

1 **Chemokines Signature and T Cell Dynamics in Leishmaniasis: Molecular insight and**
2 **therapeutic application**

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17

18 **Abstract**

19 Leishmaniasis, caused by obligate intracellular *Leishmania* parasites, poses a significant global
20 health burden. The control of *Leishmania* infection relies on an effective T cell-dependent
21 immune response; however, various factors impede the host's ability to mount a successful
22 defense. Alterations in the chemokine profile, responsible for cell trafficking to the infection
23 site, can disrupt optimal immune responses and influence the outcome of pathogenesis by
24 facilitating parasite persistence. This review aims to emphasize the significance of the
25 chemokine system in T cell responses and to summarize the current knowledge on the
26 dysregulation of chemokines and their receptors associated with different subsets of T
27 lymphocytes during Leishmaniasis. A comprehensive understanding of the dynamic nature of
28 the chemokine system during Leishmaniasis is crucial for the development of successful
29 immunotherapeutic approaches.

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DOI: 10.1017/erm.2024.36

30 **Keywords:** Leishmaniasis, Visceral Leishmaniasis, Cutaneous Leishmaniasis, Chemokines,
31 Chemokine receptors, T cell migration, Desensitization.

32 **Introduction**

33 Leishmaniasis is a neglected tropical vector-borne disease caused by the protozoan parasite
34 *Leishmania*. According to the World Health Organization (WHO), in 2022, Leishmaniasis was
35 endemic in approximately 99 countries and territories out of 200 worldwide. It manifests in
36 five different clinical forms, including visceral leishmaniasis (VL or kala-azar), post-kala-azar
37 dermal leishmaniasis (PKDL), cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis
38 (MCL), and diffuse cutaneous leishmaniasis (DCL) [1]. Among these, visceral leishmaniasis is
39 the most severe form, affecting approximately 90% of the global population and primarily
40 reported in seven countries: Brazil, India, South Sudan, Sudan, Ethiopia, Kenya, and Somalia
41 (WHO report, 2018). Visceral leishmaniasis affects the visceral organs of the host and is caused
42 by the protozoan parasite *Leishmania donovani* in Asia, Africa, and the Middle East, and
43 *Leishmania infantum* in South America and Europe. If left untreated, VL can be fatal. The
44 disease is characterized by various symptoms, including splenomegaly (enlarged spleen),
45 hepatomegaly (enlarged liver), pancytopenia (reduction in blood cell counts),
46 hypergammaglobulinemia (elevated levels of gamma globulins in the blood), weight loss,
47 weakness, and progressive anemia [2].

48 The chemokines and their receptors play a vital role in guiding immune cells to specific
49 locations during homeostasis and inflammatory conditions. Chemokines, which are a type of
50 cytokine, bind to their G-protein coupled receptors (GPCRs), known as chemokine receptors
51 (CKRs), and initiate signaling through coupled heterotrimeric G-proteins [3]. This signaling
52 pathway leads to the activation of integrins, enabling leukocytes to firmly adhere to endothelial
53 cells and extravasate into the tissue microenvironment [4]. Chemokine receptors are designated
54 based on the type of chemokine(s) they bind, such as CXC, CC, XC, and CX3C, followed by
55 'R' (for receptor) and a number indicating the order of discovery. The chemokine system plays
56 a crucial role in immune cell migration and the composition of immune cells at a specific site
57 depends on various factors, including chemokine expression. This composition of immune
58 cells also influences the host's susceptibility to infection. During inflammation, various types
59 of immune cells, including neutrophils, macrophages, and lymphocytes, as well as non-
60 immune cells such as endothelial cells, epithelial cells, fibroblasts, and adipocytes, produce
61 chemokines. This results in the migration of different cell types, such as macrophages,

62 neutrophils, and T cells, to the specific location of inflammation [5,6]. The secretion of
63 cytokines from these cells in the inflamed zone affects the behavior of infiltrating cells and
64 disease progression [7]. For instance, CXCL8 secreted by endothelial cells, wounded epithelial
65 cells recruit neutrophils which can further release some more CXCL8 and attract even more
66 neutrophils, and other types of leukocytes to the inflamed zone [5,8,9]. T lymphocytes, a subset
67 of immune cells, have a central role in combating intracellular infections and coordinating
68 adaptive immune responses. T lymphocytes can produce proinflammatory or anti-
69 inflammatory cytokines and can eliminate unwanted cells [10]. They express a range of
70 chemokine receptors on their surface and also produce various chemokines, including CXCR3,
71 CCR5, CCR4, CCR8, CCL3, CCL4, CCL5, CXCL8, etc. (Table-1).

72 However, the chemokine system associated with T cells, particularly in Leishmaniasis, has
73 received limited attention. Understanding the complex interactions between the chemokine
74 system and T cells is crucial to elucidate the impaired migration and functioning of immune
75 cells during *Leishmania* infection. This understanding can contribute to the identification of
76 potential drug targets against chemokines and chemokine receptors, facilitating the
77 development of novel therapeutic strategies.

78 **T- cell associated chemokine system: at the crossroad of infection or protection**

79 The chemokines profile plays a critical role in the migration of immune cells during
80 homeostatic and inflammatory conditions [11]. Chemokine receptors (CKRs) are expressed on
81 the surface of immune cells and exhibit differential expression patterns [12]. The promiscuous
82 nature of the chemokine system allows multiple chemokines to bind to a single receptor, and
83 conversely, a single chemokine can interact with multiple receptors [13]. This complex
84 interaction between chemokines and receptors influences the migratory behavior and
85 functional consequences of immune cells [14,15]. Chemokines belonging to the CC family,
86 such as RANTES (CCL5), can bind to multiple chemokine receptors, including CCR1, CCR3,
87 and CCR5. Similarly, CC chemokine receptor 5 (CCR5) can interact with different chemokines
88 like MIP-1 β , MIP-1 α , and RANTES [16]. This promiscuity allows for versatile chemokine-
89 receptor interactions, expanding the repertoire of migratory signals that immune cells can
90 respond to. The expression pattern of chemokine receptors on the cell surface determines the
91 migratory behavior of immune cells in response to specific chemoattractant sources. Instead of
92 directly migrating to a specific site, cells pass through different zones expressing different
93 chemokines. This multistep directional migration is guided by the combinatorial expression of

94 chemokine receptors on the cell surface [17]. For example, naïve T cells require CCR7 to
95 migrate to the T cell zone, expressing CCL19, and once there, desensitization or
96 downregulation of CCR7 allows them to migrate to the B-cell zone, guided by
97 CXCR5/CXCL13 axis [18].

98 The expression of chemokine receptors is tightly regulated during cell development and
99 differentiation [19]. This regulation allows for the distinction of different forms of CD4⁺ and
100 CD8⁺ T cells, such as naïve T cells, effector T cells, and memory T cells, based on the specific
101 chemokine receptors they express. Each T cell subset uniquely expresses various chemokine
102 receptors that define its identity and functional characteristics [10]. The host employs various
103 strategies to combat pathogenesis during infection. The development of resistance in the host
104 largely depends on the orchestrated response of cells that possess the ability to eliminate
105 pathogens. Chemokines play a crucial role in directing selective cell migration towards the site
106 of infection. Depending on the specific chemokine signals present, the host may mount a
107 protective response or experience tissue damage [20]. The chemokine receptors associated with
108 different subsets of T lymphocytes is under various inflammatory conditions is given in Table-
109 1.

110 **Migratory control over naïve and central memory T cells:**

111 Naïve T cells (Th0) and central memory T cells (Tcm) express crucial homing receptors, such
112 as CCR7 and CXCR4, which are involved in their migration to secondary lymphoid organs
113 (SLOs) where they can actively participate in immune surveillance and responses [21–23].
114 Naïve T cells are those that have not been previously exposed to antigens, circulate in the
115 bloodstream and travel to lymph nodes, where they scan for antigens presented by antigen-
116 presenting cells (APCs) to initiate an immune response. CCR7 facilitate rolling over the
117 endothelium of blood vessels during transmigration. Homeostatic chemokines CCL19 and
118 CCL21, which are secreted by high endothelial venules (HEV), stimulate the CCR7 receptor
119 on T cells [24]. The interaction between CCR7 and its ligands increases the affinity of the
120 integrin LFA-1 (found on lymphocytes and other leukocytes) for its ligand ICAM-1 (expressed
121 on HEV). This firm attachment to the endothelium enables T cells to migrate through the HEV
122 and enter the lymph node [25,26]. Experimental studies using mutant mice lacking CCR7
123 (CCR7^{-/-}) have demonstrated impaired immunogenic responses due to restricted entry of
124 lymphocytes from the bloodstream to SLOs [27]. Similarly, Tcm cells also express CCR7
125 which facilitates its retention in SLO. Another homing receptor, CXCR4 interact with

126 CXCL12 (SDF-1) and is involved in memory T cell maintenance, cell growth, cell survival,
127 and the recirculation of T cells within SLOs. Bone marrow stromal cells express CXCL12
128 which attract T cells expressing CXCR4 on its surface [28,29]. Its expression is reduced once
129 T cells are activated [30]. CXCR4 is a remarkable marker expressed constitutively on both
130 naïve CD4⁺ and CD8⁺ T cells, but predominantly on naïve and central memory CD8⁺ T cells
131 [28,31,32].

132 CCR7 is highly expressed on resting naïve CD4⁺ T cells (CD45RA⁺ CCR7⁺), however, most
133 activated T cells lack CCR7 on their surface, and if they do, it is expressed at a very low level
134 [33]. Tcm cells do not possess effector functions but can differentiate into effector memory T
135 (Tem) cells upon antigenic stimulation having lower CCR7 but upregulated some other
136 chemokine receptors like CCR5, CXCR3, CCR4 [34,35]. This transition allows them to migrate
137 to peripheral tissues to provide robust immune responses rather than to rest within the lymphoid
138 tissues.

