentially-pathogenic states with ages and inflammations [16]. Also, The hepatic granuloma numbers were significantly reduced in comparison with the controls. Devender, et al, (2023) showed that the further measurement of IgG2a antibody levels, a marker of Th1 immunologic responses in visceral leishmaniasis, showed a significantly higher serum levels in immunized mice in comparison with the control groups. Splenic cells induced by a soluble Leishmanial antigen (SLA) exhibited significant elevation in the levels of ROS and NO in comparison with the controls [21]. On other hand Murray, et al, (2022) reported that IL-10 is believed to enhance intracellular infections, such as human VL via Th1 cell type response disabling and/or parasitized tissue macrophage's deactivation. For development of a rationale for the inhibition of IL-10 as a therapy for visceral infections, there have been a characterization for responses of Th1 cytokine-driven in Leishmania donovani-infected BALB/c mice where IL-10 was overexpressed or not present or its receptors (IL-10R) was obstructed. The knockouts of IL-10 and normal mice treated prophylactically with anti-IL-10R showed enhanced granuloma assemblies and fast parasitic killings without untoward inflammations of tissues [22].

There were a direct correlation between Leishmaina donovani mice IgG antibody levels and IL-10 levels with (r=. 337*,. 337*) respectivelly. The correlations were highly significant (P=0.05), while our findings also showed negative correlations between Leishmaina donovani mice IgG antibody level and ages at (r=-.-.001) and sex at (r=-.042) with (P= .994) and (P=.775) respectively, as seen in table (5).

Table (5): Correlation analysis of studied parameters

		Age	**sex**	**IL10**	**IgG**
IL10	Pearson Correlation	-.055	.085	1	.337*

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	P-value	.702	.555		.017
	N	50	50	50	50
IgG	Pearson Correlation	-.001	-.042	.337*	1
	P-value	.994	.775	.017	
	N	50	50	50	50

* Correlation significant at (0.05) level (2-tailed).

* Correlation significant at (0.05) level (2-tailed).

The correlations between Leishmaina donovani mice IgG antibody levels and IL-10 levels was shown by (Tadesse, et al, 2021) who revealed that the typical symptomatic VL outcome is affected by the immunologic responses developed by the host's systemic infections, with the parasite's spread to liver, spleen, bone marrow, lymph node as well as other organs along with high circulating antibody titers, marked up- IL-4 and IL-10 regulations [16–18], and unresponsiveness to Type1 T cell mediated immunities. The regulatory Th cell subsets share the significant tasks of controlling over-exuberant immunologic response with utilization of IL-10 productions. The increased serum IL-10 levels in human studies were mentioned during active visceral leishmaniasis and disease cure is related to a decreased levels of IL-10 mRNA [23]. Increased antibody titer and immunologic complex formations can be involved in the high levels of IL-10 detected in patients with visceral leishmaniasis and the progressive declined immunologic state in those patients. The above evidence shreds indicate that IL-10 plays essential roles in the immunologic pathways resulting in the systemic spreading of leishmanial parasite in human visceral leishmaniasis [23]. Also Olías-Molero, et al, (2020) reported that the immunologic regulations of leishmaniasis was widely analyzed in 13 mice models of visceral leishmaniasis. Susceptibility was shown to be related to the Th2-polarized responses with the IgG1 and IgE production, while resistant lines of mice could mount Th1-based responses with specific IgG2a14 production The frame work of Th1/Th2, along with the dichotomy causing leishmanial proliferation or control, although they are relatively well characterized in mice, with refractory and susceptible strain, are obviously considered as oversimplifications, and essential roles of Treg and some cytokines were described in Leishmania-host interface tuning [24].

Amplification of IL-10 spesific region of mice blood samples in gel electrophoresis at 100bp ladder resemble 961bp PCR product is shows in figure (1).

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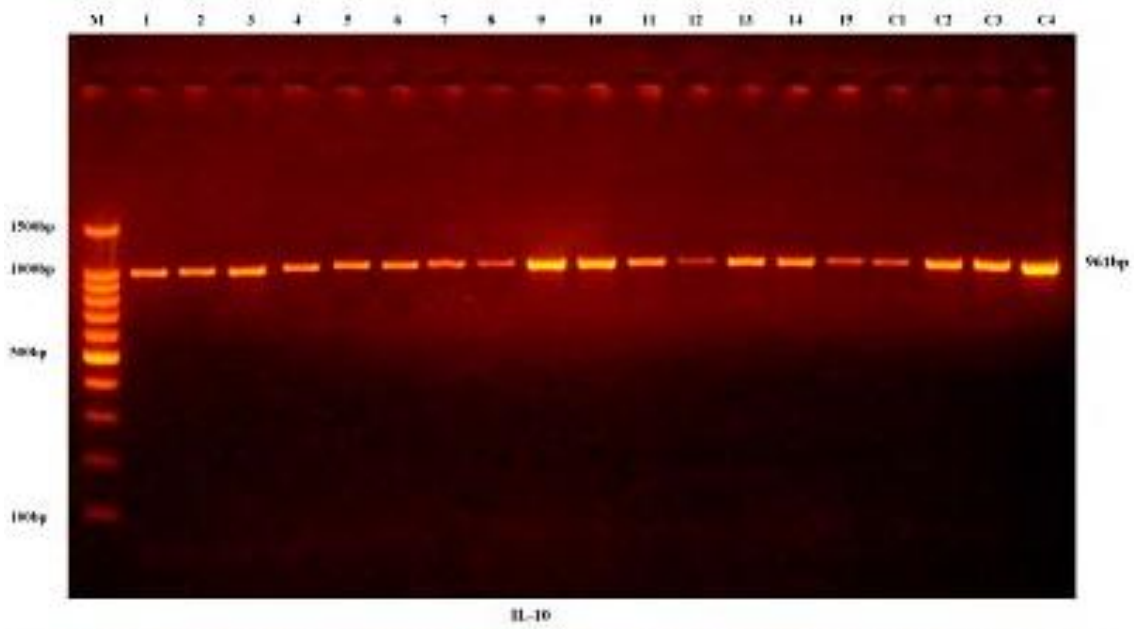

