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Role of Chemokines and Trafficking of Immune Cells in Parasitic Infections

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Abstract

Parasites are diverse eukaryotic pathogens that can have complex life cycles. Their clearance, or control within a mammalian host requires the coordinated effort of the immune system. The cell types recruited to areas of infection can combat the disease, promote parasite replication and survival, or contribute to disease pathology. Location and timing of cell recruitment can be crucial. In this review, we explore the role chemokines play in orchestrating and balancing the immune response to achieve optimal control of parasite replication without promoting pathology.

Keywords

Chemokine; parasite; cell trafficking; *Toxoplasma*; CCL21; CCR7

Introduction

As with all infections, parasites induce inflammation - that is mobilization, proliferation and recruitment of leukocytes to the site of infection. This immune cell trafficking and the effector functions of these cells can serve to control the pathogen or exacerbate pathology. In comparison to viral or bacterial invasion, parasites are complex eukaryotic pathogens often with multiple lifecycle stages within the mammalian host. Their characteristic ability to manipulate the host immune response and tendency to cause chronic infections adds further complexity to the recruitment and maintenance of cellular immune responses within infected tissues.

Chemokines are essential regulators of cell trafficking. They are a large family of small cytokines named for their ability to induce chemotaxis of cells expressing the appropriate receptors and categorized into four subfamilies (C, CC, CXC, CX₃C), depending on the sequence position of conserved cysteine residues. Chemokines play multiple roles in physiology, including development for directed cell guidance and hematopoiesis in addition to mediating inflammatory responses [1–6]. However, perhaps because of the inherent requirement for continuous migration of cells, the influence chemokines exert on the

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Conflict of Interest

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immune system has been extensively studied. This includes the role they play in lymphocyte homeostasis, which requires several chemokines, primarily CCL19 (ELC, EBV-induced chemokine, MIP-3 β) and CCL21 (SLC, exodus 2), the ligands for CCR7. CCL21 is required for T cell circulation within and between primary and secondary lymphoid organs as well as the homeostatic expansion of naïve CD4⁺ T cells as well as the homeostatic expansion of naïve CD4⁺ T cells [7–10]. While CXCL13 controls B cell retention and organization within the B cell follicle of secondary lymphoid tissues. Moreover, CCR7 signaling cooperates with CXCR5 signaling on B cells to orchestrate B cell migration within the B cell follicle, allowing B cell access to T cell help [11–13]. However, ultimately the immune system has evolved for efficient and optimal defense against invading pathogens. In this review we will focus on the role chemokines and subsequent cell trafficking play in the rapid, coordinated and long-term immune defense against parasitic infection.

Initial Exposure

The earliest stages of infection are a parasite's first opportunity to establish itself within its host. Conversely, it is also the host's chance to mount a rapid and effective response to clear, or at least control the infection. Local parasitemia generally leads to acute systemic cytokine production. This has a profound effect on the mobilization of immune cells. Recent work has demonstrated that IFN- γ signaling following *Plasmodium* infection leads to the production of CCL2 from stromal cells, contraction of myelopoiesis in the bone marrow and CCR2 dependent migration from the bone marrow to the spleen [14]. The IFN- γ -induced migration of CCR2⁺ progenitor cells leads to proliferation and differentiation in the spleen that is critical for clearance of the blood stage of *Plasmodium*. As this process is independent of TLR signaling it is possibly occurring during all protozoa infections and may explain defects in the recruitment of innate effector cells during IFN- γ deficiency [15]. Depending on the route of entry the parasite needs to negotiate several physical barriers. This breaching is in and of itself damaging, and leads to chemokine production and recruitment of innate inflammatory cells. In addition, the type of parasite and the anatomical location determines the specificity of cellular recruitment.

Skin: neutrophils

All parasites introduced via the bite of an insect vector have their initial exposure to the mammalian immune system within the skin. This includes the protozoa *Leishmania*, *Plasmodium* and *Trypanosome* as well as the helminths that cause filariasis and onchocerciasis. In addition, the burrowing activities of schistosome cercariae and infective *Nippostrongylus* and *Strongyloides* larvae facilitate parasite entry directly into and across the skin barrier. The profound itching that results from entry of these parasites into the skin is due to rapid recruitment of immune cells. Neutrophils are the first and most abundant cell type recruited to the injury site and arrive following the production of CXCL1 (GRO α , KC, MSGA- α , NAP-3), CXCL2 (GRO β , MIP-2 α), CXCL8 (IL-8) [16–19] and the complement fragment C5a [20]. In response to sterile injury, cues that draw neutrophils from the blood begin to be secreted by the vascular endothelium in a cell-death mediated manner [21, 22]. Stress from sterile injury induces necrosis or apoptosis, and subsequent release of danger signals like adenosine triphosphate (ATP) [21] or apoptotic bodies containing IL-1 α [22].