139 Similarly, CD8⁺ T cells also express CCR7 on their surface and migrate towards SLOs, like
140 CD4⁺ T cells as discussed earlier [36]. CXCR4 is a remarkable marker expressed constitutively
141 on both naïve CD4⁺ and CD8⁺ T cells, but predominantly on CD8⁺ T cells [31]. It interacts with
142 its ligand, stromal cell-derived factor 1 (SDF-1 or CXCL12), and regulates the migration of
143 CXCR4⁺ T cells by facilitating their adhesion to the venules of SLOs. The presence of CXCR4
144 has been discovered to provide essential signals for the survival of thymocytes during their
145 maturation process. Disrupting the function of CXCR4 has an impact on thymic development
146 [37]. CXCL12/CXCR4 signaling is crucial for TCR-induced immunological synapse
147 development, early signaling molecule phosphorylation, and thymic β selection [38]. CXCR4
148 mediates the migration of naïve and central memory (Tcm) CD8⁺ T cells to the bone marrow
149 and is critical for homeostatic proliferation of CD8⁺ Tcm cells. It also maintains the reservoir
150 of memory CD8⁺ T cells [28]. Their expression decreases during differentiation into effector
151 memory cells (CD8⁺ Tem) as negatively correlated with perforin expression [31].

152 **Migratory control over effector memory T cells:**

153 As naïve T cells differentiate into effector T cells, they begin to express additional chemokine
154 receptors (Table-1) that are necessary for their migration and positioning within target tissues
155 [39,40]. Effector memory T cells (Tem) are CCR7^{low} and express other chemokine receptors
156 that facilitate their circulation in the peripheral blood and migration to inflamed tissues, where
157 they can exert their protective functions against infections [41].

158 Different subsets of CD4⁺ effector cells, such as Th1 and Th2 cells, express distinct arrays of
159 chemokine receptors. Th1 cells preferentially express CCR5 and CXCR3, while Th2 cells, on
160 the other hand, preferentially express CCR3, CCR4 and CCR8 [42,43] which are involved in
161 their migration to inflamed tissues. CXCR5 is a chemokine receptor that directs the migration
162 of T cells into B cell follicles. While subsets of both CD4⁺ and CD8⁺ T cells express CXCR5,
163 its high expression is found on T follicular helper cells (Tfh), a subset of CD4⁺ T cells [44].
164 The ligand for CXCR5, CXCL13 is released from 'B cell zones' in secondary lymphoid organs
165 and guides the migration of Tfh cells towards B cell follicles, where they assist in affinity
166 maturation [45]. Deletion of CXCR5 or CXCL13 in mice leads to altered and impaired
167 microarchitecture of secondary lymphoid organs [46,47]. CXCR5⁺ central memory T cells
168 (T_{cm}) play a crucial role in the generation of antibody-mediated secondary immune responses
169 [48]. The immunosuppressive CD25⁺ regulatory T cells (Tregs) found to be associated with
170 many C-C chemokine receptors such as CCR4, CCR5, CCR6, CCR7 & CCR8 but majorly
171 express CCR4 and CCR8 [49–51]. Previously, it was found that CXCR4 expression decreases
172 with T cell activation, however subsequent discoveries have also shown that its expression
173 increases on CD4⁺ T cells in diseased condition as reported in HIV-infected patients where it
174 acts as a coreceptor for HIV-entry [30,32,52].

175 Effector CD8⁺ T cells express chemokine receptors such as CXCR3, CXCR6, CCR4, CCR6,
176 CCR9 and CCR10, which direct their migration to specific tissues during inflammatory
177 responses [36,53]. IFN- γ producing CD4⁺ T cells affect the recruitment of effector CD8⁺ T cells
178 by upregulating the production of CXCL9 and CXCL10 (ligands for CXCR3) at the site of
179 infection [36]. CXCR3^{high} has been found to be a determination factor of cytotoxic response, as
180 studied during influenza pathogenesis [14]. CXCR3 expression is induced on naive CD8⁺ T
181 cells upon activation and remains preferentially upregulated on effector CD8⁺ T cells. CXCR3
182 is involved in the migration of CD8⁺ T cells to inflammatory sites. Antigen-specific CD8⁺ T
183 cells that lack CXCR3 skewed towards more memory cells with decreased activation property
184 and fewer short-lived effector cells [53,54]. CCR9 promotes migration to the gut, while CCR10
185 facilitates migration to the skin [55], indicating that the draining lymph node plays a significant
186 role in determining the migratory properties of activated CD8⁺ T cells, guiding them toward
187 specific locations.

188 In summary, the expression of specific chemokine receptors on effector memory T cells
189 determines their migratory behavior and allows them to migrate to the appropriate tissues

190 during an immune response. The differential expression of chemokine receptors on different
191 subsets of T cells contributes to their specialized functions and distribution within the body.

192 **Chemokine Signaling**

193 Chemokine receptors (CKRs) are a type of G protein-coupled receptors (GPCRs) that play a
194 crucial role in cell signaling. The signaling of CKRs involves various molecules, including
195 heterotrimeric G proteins, G protein receptor kinases (GRKs), and β -arrestins. These
196 components work together to initiate and regulate signal transduction pathways, leading to a
197 wide range of biological functions [56]. When a specific stimulus binds to a heptahelical
198 chemokine receptor, it activates specific heterotrimeric G proteins. These G proteins consist of
199 an alpha subunit ($G\alpha$) and a beta-gamma subunit ($G\beta\gamma$). Different $G\alpha$ subunits have been
200 identified on the basis of sequence and functional similarities (Table-2) - stimulatory subunit
201 ($G\alpha_s$), inhibitory subunit ($G\alpha_i$), $G\alpha_{12/13}$, and $G\alpha_q$ [57]. Initially, the $G\alpha$ subunit is bound to GDP
202 (guanosine diphosphate), but upon stimulation, guanine nucleotide exchange factors (GEFs)
203 stimulate the exchange of GDP for GTP (guanosine triphosphate) on the $G\alpha$ subunit. The
204 binding of GTP to $G\alpha$ leads to its activation and activated $G\alpha$ subunits can then interact with
205 various downstream effectors like adenylate cyclase (AC), GTPase of rho-family, protein
206 kinase A (PKA), protein kinase C (PKC) etc. in order to perform effector functions, including
207 cell migration [58–62]. For example, $G\alpha_q$ can activate an enzyme called phospholipase C
208 (PLC), which is associated with the cell membrane. PLC cleaves phosphatidylinositol (4,5)-
209 bisphosphate (PIP₂) into two second messenger molecules: diacylglycerol (DAG) and inositol
210 triphosphate (IP₃). DAG activates protein kinase C (PKC), while IP₃ triggers the release of
211 calcium ions from intracellular stores, such as the endoplasmic reticulum [63–65]. These events
212 initiate multiple signaling cascades that ultimately lead to various cellular responses, including
213 actin polarization and chemotaxis (Figure 1) [57,66].

214 To regulate the ongoing signaling, there is a regulator of G protein signaling (RGS) proteins
215 act as GTPase-activating proteins (GAPs) for $G\alpha$ subunits. They facilitate the hydrolysis of
216 GTP bound to $G\alpha$, thereby switching off the ongoing signaling processes. On the other hand,
217 the $G\beta\gamma$ dimer, which remains bound together, acts as a signaling molecule itself. It can initiate
218 signaling pathways independently and also regulate the activity of $G\alpha$ subunits. Some of the
219 pathways regulated by $G\beta\gamma$ include the Akt pathway, MAP kinase pathway, and calcium-
220 dependent pathway, which can lead to cellular responses like cell migration [67]. $G\beta\gamma$ subunit
221 mainly negatively regulate $G\alpha$ subunit when bind with it. Intracellular GPCR kinases (GRKs)

222 play a role in the regulation of CKRs. Upon continuous stimulation with chemokines, GRKs
223 phosphorylate the CKRs. This phosphorylation allows for the binding of arrestin proteins,
224 leading to the desensitization or internalization of the CKRs. This process can ultimately result
225 in the degradation of the receptors or their recycling back to the cell surface. Different
226 chemokines can activate the same CKR through different GRKs. For example, CCR7 can be
227 activated by both GRK3 and GRK6 in response to CCL19, while CCL21-induced CCR7
228 signaling is mediated only by GRK6 [68]. A phenomenon known as oligomerization is the
229 formation of complexes between either the same or different CKRs, has also been reported.
230 This can lead to altered receptor activity and crosstalk between signaling pathways, which may
231 affect normal signaling and result in a variety of cellular responses, including the regulation of
232 cell migration [69]. As studied in case of CCR7, oligomerization is necessary for the effective
233 cell migration. If oligomerization were to somehow fail, cell movement would be hampered
234 [70].

235 **Role of T cells during Leishmaniasis**

236 The orchestration of T lymphocytes on the targeted site plays central role during adaptive
237 immunity. An optimal T cell dependent immunoprotective response is essential to combat
238 infection caused by obligate intracellular *Leishmania* parasites in the mammalian host.
239 Different subsets of T cells have been discovered to play various roles in different clinical
240 forms of Leishmaniasis, highlighting the importance of understanding the types of T cells that
241 exhibit protective and destructive responses during infection (Figure 2).

242 **CD4⁺ T cells**

243 CD4⁺ T cells, a major group of T cells, provide protection to the host during Leishmaniasis
244 which relies on the expression of various antiparasitic molecules (eg. reactive oxygen species,
245 nitric oxide) in phagocytic cells that get activated on IFN- γ productions [71]. Various subsets
246 of CD4⁺ T cells, including Th1, Th2, Th17, Th22, Th9, Treg and Tfh cells, have been identified
247 based on their distinct cytokine profiles (Table-3). These subsets are responsible for different
248 immune responses and can determine resistance or susceptibility to *Leishmania* infection,
249 depending on which subset dominates the infected site. Treg cells possess immunosuppressive
250 properties during infection. They play a regulatory role in dampening immune responses and
251 can contribute to the persistence of the parasite [72].