Results of the amplification of IL-10 specific region of mice blood sample were fractionated on 2% agarose gel electrophoresis stained with Eth. Br. M: 1oobp ladder marker lanes 1–C4 resemble 961bp PCR product.

It was revealed in figure (2) and table (6) that a mutation happened in IL-10 genes at rs1800876 SNPs, and wild TT is altered to CC & TC respectively in comparison to control group with visceral leismania mice infection.

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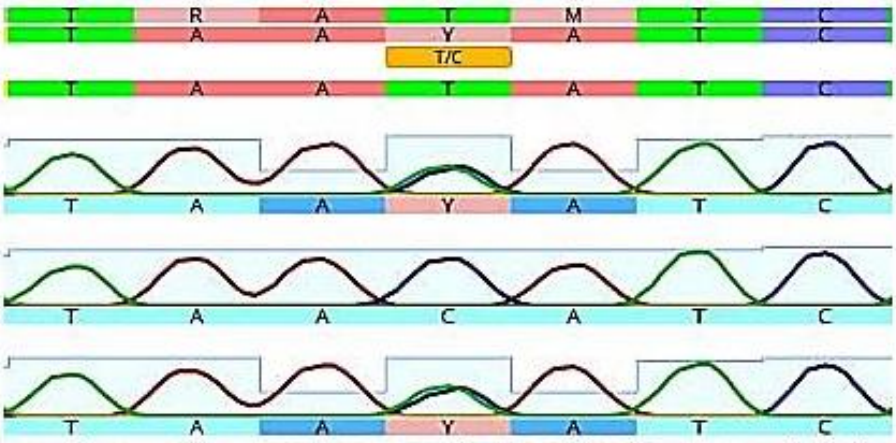

Analysis of SNP *rs1800871* of IL-10 gene using sequencing single "T" peak indicative of a T homozygous allele. single "C" peak indicative of a C homozygous allele. Presence of "T" and "C" peak T/C allele.

Table (6): Variation of wild SNPs of IL-10

IL10 GENE ID 3586	
SNPs	**rs1800876**
Wild	**TT**
Variation	**T>C**
Samples	
1	CC
2	TC
3	TC
4	CC
5	TC
6	TC
7	CC
8	TC
9	CC
10	CC
11	CC
12	TC
13	TC
14	CC
15	CC
C1	CC

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C2	CC
C3	CC
C4	CC
C5	CC

There is a genetic mutation on the interleukin 10 gene sequence and these results are consistent with (HAJILOOI, et al, 2014) who proved that the polymorphisms at the position of IL-10 -1082 (A/G) was highly related to visceral leishmaniasis and that genotypes of A/G were significantly greater in patients with visceral leishmaniasis in comparison with group 2 and group 3 (P< 0.001). Nevertheless, our results revealed no association between A & G alleles with visceral leishmaniasis [25]. Furthermore (Vieira, et al, 2024) found that genetic alterations in genes that encode for cytokines can be related to their expression's alteration and, as a result, with clinical resistances or susceptibilities developments of the infection. The aim of this systematic review and meta analysis was assessing whether the clinical consequences of visceral leishmaniasis is influenced by single nucleotide polymorphisms (SNPs) in interleukin genes [26]. Also former investigations recognized 91 genes changed in the atypical cutaneous leishmaniasis in comparison with typical visceral-associated leishmaniasis involving a mutation in the genes of RagC and Raptor which are parts of eukaryotic conserved TOR pathways and their upstream sensing pathways. In our current study, we investigated whether the mutations of RagC R231C found in atypical cutaneous Leishmania donovani introduced into the chromosome of virulent type Leishmania donovani 1S2D through CRISPR gene editing can have an effect on virulence to survive in a visceral organ. We also studied, via bioinformatic analysis, the existence of sensing pathway component upstreams of TOR in donovani which included RagC-complexing protein, RagA and Raptors. Leishmania donovani 1S2D edited for expression of mutant RagC R231C were shown to be viable in promastigotes but developed low visceral parasitemias in BALB/c mice infected with leishmaniasis (Lypaczewski, et al, 2021), [27].

Conclusion

The study proved that there is a very high impact on the levels of interleukin 10 due to the infection of mice with visceral leishmaniasis with the presence of genetic mutations in the gene for interleukin 10.

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