Upon extravasation into the skin, neutrophil recruitment to the lesion has been described as occurring in three distinct phases [23]. Within 15 minutes after needle scratch or laser ablation, neutrophil behavior is described as scouting, where a few cells migrate toward and begin to accumulate at the site of injury. This phase most heavily relies on chemokine-mediated recruitment, as it is significantly reduced by treatment with pertussis toxin [23]. Next, amplification of neutrophil numbers occurs, followed by a plateau with cell numbers remaining stable for up to one hour. This response to a non-infectious stimulus differs from the swarming behavior observed in the context of parasite infection, where neutrophils dynamically migrate into and out of large clusters. During sterile injury, neutrophils clean up debris from locally damaged tissue. However, infection initiates attempts at immunity and the other function of neutrophils is to phagocytose pathogens and migrate into the draining lymphatics [24].

While the severity of the host's reaction to bites can vary, components of mosquito and sand fly saliva, such as the 200kDa neutrophil chemotactic factor (NCF) isolated from *A. stephensi*, serve as potent chemoattractants for neutrophils [25, 26] (Figure 1A), and depending on the species of sand fly, eosinophils as well [26, 27]. Mosquito bites also induce dermal mast cell degranulation, contributing to a rapid influx of neutrophils to the skin [28]. This neutrophil influx depends on mast cell release of TNF α and CXCL2 [29] and is significantly reduced in mice that lack mast cells [28]. This first line of defense works against both *Plasmodium* and *Trypanosoma*. Large numbers of neutrophils are recruited to the chancre formed after a tsetse fly bite [30], which is beneficial for the host as they are the main cell type that phagocytose the parasite at this stage, leading to a decrease in parasitemia [31–33]. However, neutrophils have been shown to promote *Leishmania* survival as the parasite can temporarily reside within these cells [34, 35].

Skin: macrophages and dendritic cells

Skin resident dendritic cells (DCs), including Langerhans cells (LCs) and dermal DCs, act as important sentinels for breaches in this barrier. These two subsets of DCs are distinct in their behavior. LCs are found concentrated ~15 μ m below the outer cuticle and unlike other DCs, are relatively sedentary. Rather than patrolling the epidermis, they extend and retract their dendrites to probe their environment [36] (Figure 2A). This is in contrast to dermal DCs sitting between 20–40 μ m below the basement membrane within the extracellular matrix of the dermis. Dermal DCs are less concentrated and are continuously migrating in a manner dependent on chemokine receptor signaling [37, 38]. LCs are slower and less likely to migrate to the lymph [39, 40]. It also seems that they are less dependent on CCR7-CCL21 interactions than dermal DCs [41]. During *Leishmania* infection dermal DCs primarily phagocytose parasites. Using *in vivo* imaging, dermal DCs can be seen extending long pseudopods and capturing parasites at a considerable distance from the main cell body [37]. This is a specific behavior not induced by beads or a simple random event, and is not dependent on LPG sensing by the DC. This may suggest rapid cell-cell communication and highly localized chemokine gradients.

During inflammation of the skin, neutrophil infiltration is quickly followed by trafficking of monocytes, which differentiate into macrophages and DCs, and are normally recruited to the

inflamed site by local production of CCL2 (MCP-1), CCL3, CCL4, and CCL5 (RANTES) [42]. Although mosquito saliva is a potent chemoattractant for neutrophils, it can also inhibit DC migration as the number of DCs recruited to the site of *Plasmodium* sporozoite inoculation is significantly reduced in the presence of the saliva, allowing the parasite to persist in the skin for several hours [43, 44]. This inhibition in DC migration is thought to benefit the parasite, by delaying adaptive immune responses, and allowing infection to establish in the liver. In contrast, sand fly saliva is a potent chemoattractant for monocytes [27] yet this opposing strategy benefits *Leishmania* survival as neutrophils recruited to the bite site are invaded by *Leishmania* and induced to secrete CCL4, which enhances the recruitment of macrophages [34]. Recruited macrophages then phagocytose infected neutrophils, allowing the parasite to enter and replicate within the macrophage - the major reservoir for *Leishmania* infection. Similar recruitment kinetics have been reported following tsetse fly bites [30]. Smears from chancres revealed that a few days following neutrophil recruitment to the bite site, an expansion in the number of macrophages was observed [30]. Chancre histology revealed disorganized cellular infiltration with no effort to surround or contain replicating parasites as has been observed during other protozoan infections [30].

Schistosome cercariae do not rely on an insect vector for transmission and instead, actively penetrate the skin. Tissue damage caused by the burrowing action of cercariae, as well as parasite antigens, induce the production of CXCL1, CXCL2, and CXCL8. It is unclear if the cercariae themselves or the resulting tissue damage serves as the primary trigger for immune cell recruitment, but it is clear that neutrophils and skin-resident antigen presenting cells (APCs) are the first to arrive followed by eosinophils. Control of schistosomes in the skin is dependent on the recruitment of eosinophils. Macrophages and mast cells, perhaps recruited by CCL3 (MIP-1 α) and CCL4 (MIP-1 β), [45, 46] closely follow eosinophils to skin lesions caused by cercariae.