252 In VL, Th1 cells produce pro-inflammatory cytokines such as IFN- γ and TNF- α , which induce
253 phagocytic activity and control parasitic growth while Th2 cells produce higher level of IL-4,
254 IL-5, IL-13, IL-10 that leads to susceptibility towards infection [73,74]. Another
255 proinflammatory subset of CD4⁺ T cells, Th17 produces IL-17 and IL-22 that recruit
256 neutrophils and inflammatory cells at the inflammatory site, thus playing a protective role
257 during VL [75,76]. It was observed that the cytokines IL-10, TGF- β and IL-35 released by these
258 cells hinder the functioning of IFN- γ , TNF- α and IL-17 during chronic VL as studied on *L.*
259 *donovani* infected mice model [77,78]. T follicular helper (Tfh) cells, an important CD4⁺ T cell
260 subset that regulate B lymphocytes activation during humoral immune responses, produce IL-
261 21 and IL-4 [79]. It has been found that IL-21 mRNA expression was upregulated in CD3⁺ T
262 cells of VL patients which is responsible for the expansion of IL-10 producing cells [80,81].
263 As, IL-21 also assists in antibody production, their increased level in serum of chronic VL
264 patients may be responsible for generating autoantibodies [82,83]. Th9 subset secrete IL-9
265 during infection. CD4⁺ T cells releasing IL-9 have been found to be upregulated in human VL
266 during acute phase and leads to immunopathogenesis [84].

267 In CL caused by *Leishmania (V.) braziliensis*, patients with active lesions exhibit a mixed
268 Th1/Th2 response, producing cytokines like TNF- α , IFN- γ , IL-12, IL-4, and IL-1. However,
269 individuals who have been cured of the infection primarily produce IFN- γ (Th1 response),
270 which is associated with a protective immune response [85]. Although IFN- γ and TNF- α
271 provide protection to the host against Leishmaniasis but their overproduction may cause tissue
272 damage [86]. IL-22, released by Th22 and Th17 cells both, found to provide protection against
273 tissue destruction during CL [87]. IL-17 was considered as a predictive marker of disease
274 progression in *L. guyanensis* infected CL patients [88]. High production of IL-17 cytokine has
275 been directly associated with disease severity in CL [89]. Primarily IL-9 produced by Th9
276 subset, but Th17 and Treg cells also produce this cytokine at low level and is involved in CL
277 pathogenesis [90,91].

278 During PKDL, there is an increase in the production of Th1 cells specific cytokines, namely
279 IFN- γ , TNF- α and IL-12, as well as IL-17A, IL17F and IL22 specific to Th17 cells shows
280 protective role during infection. IL-17 may contribute to resistance by increasing the
281 production of TNF- α , NO, and antimicrobial peptides (like β -defensin) in conjunction with IL-
282 22 [74]. Th2 cells produces higher level of IL-4, IL-5, IL-13, and IL-10 that leads to
283 susceptibility towards infection and promote parasite persistence during PKDL. The

284 progression of VL to PKDL is associated with overproduction of Th2-related cytokines in the
285 skin [91]. The simultaneous overproduction of IL-10 diminishes the effectiveness of IFN- γ and
286 TNF- α [92]. It was also found that the patients with PKDL had lower levels of serum IFN- γ ,
287 IL-10, and IL-6 compared to VL patients and comparable levels to healthy persons. However,
288 the levels of TNF- α in PKDL patients were considerably higher than in VL patients or healthy
289 participants [93]. Different kinds of PKDL have varying levels of these cytokines, polymorphic
290 PKDL had greater serum levels of IFN- γ and IL-10 than macular PKDL, while macular lesions
291 had lower levels of IFN- γ and TNF- α than nodular PKDL [74].

292 **CD8⁺ T cells** The role of CD8⁺ T cells in Leishmaniasis has received relatively less attention
293 compared to CD4⁺ T cells. Nonetheless, studies have demonstrated that CD8⁺ T cells,
294 specifically the Tc1 subset, do play a protective role in protozoan infections, including
295 Leishmaniasis. CD8⁺ T cells exert their protective effects through various mechanisms. They
296 produce inflammatory molecules such as IFN- γ and TNF- α , which contribute to the activation
297 of macrophages and the control of intracellular pathogens like *Leishmania*.

298 In VL, CD8⁺ T cells play a role in defending against the development of the disease. They
299 secrete IFN- γ , perforin, and granzyme, which contribute to the control of *Leishmania* infection
300 [94,95]. However, during the progression of human VL, there is often a depletion of CD8⁺ T
301 cells possessing anergic phenotype, which reduces their protective potential against the parasite
302 [96]. There are two distinct groups of CD8⁺ T cells have been identified, one is CD8^{low} which
303 was present during onset and VL progression, and the other one is CD8^{high} which increases
304 after the cure of disease [97]. Despite the challenges observed in human VL, studies in mouse
305 models have shown promising results regarding CD8⁺ T cell-based vaccines. These vaccines
306 rely on the chemokine CXCL10, which plays a crucial role in attracting CD8⁺ T cells to the
307 sites of infection. By enhancing the recruitment and activation of CD8⁺ T cells, CXCL10-based
308 vaccines have demonstrated effectiveness in reducing the parasitic burden in organs [98].

309 The production of IFN- γ , TNF- α and cytolytic molecules by CD8⁺T cells play protective role
310 during CL also [99]. The cytolytic genes are highly expressed in lesion and is positively
311 correlated with the recruitment of granzyme B⁺ CD8⁺ T cells [100]. CD8⁺ T cells contribute to
312 resistance against *L. major* infection by increasing the development of Th1 cells and
313 suppressing the development of Th2 cells, via the production of IFN- γ [101]. Additionally,
314 CD8⁺ T cells also responsible for the host immunopathology during CL [102]. [102] A previous
315 report found association between granzyme B and disease outcome. It was observed that on

316 inhibiting the granzyme release from CD8⁺T cells during CL reduces disease severity [103].
317 CD8⁺ T cell mediated pathology has been linked with the induction of inflammasome NLRP3
318 formation and release of IL-1 β which is confirmed by the increased level of this cytokine in
319 the lesions of patients infected with *L. braziliensis* [104]. This suggest that CD8⁺T cells possess
320 protective as well as immunopathogenic nature during *Leishmania* infection.

321 The frequency of IL-10 producing CD8⁺ T cells was considerably elevated in individuals with
322 PKDL caused by *L. donovani*, but it decreased after successful treatment [105]. Increased
323 expression of exhaustion markers such as programmed death-1 (PD-1), while reduced
324 expression of perforin and granzyme was also observed at lesional site [106]. This implies that
325 the conditions are favourable for the survival of parasites and leads to the progression of
326 diseases.

327 $\gamma\delta$ T cells

328 Gamma delta T cells or $\gamma\delta$ T cells accounting for 2–5% of the overall cell population in healthy
329 persons and possess a $\gamma\delta$ T-cell receptor (TCR) on their cell surface rather than $\alpha\beta$ TCR chains
330 as found in case of CD4⁺ and CD8⁺ T cells. A previous study demonstrated that mice infected
331 with *L. major* subcutaneously exhibited elevated levels of $\gamma\delta$ T-cells in the spleen and draining
332 lymph nodes of both susceptible BALB/c and resistant CBA/J mice. This suggests that $\gamma\delta$ T-
333 cells involve in protective inflammatory responses associated with the infection by promoting
334 granuloma formation [107–109]. In VL patients, elevated $\gamma\delta$ -T cells were observed to stimulate
335 the proliferation and differentiation of B-cells which is achieved through the secretion of
336 growth factor (BCGF) and differentiation factor (BCDF). This results into abnormalities in
337 humoral immune responses and hypergammaglobulinemia, suggesting an immuno-suppressive
338 and pathogenic response [110]. In another study of VL patients infected with *L. donovani*, a
339 substantial production of IL-10 was found which suggests an immunomodulatory function of
340 $\gamma\delta$ T cells [111]. In an experimental model of C57BL/6 mice infected with *L. donovani*, it was
341 shown that IL-17, which is generated by $\gamma\delta$ T cells, has an inhibitory effect and restricts the
342 proliferation of parasites in the liver [112].

343 Natural killer T cells (NKT)

344 NKT cells are specialized lymphocytes that share surface markers and functional
345 characteristics with both natural killer cells (NK) and T cells [113]. They may express CD4 or
346 CD8 marker on their surface and secrete IFN- γ , TNF- α , IL-4, IL-10, and IL-13 and constitute

347 0.1–0.5% of peripheral blood leukocytes [114,115]. IFN- γ producing CD8⁺ NKT cells was
348 shown to be protective in nature, whereas CD4⁺ NKT cells expressing CD25, Foxp3 and IL-
349 10 was found to be pathogenic during *L. donovani* infection [116]. These CD4⁺ NKT cells
350 accumulate at the infection site and it may be due to expression of CCR5 on its surface during
351 infection [117]. In a previous study on peripheral blood of VL patients, it was observed that
352 CD8^{dim} CD56⁺ NKT cells are the subset which express more granzyme B and are more
353 cytotoxic than CD8^{bright} CD56⁺ NKT cells [118].

354 In CL, CD3⁺ CD56⁺ CD8⁺ NKT cells were also found to be protective in nature and shown to
355 be associated with a cytotoxic response against *L. braziliensis* [117,119]. In CD1d^{-/-} and J α 18^{-/-}
356 mice, which lack NKT cells, exhibited a delay in clearing $>10^6$ *L. major* parasites during
357 infections [120].

358 However, despite the presence of the defensive properties of CD4⁺T cells and CD8⁺T cells,
359 immune responses are ineffective to control parasitic growth and thus disease progression
360 occur during chronic infections. Furthermore, hyporesponsive T cells expressing several
361 exhaustion markers (eg. PD-1, CTLA-4, LAG-3, TIM-3) leads to ineffective immune responses
362 and high parasitic load that depends on infection duration and host immunity [121]. The
363 understanding of the role of chemokines and their receptors associated with different T cell
364 subsets during Leishmaniasis, we can get valuable information on the key factors driving
365 disease progression and prognosis, potentially leading to better clinical management of the
366 disease. Targeting specific chemokines and their receptors holds potential for modulating T
367 cell responses and enhancing protective immunity against *Leishmania* infection.

368 **Hepatic granuloma formation during VL is a function of T- cell associated chemokine** 369 **profile**

370 The formation and maturation of granulomas in response to infection, including Leishmaniasis,
371 are dependent on the active cell recruitment [122]. Granulomas are complex inflammatory
372 structures that develop around infected cells, such as Kupffer cells in the liver. It includes a
373 variety of immune cells, including several types of T cells, particularly CD4⁺ T cells that
374 produce protective IFN- γ [5]. Kupffer cells phagocytosed parasites but were unable to eliminate
375 it solely and as formation of mature granuloma progresses, T cells become a central component
376 of the mature granuloma and contribute to the leishmanicidal activity of infected Kupffer cells
377 [123–125]. These cells work together to provide a targeted immune response and prevent the

378 parasites from spreading to other tissues. Chemokines play a crucial role in orchestrating the
379 formation and maturation of granulomas. They regulate the recruitment and infiltration of
380 various immune cells into the granuloma, allowing for a more effective immune response
381 against the infection. Chemokines secreted by activated Kupffer cells, such as CCL2, CCL3,
382 CXCL10 [126] attract immune cells like monocytes, T cells, neutrophils, and invariant natural
383 killer T (iNKT) cells to the site of infection. iNKT cells, upon activation, are necessary for the
384 sustained expression of CXCL10, an inflammatory chemokine that binds to CXCR3 and recruit
385 some more iNKT cells. This promotes the initiation of the granuloma formation where iNKT
386 cells are predominantly present [127,128]. In an in vivo model of VL, CXCL10 shown to
387 generate a protective proinflammatory environment by upregulating Th1 cytokines (IL-12,
388 IFN- γ , TNF- α) and downregulating anti-inflammatory IL-10 & TGF- β cytokines [129,130],
389 creating an environment favorable for the immune response against the infection. In the
390 inflammatory environment, the presence of IFN- γ cytokine can induce the expression of the
391 inflammatory chemokine CXCL9, CXCL10 and CXCL11 which attracts some more CXCR3⁺
392 T cells to the site of infection [131], suggests a positive feedback loop around these chemokines
393 and IFN- γ . Other chemokines, such as CCL19, CCL27, CXCL16, CCL9, and CCL25, that
394 selectively attract lymphoid cells have also been observed to be expressed during an early
395 infection [128]. The recruitment of T cells contributes to the immune defense against parasite
396 *L. donovani* by promoting the maturation of granulomas and facilitating the elimination of
397 infected cells [132]. The protective inflammatory environment created due to accumulated T
398 cells (CD4⁺ T cells, CD8⁺ T cells etc.) highlights their importance in the liver immune response
399 against parasite as observed in an experimental mice model infected with *L. donovani* [133–
400 135] (Figure 3). [123–125]

401 Overall, the interplay between the chemokine system and T cells is critical for the development
402 and function of hepatic granulomas in Leishmaniasis. Understanding the specific chemokines
403 and receptors involved in T cell recruitment and function within granuloma provides insights
404 into the potential points of intervention that help in pathogen clearance.

405 **Altered chemokine profiles during Leishmaniasis: protection vs parasite persistence**

406 *Leishmania* infection induces the expression of several chemokines and chemokine receptors
407 that promote the migration of specific immune cell subsets. The parasites have the ability to
408 modify the expression of chemokines and chemokine receptors, either upregulating or
409 downregulating them, in order to persist within the host [136,137]. This suggests that the

410 modified chemokine expression profiles and impaired immune cell migration are related to the
411 disease and its pathogenesis. In the liver of *L. donovani* infected BALB/c mice, the resolution
412 of infection initially occurs independently of T cells. This suggests that mechanisms other than
413 T cell-mediated responses are involved in controlling the infection during the early stages.
414 However, as the infection progresses, T-cell dependence becomes crucial for the expression of
415 chemokines and recruitment of inflammatory cells [138]. Immune cells are likely to migrate
416 from secondary lymphoid organs to sites of higher chemokine concentration during an immune
417 response.

418 The alteration in chemokine receptor expression can modulate the migratory properties of T
419 cells. Activated T cells exhibit a switch in chemokine receptor expression from constitutive to
420 inflammatory, contributing to the altered migration of these cells. Specific chemokines such as
421 CCL2 (MCP-1), CCL3 (MIP-1 α), and CCL4 (MIP-1 β) are known to stimulate the migration
422 of activated CD4⁺ and CD8⁺ T lymphocytes to the infected sites where an immune response is
423 being mounted [139,140]. The parasite *L. major*, which causes CL, has been demonstrated to
424 influence the mRNA expression of chemokines such as CCL2 and CXCL8, providing more
425 evidence that the infection affects chemokine expression [141]. [141]CCL2 that interact with
426 CCR2 is found to be upregulated in early lesions of human CL infection with *L. braziliensis*
427 when compared with their healthy controls [142]. CCL2 is believed to be a biomarker of cure
428 because it was upregulated in cured VL patients [143]. CCL3 and CCL5 (RANTES), which are
429 ligands for CCR1 and CCR5, selectively attract Th1 cells and are produced in high levels
430 during a Th1 response [144,145]. Elevated levels of CCL5 have been reported in *L. major*-
431 infected mice model and correlated it with parasite control [146]. Although increased CCL3
432 expression is linked to early control of parasitic load and the establishment of an anti-
433 leishmanial milieu, it also facilitates parasite survival during the later phases of *L. donovani*
434 infection [125]. CCL7 (MCP-3) interact with several receptors (CCR1, CCR2, CCR3, CCR5
435 and CCR10) and was found to be upregulated during *L. major* infection [147] and promote Th2
436 cell migration [148]. Chemokine expression profiles have also been used to define different
437 clinical forms of Leishmaniasis. Elevated levels of chemokines such as CCL2, CXCL9, and
438 CXCL10 have been observed in the lesions of patients with localized CL while diffused CL
439 patients have upregulated CCL3 [149]. Upregulation of these chemokines may indicate an
440 attempt to recruit immune cells and initiate an effective immune response despite the disease
441 progression.

442 In human MCL caused by *L. braziliensis*, there is an increase in mRNA and serum levels of
443 CXCL10. This upregulation of CXCL10 suggests its involvement in the immunopathogenesis
444 [150]. CXCL9 and CXCL10 expression is also upregulated during active VL which is known
445 to recruit CXCR3⁺ Th1 cells, may contribute to tissue damage and disease severity
446 [136,151,152]. The increased expression of CXCL10 during a long infection period in *L.*
447 *donovani*-infected mice further supports its role in the immune response against the parasite
448 [153]. Further, the reduced presence of CXCR3⁺ Treg cells in CXCL10^{-/-} *L. donovani*-infected
449 mice suggests that CXCL10 is important for their recruitment. This altered Treg cell trafficking
450 may contribute to a decrease in the regulatory mechanisms that control the immune response
451 against the parasite, ultimately resulting in a lower parasitic load [154]. This suggests that
452 CXCL10 is involved in creating a favorable immune environment for parasite control.

453 While information on T cell trafficking during *Leishmania* infection may be limited, the role
454 of certain chemokine receptors expressed on T cells has been investigated in the context of
455 Leishmaniasis. Some important chemokine receptors and their potential roles in different
456 phenotypes of Leishmaniasis are discussed below:

457 **1. CXCR3**

458 In *L. infantum* infected mice, *Cxcr3* gene is found to be associated with the activated T
459 lymphocytes, including effector cells and regulatory cells, suggesting their initial migration
460 towards affected spleen [125]. It is a crucial chemokine receptor involved in the trafficking of
461 activated CD4⁺ T cells and CD8⁺ T cells during infection [155,156]. It interacts with its ligands,
462 CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC), and promote integrin activation and
463 immune cell migration [157]. CXCR3 is a remarkable marker of Th1 cells and their lower
464 expression causes less trafficking of Th1 cells to the inflamed tissues during VL. It leads to
465 less IFN- γ production that affect host protective response against parasite [158]. In an
466 experimental model of VL, reduced number of CXCR3⁺ CD4⁺ T cells have been observed in
467 the spleen compared to liver during chronic phase of infection, and this impairment is
468 associated with a high parasitic burden in the organ, suggesting the importance of CXCR3 in
469 host immunity. However, their upregulated expression on T cells doesn't prevent from
470 developing VL as studied in transgenic mice that overexpressed CXCR3 on all T cells [159]. A
471 prior study on CXCR3^{-/-} C57BL/6 mice have shown that CXCR3 plays a crucial role in
472 resolving disease during *L. major* infection as it is necessary for T cells trafficking in skin, but
473 it is not essential during *L. donovani* infection, as mutant mice still able to recruit T cells to the

474 affected organs at later stages and exhibit a Th1 response, and effectively clear the infection
475 similar to CXCR3^{+/+} mice [160]. This is suggesting that the CXCR3 is necessary for T cells
476 trafficking in skin during *L. major* infection. Also, higher frequency of infiltrating cells was
477 IFN- γ producing Th1 and Tc1 cells expressing CXCR3, accounting for resolution of dermal
478 lesions [161].

479 2. CCR1

480 CCR1 belongs to the beta-chemokine receptor family which interacts with several ligands,
481 including Regulated on Activation Normal T Expressed and Secreted Protein
482 (RANTES/CCL5), Macrophage Inflammatory Protein 1 alpha (MIP-1 α /CCL3), Monocyte
483 Chemoattractant Protein 3 (MCP-3/CCL7), and Myeloid Progenitor Inhibitory Factor-1
484 (MPIF-1/CCL23). While CCR1 expression is preferentially found on CD4⁺Th1 cells [162] and
485 is involved in recruiting effector cells to infection sites, the specific role of CCR1 in the
486 immune response to Leishmaniasis can vary depending on the context and the specific species
487 of *Leishmania* involved. In C57BL/6 mice infected with *L. major*, it was found that CCR1
488 could actually contribute to susceptibility to CL, associated with an enhanced production of
489 interleukin-4 (IL-4) and interleukin-10 (IL-10) which suggests a shift towards a Th2 immune
490 response [163]. Previous research has revealed the expression of CCR1 by CD8⁺ T cells [164]
491 in different diseases but no studies have been conducted to investigate this expression in the
492 context of Leishmaniasis.

493 3. CCR2

494 CCR2 is the main receptor for the chemokine monocyte chemoattractant protein 1 (MCP-1),
495 also referred as CCL2. It also binds with other chemokines such as CCL7 and CCL12. When
496 CCR2 interacts with its ligands, it initiates signaling pathways that increase intracellular
497 calcium levels (Ca²⁺) and leads to the recruitment of memory T cells, monocytes, and dendritic
498 cells to inflamed tissues [165–167]. CCR2 has been shown to promote the differentiation of T
499 cells into Th17 cells, which are characterized by the production of interleukin-17 (IL-17) and
500 contribute to inflammatory responses in colon. While in the absence of CCR2 signaling as
501 studied on RAG1^{-/-} immunocompromised mice transferred with CCR2^{-/-} T cells, there is an
502 increase in the conversion of T cells into FoxP3⁺ regulatory T cells (Tregs), which are involved
503 in immune tolerance and suppression of immune responses [168]. It suggests that presence and
504 absence of CCR2 signaling play an important role in differentiation of T cells.

505 The association between CCR2 and T cells in the context of Leishmaniasis has not been
506 extensively studied compared to other chemokine receptors such as CCR1, CCR3, and CXCR3.
507 The research focus has primarily been on these other receptors and their involvement in the
508 immune response to *Leishmania* infection. However, considering the role of CCR2 in
509 recruiting monocytes and dendritic cells, it is plausible that CCR2 may also play a role in
510 modulating T cell responses during *Leishmania* infection. The recruitment and activation of
511 these antigen-presenting cells by CCR2 may influence the subsequent T cell responses and the
512 overall immune response against the parasite. To fully understand the specific involvement of
513 CCR2 in T cell responses and its impact on the immune response to Leishmaniasis, further
514 studies are needed.

515 4. CCR4

516 CCR4 is primarily expressed on activated T cells, particularly Th2 cells, antigen-specific skin-
517 homing T cells and Treg cells [169,170]. When CCR4 interacts with its ligand, CCL17 (also
518 known as thymus and activation regulated chemokine; (TARC), it can lead to an increase in
519 intracellular calcium levels [171]. While CCR4 is predominantly expressed on Th2 cells, other
520 cell types, which may not necessarily be IL-4 producers, can also express CCR4. In human
521 VL, higher expression of CCR4 on regulatory T cells (Tregs) has been observed, and this
522 increased expression may contribute to the accumulation of Tregs in the bone marrow of VL
523 patients. The accumulation of CCR4-expressing Tregs in the bone marrow may suppress local
524 effector T cell responses, thereby dampening the immune response against *Leishmania*
525 parasites in this compartment [72]. In late localized CL caused by *L. braziliensis* and *L.*
526 *amazonensis*, it has been reported that there is an increased in CCR4 expression on Tregs that
527 facilitates their recruitment and accumulation in the affected skin tissue. This accumulation of
528 CCR4-expressing Tregs suggests a potential role for CCR4 in regulating immune responses
529 and contributing to the immunosuppressive environment at the inflammatory sites [142,172].
530 These cells produce significant amounts of IL-10 and TGF- β , which regulate the functions of
531 effector T cells and thus the disease outcome [173]. CCR4-expressing Th2 cells and Treg cells
532 promotes the development of PKDL [174]. The trafficking of CCR4 expressing CD8⁺ T cells
533 in response to CCL17 and CCL22 in the dermal lesion have been reported during PKDL [106].

534 [142]5. CCR5

535 CCR5 is a chemokine receptor that specifically binds to chemokines such as regulated on
536 activation, normal T cell expressed and secreted (RANTES), macrophage inflammatory protein
537 1 alpha (MIP-1 α), and macrophage inflammatory protein 1 beta (MIP-1 β). Its expression on
538 cells is indicative of their activation state, and it is known to be expressed at higher levels on
539 Th1 cells [175] which can be upregulated by the cytokine interleukin-2 (IL-2) [176]. In early
540 infection with *L. donovani*, mice lacking CCR5 (CCR5^{-/-}; hybrid mice) showed impaired
541 interferon-gamma (IFN- γ) responses following T cell receptor (TCR) stimulation [177]. This
542 suggests that CCR5 plays a role in facilitating IFN- γ production by T cells during the early
543 stages of *Leishmania* infection and participate in the host defense mechanism. CCR5 has also
544 been identified as a crucial marker for the migration of naturally occurring regulatory T cells
545 (Tregs) to infected dermal skin during chronic cutaneous infection caused by *L. major* parasite
546 [50,178]. This indicates that CCR5 is involved in the recruitment of Tregs to sites of infection,
547 potentially influencing immune regulation and the balance between effector and regulatory
548 responses and promote parasite persistence.

549 Furthermore, in other protozoan infections like Chagas disease caused by *Trypanosoma cruzi*,
550 CCR5 expression has been found to be upregulated on CD4⁺ and CD8⁺ T cells. This
551 upregulation of CCR5 is associated with increased trafficking of these T cells to pathological
552 sites and has been correlated with pathogenic conditions [179]. Overall, CCR5 plays a role in
553 immune responses by regulating T cell activation, migration, and cytokine production in
554 various infectious diseases, including Leishmaniasis and Chagas disease. Its involvement in
555 these processes highlights its significance in modulating immune cell responses and potentially
556 impacting disease outcome.

557 **6. CCR6**

558 CCR6 is a chemokine receptor that regulates the migration of T cells during homeostatic and
559 inflammatory responses [180]. Interaction between CCR6 and ligand CCL20 leads to an
560 increase in intracellular calcium ion levels, which then triggers intracellular signaling and
561 cellular responses [181]. CCR6 is expressed on both anti-inflammatory regulatory T cells
562 (Tregs) and pro-inflammatory Th17 cells during inflammatory diseases, and promote immune
563 regulation or inflammatory responses, respectively [182–184]. It plays a role in the recruitment
564 and migration of T cells to specific sites of inflammation [185]. In the context of *L. major*
565 infection, studies using CCR6-deficient (CCR6^{-/-}) mice have shown that CCR6 is involved in
566 the trafficking of Treg cells. CCR6 deficiency resulted in hampered migration of Treg cells and

567 increase in inflammatory responses while no effect on Th17 cell migration [186]. This indicates
568 that CCR6 is important for the proper trafficking and localization of Treg cells to the site of
569 infection to prevent disease severity during *L. major* infection. However, further research is
570 needed to fully understand the precise mechanisms by which CCR6 influences T cell migration
571 and the implications for the immune response to *Leishmania* and other inflammatory
572 conditions.

573 **7. CCR7**

574 CCR7 is a crucial receptor involved in the homing of cells to lymph nodes and interacts with
575 its ligands, CCL19 and CCL21. CCR7 plays a significant role in regulating the migration and
576 homeostasis of memory T cells in lymphoid tissues where priming of antigen-specific T cells
577 occurs [187,188]. During VL, an increase in CCR7 expression has been reported on peripheral
578 blood mononuclear cells (PBMCs). As CCR7 is marker of naïve and central memory T cells
579 (T_{cm}), the upregulated CCR7 may contribute to their trafficking in lymphoid tissues where
580 naïve cells encounter antigen-presenting cells (APCs) during the course of the infection and
581 T_{cm} cells reside within SLOs and rapidly respond upon re-exposure to antigen [158]. Reduced
582 expression of CCR7 on activated dendritic cells (DCs) reduces their migration to the draining
583 lymph node and found to promote pathogenesis during CL and VL [189,190]. In cured CL
584 patients, it has been observed that CCR7⁻ CD4⁺ effector memory T (T_{em}) cells are present in
585 larger numbers. These cells are capable of producing interferon-gamma (IFN- γ) when
586 stimulated with soluble *Leishmania* antigens (SLA). The presence of CCR7⁻ CD4⁺ T_{em} cells
587 producing IFN- γ suggests a potential role for these cells in the immune response and resolution
588 of CL [191]. These studies highlight the dynamic regulation of CCR7 and its potential
589 implications in the immune response against *Leishmania* parasites.

590 **Factors shaping chemokines and chemokine receptors expression during Leishmaniasis**

591 The dysregulation of the chemokine system during infection may result from a complex
592 interplay between the parasite, host immune cells, and the local microenvironment. Interaction
593 between the host and the *Leishmania* parasite can lead to the modulation of the chemokine
594 system. *Leishmania* has been reported to secrete molecules that can degrade chemokines, such
595 as CXCL1, resulting in the downregulation of their expression [192].

596 However, various factors such as cytokine levels, epigenetic changes, and mutations contribute
597 to the modulation of chemokine receptor expression and downstream signaling pathways.

598 These factors can directly or indirectly influence the behavior of the chemokines profile during
599 infection. The possible causes for the altered chemokines profile during *Leishmania* infection
600 has been discussed below:

601 **1. Cytokines**

602 There is a complex interplay between cytokines and the expression of chemokines and
603 chemokine receptors, which contributes to the heterogeneity observed in the immune response
604 during Leishmaniasis. Cytokines such as IFN- γ , IL-10, TGF- β , TNF- α , IL-17, among others,
605 play a crucial role in regulating the expression of chemokines and chemokine receptors on
606 immune cells, ultimately shaping the cellular landscape at the site of infection (Table-4). IFN-
607 γ , for example, has been shown to induce the expression of chemokines such as CXCL9,
608 CXCL10, and CXCL11 [193]. Therefore, changes in the expression levels of CXCL9 &
609 CXCL10 observed during Leishmaniasis [158,194] may be due to influence of IFN- γ .
610 Additionally, cytokines like IL-2, IL-4, IL-7, and IL-15, which utilize the common gamma c
611 (γ c) chain receptors, can induce CXCR4 expression on T cells through the JAK/STAT
612 signaling pathway [195]. The role of IL-4 in modulating chemokine expression has also been
613 demonstrated. Blocking IL-4 in *L. major*-infected dermal tissue resulted in increased
614 expression of Th1 cell-recruiting chemokines such as CXCL9, CXCL10, CXCL11, and CCL5,
615 coinciding with increased IFN- γ production at the inflamed region [196].

616 Furthermore, TGF- β , which is increased during *Leishmania* infection, can inhibit macrophage
617 activation and contribute to increased susceptibility to the disease [197]. TGF- β has also been
618 shown to inhibit CCR3 expression, which is associated with decreased Th2 cell development.
619 Conversely, IFN- α , a type I interferon, decreases CCR3 and CCR4 expression while increasing
620 CXCR3 and CCR1 expression, promoting Th1 cell polarization by upregulating these
621 chemokine receptors [131]. IL-17, a proinflammatory cytokine, can induce the production of
622 CXCL chemokines, which recruit neutrophils and Th1 cells to the site of infection, thus
623 showing its protective role in patients with VL [76]. A positive correlation was found in
624 between IL-17/CCL3 and IL-17/CCL4 in patients infected with *L. guyanensis* [88]. On the other
625 hand, IL-10, which is responsible for impairing inflammatory immune responses, has been
626 shown to decrease the production of chemokines such as CCL5 and CCL2 in *L. amazonensis*-
627 infected mice [198].

628 Therefore, the presence of various cytokines in the microenvironment at the site of infection
629 directly and indirectly influences the outcome of the disease by regulating the expression of
630 chemokines and chemokine receptors, ultimately shaping the immune response and cellular
631 profiles observed in Leishmaniasis.

632 **2. Epigenetics**

633 The expression of chemokines and chemokine receptors can be modulated by the parasite
634 through various mechanisms, including the alteration of host gene expression and epigenetic
635 pathways [185]. Endogenous processes such as DNA methylation and histone modification can
636 inhibit the expression of chemokines and chemokine receptors, resulting in decreased
637 infiltration of immune cells [199–201]. *Leishmania* has been shown to produce effector
638 molecules such as exosomes or microRNA that can modify the host immune transcriptome and
639 induce changes in chemokine expression [202,203]. Additionally, the parasite has been shown
640 to regulate chemokine expression through the modulation of host microRNA levels. Several
641 chemokines, including CCL2, CCL5, CXCL10 found to be inhibited by the activity of
642 upregulated miRNA in *L. major* infected macrophages [204]. These epigenetic mechanisms
643 could contribute to the fluctuations observed in the expression levels of the chemokines profile
644 at different stages of infection. It is likely that *Leishmania* employs these mechanisms to evade
645 the host immune system and establish persistence within the host. However, the role of
646 epigenetic regulation in parasitic diseases, including Leishmaniasis, is not yet extensively
647 studied. Similar mechanisms have been observed in certain cancers, such as pancreatic cancer,
648 where abnormal methylation can lead to lower expression of CXCR4 [205].

649 Further research into the epigenetic modulation of the chemokine system during Leishmaniasis
650 and other parasitic diseases is necessary to better understand the mechanisms employed by the
651 parasite to manipulate the host immune response as evasion strategy, or by the host that employ
652 epigenetic mechanisms as a protective response against parasitic disease.

653 **3. Mutation**

654 The N-terminal region of chemokines is crucial for their biological activities and interaction
655 with chemokine receptors [206], mutations in this region can disrupt their binding to their
656 respective receptors, rendering them unable to activate the receptors. For instance, mutation at
657 a phosphorylation site can reduce receptor phosphorylation, impair β -arrestin binding, and
658 subsequently reduce receptor internalization in response to ligand binding [207]. Mutation in

659 residues of two CKRs failed to oligomerize together and cells expressing such receptors not
660 migrate even in the presence of their cognate antigens as observed in the case of CCR7 and
661 CCR5 [70,208].

662 Mutation at gene level is also capable to make changes in chemokines/and chemokine receptors
663 expression, potentially resulting in their aberrant expression. It has been reported that
664 *Trypanosoma cruzi* infected patients with no cardiac disease showed lower CCR5 expression
665 than those with cardiac disease due to a higher frequency of point mutations found in the
666 promoter region [209]. As it is known that CCR5 expression is associated with protective Th1
667 cells, an increased frequency of mutation in CCR5/ Δ 32 alleles have been reported in the lesions
668 of american CL (ACL) patients which suggest that this mutation may reduce Th1 cells
669 trafficking to the lesions and contribute to the pathogenesis in ACL patients [210].

670 While mutations have not been extensively studied in the context of Leishmaniasis, they have
671 the potential to play a role in modulating the immune response. Further research is needed to
672 elucidate the specific roles of mutations in the context of Leishmaniasis and their impact on
673 the chemokines profile and immune response.

674 **Modulation of chemokine machinery: plausible mechanisms**

675 In addition to the factors that have been discussed above, there are some other mechanisms that
676 influence the expression of chemokine machinery which includes chemokine availability,
677 receptor desensitization, decoy receptors, allosteric effects, post-translational modification etc.
678 However, these aspects have not been investigated in the context of Leishmaniasis, and they
679 may be plausible mechanism of aberrant expression observed in the chemokine profiles which
680 should be further investigated. The most significant mechanisms which have not been explored
681 yet are discussed below:

682 **1. Chemokine availability and desensitization**

683 The process of desensitization is an important mechanism for regulating chemokine receptors
684 (CKRs). Phosphorylation of CKRs triggers a series of events that regulate their signaling and
685 trafficking. Upon phosphorylation, CKRs become uncoupled from G proteins and recruit β -
686 arrestin. β -arrestin binding blocks further coupling to G proteins and facilitates the
687 internalization of the receptor via clathrin-coated pits [211]. This internalization process is
688 important to prevent chemokine overstimulation and allows for directional cell migration.

689 Homologous desensitization, which is chemokine-dependent, involves the internalization and
690 degradation or redistribution of the receptor. It plays a crucial role in regulating the chemokine
691 receptor response and maintaining appropriate chemotactic responses [212]. Heterologous
692 desensitization, on the other hand, is chemokine-independent and leads to the uncoupling of
693 G-protein and downregulation of chemokine receptors. It is usually due to cross-talk between
694 two CKRs, where signaling of one CKRs on chemokine binding impacting another chemokine
695 free CKRs and modulating their chemotactic response towards chemoattractant by
696 downregulating them [213]. [14] It was shown that CCL2 caused a reduction in the expression
697 of CCR2 on the surface of monocytes over time, due to desensitization mechanism [214].
698 Another study on human cells revealed the existence of desensitization mechanism where
699 CCL22 binding leads to internalization of CCR4 and hence reduces surface expression on Th2
700 cells [215]. However, no studies have been performed in case of Leishmaniasis. It is possible
701 that the reduction in chemokine receptor expression and the lower number of T cells recruited
702 to the infected tissue during Leishmaniasis may be attributed to these desensitization
703 phenomena. The expression of chemokines and chemokine receptors are interdependent. It has
704 been reported previously that high chemokine levels lead to lower CKR expression specific to
705 that chemokine [136]. Particularly for chemokines that signal through multiple receptors, the
706 absence of one receptor can result in high levels of circulating chemokines, which may reduce
707 the availability of alternate receptors due to ligand-mediated desensitization [216]. These
708 processes highlight the dynamic interplay between chemokines and their receptors, and the
709 regulation of chemokine receptor expression and responsiveness is critical for appropriate
710 immune cell recruitment and migration during other inflammatory responses.

711 **2. Chemokine scavenging decoy receptors**

712 The presence of non-signaling or silent chemokine receptors acting as ‘decoy and scavengers’
713 play an important role in suppressing host inflammatory responses and immunity. The silent
714 receptors compete with the signaling chemokine receptors by binding their ligands with high
715 affinity and thus preventing the cell from activation [217]. Functional decoy receptor has been
716 reported for inflammatory chemokine receptors such as CCR1, CCR2 and CCR5, in monocytes
717 and dendritic cells and despite increased expression of these chemokine receptors, they do not
718 respond to their ligands [218,219]. It has been reported previously that IL-10 may generate
719 chemokine decoy receptors in monocytes and dendritic cells in an inflammatory environment,
720 leading to the termination of the early inflammatory phase in the brain of *L. donovani* infected

721 mice [220]. Despite little knowledge about decoy receptors in the context of Leishmaniasis and
722 other parasitic disease, investigating their role will contribute to our understanding of infection
723 and the progression of the disease.

724 The higher expression of chemokine receptors observed during Leishmaniasis may be a host
725 strategy to address the urgent requirement for receptor-based signaling and prevent disease
726 progression. However, the presence of related decoy receptors limits the responsiveness of
727 immune cells to these chemokines. Consequently, despite the higher expression of chemokine
728 receptors, migration to the inflamed zone may be limited. Decoy receptors also act as
729 "scavengers" for chemokines, reducing their availability through intracellular degradation. This
730 mechanism helps regulate proinflammatory chemokines and chemokine receptors. The
731 presence of decoy and scavenger receptors highlights the complexity of the chemokine system
732 and its regulation during infection. Understanding the interplay between signaling and decoy
733 receptors is crucial for deciphering the immune response dynamics.

734 **Future Prospects and Concluding Remarks**

735 The chemokines and chemokine receptors play a crucial role in immune cell trafficking and
736 the inflammatory responses associated with *Leishmania* infection. Dysregulation of the
737 chemokine system is observed during Leishmaniasis, and investigating the involvement of
738 chemokines and their receptors in disease symptoms helps us understand how the effective
739 immune responses are orchestrated and how the pathological inflammation develops. The
740 redundancy and large production of multiple chemokines during infection may contribute to
741 the effectiveness of the immune response. Alterations in the expression levels of chemokines
742 and chemokine receptors can potentially serve as diagnostic markers and immunotherapeutic
743 targets. Blocking chemokines and their receptors, particularly the CXC- and CC-chemokines,
744 could be an attractive strategy for immunotherapy, especially during the chronic phase of
745 infection. While the role of the chemokine system in other immune cells in Leishmaniasis has
746 been extensively studied, further exploration of its involvement in T cell trafficking is needed.
747 Additionally, the understanding of the factors responsible for the altered profile of chemokines
748 and chemokine receptors in leishmaniasis is still limited and requires investigation.

749 Future research should focus on identifying the factors, both derived from *Leishmania* and the
750 host, that contribute to the changes observed in the chemokines and chemokine receptors
751 expression. The properties of the recruited immune cells will ultimately determine the

752 pathogenic condition of the host, making it important to elucidate the underlying mechanisms.
753 In recent past, targeting chemokines and chemokine signaling pathways using agonistic or
754 antagonistic monoclonal antibodies has emerged as an effective and promising therapeutic
755 approach in cancer patients. This targeted approach, either alone or in combination of
756 conventional drug therapy has shown promising result in modulating the immune response and
757 enhance anti-tumor immunity. Therefore, targeting the chemokine system as an
758 immunotherapeutic approach also holds promise for the treatment of leishmaniasis. However,
759 further studies, including those specifically investigating T cell chemokine machinery and its
760 role in PKDL, are warranted to advance our understanding and develop effective interventions
761 for this neglected tropical disease.

762 **Acknowledgement**

763 SU, VKS and RT would like to acknowledge Indian Council of Medical Research (ICMR),
764 Department of Biotechnology (DBT) and Banaras Hindu University respectively for providing
765 them fellowship. The Research in authors laboratory is supported through the funding from
766 Indian Council of Medical Research (ICMR), Science and Engineering Research Board
767 (SERB) and Institute of Eminence Grant of Banaras Hindu University (BHU-IoE).

768 **Conflict of interest**

769 The authors declare no conflict of interest

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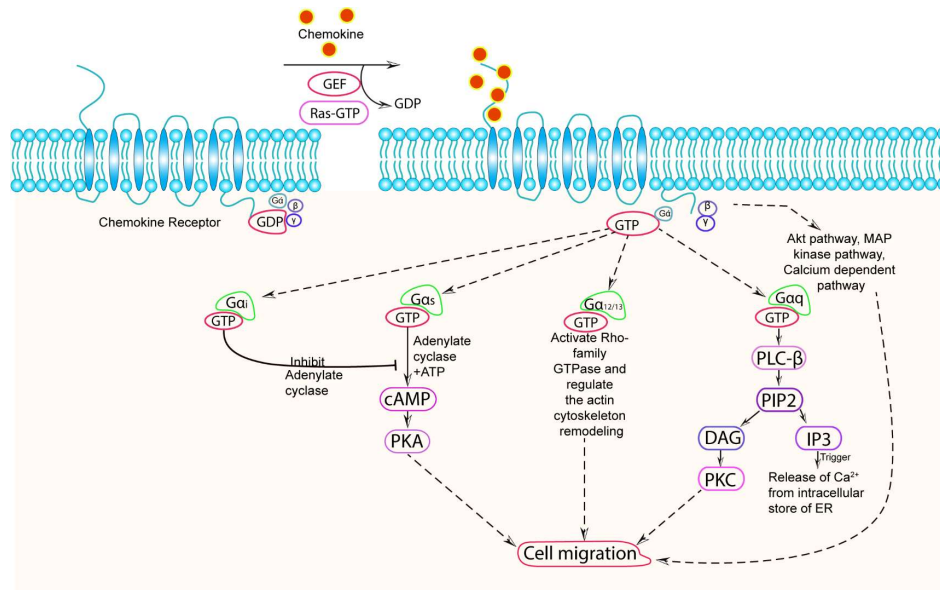
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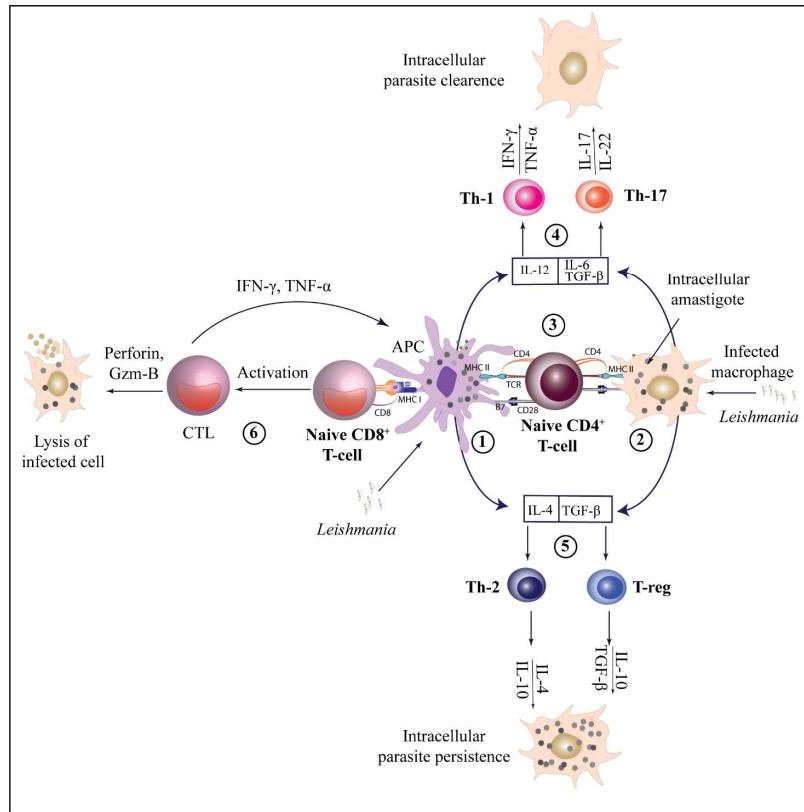
1504 **Figure 1. Chemokine signaling pathway.**

1505

1506 **Legend:** Chemokine receptor (CKR) remains in an inactive stage in which chemokine is not
 1507 associated with it, and G-protein is in inactive state and bound with GDP. CKR on interaction
 1508 with specific chemokine triggers the activation of the bound heterotrimeric G-protein
 1509 composed of $\alpha\beta\gamma$ subunits which leads to exchange of GDP with GTP and dissociation of the
 1510 heterotrimeric G protein complex into $G\alpha$ and $G\beta\gamma$ subunits where GTP remains attached to
 1511 $G\alpha$ subunit. Depending on the nature of inducing signal and types of $G\alpha$ protein, different
 1512 signaling pathways get activated. (a) $G\alpha_i$ inhibit the activity of adenylate cyclase enzyme and
 1513 reduces the cAMP generation; (b) $G\alpha_s$ stimulate the activity of adenylate cyclase enzyme and
 1514 stimulate the production of cAMP which further activate PKA; (c) $G\alpha_{12/13}$ activate rho-family
 1515 GTPase and regulate the actin cytoskeleton remodeling; (d) $G\alpha_q$ (or $G\beta\gamma$) activate PLC- β
 1516 enzyme which cleaves PIP₂, located in plasma membrane, into DAG molecules and
 1517 intracellular secondary messenger IP₃. DAG further activate PKC and IP₃ binds to its receptor
 1518 on ER causes Ca^{2+} release into the cytoplasm; (d) $G\beta\gamma$ can also activate Akt pathway, MAP
 1519 kinase pathway, Ca^{2+} dependent pathway. (d) Both the $G\alpha$ and $G\beta\gamma$ subunit capable to initiate
 1520 downstream signaling cascade that results in a range of cellular activities, including changes in
 1521 cytoskeleton dynamics and cell migration that ultimately regulate the physiological and
 1522 pathological response of the cells.

1523

1524 **Figure 2: Activation and differentiation of CD4⁺T and CD8⁺T cell subsets during**
 1525 **leishmaniasis.**

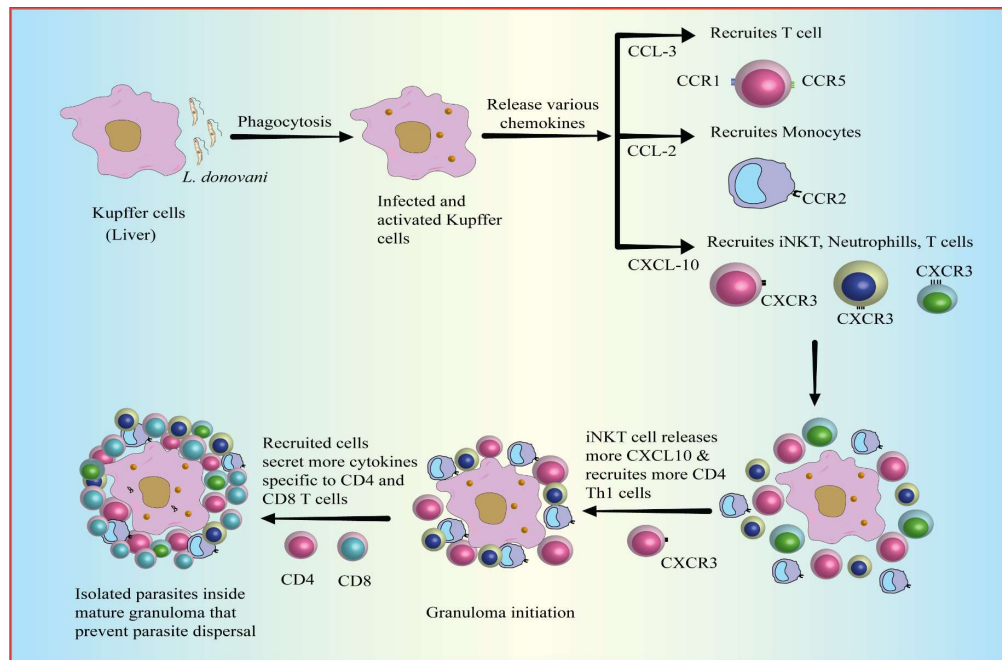


1526

1527 **Legend:** *Leishmania* antigens are presented by APCs or infected macrophages (1,2) to naïve
 1528 CD4⁺ T cells through MHC class II molecules, leading to their activation. Depending on the
 1529 cytokine environment, naïve CD4⁺ T cells can differentiate into various T-helper subsets (3).
 1530 Interleukin-12 (IL-12) facilitates the differentiation of Th1 cells, which produce IFN- γ and
 1531 TNF- α , promoting the clearance of intracellular parasites. Th17 cells, on the other hand,
 1532 produce IL-17 and IL-22, contributing to anti-leishmanial and inflammatory responses (4). Th2
 1533 cell differentiation occurs under the influence of IL-4, leading to the production of IL-10 and
 1534 IL-4 which can result in parasite persistence by inhibiting macrophage activation. Similarly,
 1535 TGF- β promotes the differentiation of T-regs, which produce IL-10 and TGF- β , contributing
 1536 to immune regulation and further supporting parasite persistence (5). Naïve CD8⁺ T cells are
 1537 activated via MHC class I molecules and can differentiate into CTLs, producing perforin and
 1538 granzyme B to target infected cells. They also produce IFN- γ and TNF- α , which support the
 1539 Th1 response for effective parasite clearance (6).

1540 [CTL- Cytotoxic T lymphocytes, APC- Antigen presenting cell, MHC- Major
 1541 Histocompatibility complex, Gzm B-Granzyme-B, TGF β - transforming growth factor- β , T-
 1542 regs - Regulatory T cells]

1543

1544 **Figure 3. Formation of Granuloma.**

1545

1546 **Legend:** Granulomas are formed as a response to infection, such as around Kupffer cells in the
 1547 liver, to elicit a targeted immune response to eliminate parasites and prevent dissemination.
 1548 Kupffer cells post infection via phagocytosis (a) gets activated thereafter releases chemokines
 1549 such as CCL2, CCCL3, CXCL10 that assist in recruitment of immune cells like monocytes, T
 1550 cells, neutrophils, and iNKT cells to the site of infection (b) leading to accumulations of
 1551 immune cell around site of infection (c). iNKT cells are essential for the expression of
 1552 CXCL10, an inflammatory chemokine, which recruits iNKT cells and initiates granuloma
 1553 formation (d). Similarly, altogether recruited cells secrete chemokines that attract lymphoid
 1554 cells, contributing to immune defense against leishmania parasites. Hepatic CD4⁺ and CD8⁺ T
 1555 cells are crucial in the liver immune response against leishmaniasis by formation of granuloma
 1556 around site of infection (e).

1557 [CCL3: chemokine ligand 3; CCL2: chemokine ligand 2; CXCL10: C-X-C motif chemokine
 1558 ligand 10; CCR: beta-chemokine receptors; iNKT: invariant natural killer T cells].

1559

1560 **Table 1: CD4⁺ T cell subsets expressing chemokine receptors and their subsequent ligands**

1561

No.	CKRs types	Chemokine receptors (CKRs)	Chemokines (corresponding ligands)	T-subsets expressing CKRs	Inflammatory conditions	References
1	CCRs	CCR1	CCL3, CCL5-9, CCL13-16, CCL23	Th1, Th2, Th9, Th17, Trm	rheumatoid arthritis, allergic rhinitis, tumor	[221,222]
2		CCR2	CCL2, CCL7, CCL8, CCL12, CCL13	Th1, Treg, Th17	tumor, melanoma, pancreatic cancer	[223–231]
3		CCR3	CCL5-8, CCL11, CCL13, CCL15, CCL24, CCL26	Th2, Th9, Treg	atopic dermatitis, cancer, experimental colitis, allergic inflammation	[223–229,232,233]
4		CCR4	CCL17, CCL22	Th2, Treg, Th17, Th22, CD8	melanoma, atopic dermatitis, cancer, allergic inflammation	[223–231,234]
5		CCR5	CCL3-5, CCL11, CCL14, CCL16	Th1, Th9, Treg, Th17	melanoma, atopic dermatitis, HIV-infection	[231,234,235]
6		CCR6	CCL20	Th17, Treg, Th9, Tfh, Th22	melanoma, tumor, pancreatic cancer, lymph-borne pathogenic	[223–231,236–239]

					response, skin inflammation	
7		CCR7	CCL19, CCL21	Tcm, Tcm, Treg, Naïve T cell	melanoma, homeostasis, self-tolerance	[231,240]
8		CCR8	CCL1, CCL18	Th2, Treg, Skin CD4 T _{rm}	allergic inflammation, lung cancer, skin disease	[234,241,242]
9		CCR9	CCL25	Th17, Th22	viral infection, intestinal inflammation	[243,244]
10		CCR10	CCL27	Th17, Th22	malignant ascites, skin pathophysiology	[223–230,245–248]
11	CXCRs	CXCR1	CXCL8, CXCL6, CXCL1	CD4, CD8	leukemia, homeostasis, viral and tumor inflammation, allergic disease	[249–256]
12		CXCR2	CXCL1-3, CXCL5-8	CD4, CD8	multiple sclerosis, cancer, experimental autoimmune encephalomyelitis (EAE)	[249,252,253,257,258]
13		CXCR3	CXCL9-11	Th1, Treg, Th9, Tfh, Th17, CD8 T _{cm} & T _{em}	melanoma, atopic dermatitis	[223–231,253,259]

14		CXCR4	CXCL12	CD4, CD8	homeostasis, HIV-infection, tumor, prostate cancer, pancreatic cancer	[223–230]
15		CXCR5	CXCL13	Th17, Tcm, Tem, Tfh, CD8	humoral responses, rheumatoid arthritis, autoimmune disease	[260–262]
16		CXCR6	CXCL16	Th1, Th17, CD8	inflamed human liver, experimental autoimmune encephalomye litis (EAE), alzheimer disease,	[231,239,26 3,264]

1562 [CCL= chemokine ligand; CXCL= C-X-C motif chemokine ligand; CCR= β -chemokine receptors;
1563 CXCR= α -chemokine receptors; Tcm= central memory T cells; Tem= effector memory T cells; Tfh=
1564 follicular helper T cells; Treg= regulatory T cells; Th= helper T cells]

1565

1566 **Table 2: G alpha protein subunits and their corresponding signaling pathways**

S.No.	G alpha subunit	Signaling Pathway
1.	G α_s (‘s’ stimulatory)	Activate adenylate cyclase and cAMP-dependent protein kinase A (PKA) [60,61]
2.	G α_i (‘i’ inhibitory)	Inhibit adenylate cyclase and protein kinase A (PKA) [60,265,266]
3.	G $\alpha_{q/11}$	Stimulate phospholipase C (PLC- β) to cleave PIP ₂ into DAG and IP ₃ and activate Protein Kinase C (PKC) and Ca ²⁺ dependent pathway [64]
4.	G $\alpha_{12/13}$	Activate Rho-family GTPase and regulate the actin cytoskeletal remodeling [267]

1567

1568

1569 **Table 3: Cytokine profiles of different CD4⁺ T cell subsets during Leishmaniasis**

1570

S.No.	CD4⁺ T cell subsets	Cytokine profiles in <i>Leishmania</i> infected patients	References
1	Th1	IFN- γ , TNF- α , IL-12	[174]
2	Th2	IL-4, IL-5, IL-13, IL-10	[91]
3	Tfh	IL-21, IL-4	[79,268,269]
4	Th17	IL-17, IL-22, IL-9	[174,270,271]
5	Th22	IL-22	[272]
6	Th9	IL-9	[273]
7	Treg	IL-10, TGF- β , IL-35, IL-9	[90,91]

1571

1572

1573 **Table 4: Influence of cytokines on chemokines/and receptors, T cell profiles, and outcome**
 1574 **of infection during Leishmaniasis.**

S.No.	Cytokines	Affect chemokines/ and chemokine receptors expression	Impact on specific T-cell subset	Outcome of <i>Leishmania</i> infection	References
1	IFN- γ	CXCL9, CXCL10, CXCL11 (\uparrow)	more CXCR3 ⁺ Th1 cells trafficking	resolution of infection	[274–278]
2	IL-2, IL-7, IL-15	CXCR4 (\uparrow)	express on central memory T cells (CD4 ⁺ T cell subset); induces T cell chemotaxis	parasite may facilitate HIV-infection of CD4 ⁺ T cells during <i>Leishmania</i> -HIV coinfection	[279–281]
3	IL-4	CXCR4 (\uparrow); CXCL9, CXCL10, CXCL11, CCL2, CCL5, CCR5 (\downarrow)	less trafficking of Th1 cells	less IFN- γ production in <i>L. major</i> infected dermal tissue; shows pathogenic T cell response	[279,280,282,283]
4	IL-17	C-X-CL types	recruit more Th1 cells	protective role in VL patients; skin inflammation in CL	[271,284,285]
5	IL-10	CCL5, CCL2 (\downarrow)	less Th1 cells migration	reduces Th1 cell development and effector functions; promote parasite persistence and pathogenesis	[286,287]

1575