Skin: eosinophils

Eosinophil recruitment is one of the hallmarks of non-protozoan parasitic infections [47, 48], serving as effector cells against invading helminths [49, 50]. Indeed, absence of eosinophil recruitment to infected tissues promotes helminth survival [51]. Eosinophils are recruited to the skin after IL-4 and IL-13 activation of dermal fibroblasts. Activation of dermal fibroblasts leads to production of CCL5 (RANTES) and CCL11 (eotaxin) [52, 53, 54], with at least three chemokine receptors, CCR3, CXCR4 and CXCR2 expressed by eosinophils playing a role in chemokine sensing and recruitment to the skin [55]. In response, parasites have developed defenses against eosinophil recruitment. For example, a metalloprotease secreted by the hookworm, *Necator americanus*, cleaves CCL11 thereby inhibiting eosinophil recruitment [56], leading to increased parasite survival.

Intestinal Mucosa

Similar to the skin, there is an immediate response to parasite infection in the gut. Helminth infection leads to marked eosinophilia that depends on both CCL11 and CCL24 (MIPF-2, eotaxin-2), although the absence of eosinophil recruitment to the intestine does not affect worm expulsion [57]. Mast cells and basophils are involved in cytokine production, and the

recruitment and differentiation of Th2 cells during helminth infection in the gut [58]. In contrast, protozoan infection, including *Toxoplasma*, induces CXCL2 [59] from infected enterocytes with significant mobilization of neutrophils. Neutrophil recruitment to discrete plaques of *T. gondii* replication can be observed in live imaging experiments [60] (Figure 1B). The number of parasite plaques increases over time, leading to speculation *T. gondii* may colonize other areas of the small intestine by escaping into the lumen, either as free parasites [60] or within infected neutrophils [61]. However, neutrophil depletion with an anti-Ly6G monoclonal antibody has little effect on host survival or parasite dissemination [62], perhaps indicating that *T. gondii*'s use of neutrophils to establish infection may be a secondary mechanism and instead may depend on the recruitment of inflammatory monocytes or DCs [63, 64].

Intestinal epithelial cells infected with *T. gondii* produce a variety of chemokines including CCL2, CCL4, CCL5, CCL7 (MCP-3), CCL8 (MCP-2) [59]. All these molecules serve as chemoattractants for monocytes, DCs, and macrophages to the gut [60, 65]. CCL2 dependent recruitment of inflammatory monocytes is necessary to control replicating parasites [15, 66–70]. These cells have several roles. They are capable of killing parasites directly by producing reactive oxygen species [69], they shape the adaptive immune response by acting as APCs [71, 72] and by secreting IL-12, and they drive the production of IFN- γ by NK and later T cells in areas where parasites are replicating [73–75]. The plaques of parasite replication in the intestine contain monocytes while DCs assemble around the plaque border [60]. This distinct localization of cell populations is not yet understood, but could be due to several causes, including the possibility that infected DCs may have already migrated out and away from the plaques at the time they were imaged, six days postinfection [60]. Analysis of local chemokine expression at the plaque center and perimeter, in addition to live cell imaging, may help explain the cellular dynamics in the inflamed small intestine. However, based on other well-defined processes it is likely that activated epithelial cells are producing CCL2 to recruit monocytes and DCs in a CCR2 dependent manner [62].

Transition to the Adaptive Immune Response

After DCs encounter antigen they present it in the secondary lymphoid organs to initiate an adaptive immune response. Studies have revealed this critical function takes place in two phases. First, lymph node resident DCs can acquire antigen from the lymph draining from the infection site. Then, a second wave of DCs arrive in the lymph node from the infected tissue, carrying antigen to present to T cells [39]. To do this, peripheral DCs upregulate the chemokine receptor CCR7 and follow immobilized gradients of CCL21 [76] to find lymphatic vessels present within tissue (Figure 2A). Evidence for the presence of these gradients is sparse, but growing. For example, ten years ago the prevailing view was that lymphocytes migrate randomly within lymphoid organs [77]. Later, as evidence for directional migration of cells mounted, a gradient of CCL21 was detected by immunohistochemical staining in the lymph node segregating B and T cell zones [11], and a gradient of CCL2 was shown in the context of sterile inflammation in the liver [21]. Now it is known that CCL21 secreted by lymphatic endothelial cells is immobilized within tissue by heparin sulfate that peppers the extracellular matrix. This CCL21 secretion is necessary for

DC guidance to the lymphatic vessels, as application of exogenous CCL21 lead to misguided migration [76]. Once within lymphatic vessels, DCs migrate to the draining lymph node, and under the influence of CCL21 and CCL19 migrate randomly [78] presenting antigen to T cells (Figure 2B). As T cells also express CCR7, they are crawling along the same CCL21 networks maximizing the chances of encountering a DC presenting cognate antigen [79]. Efficient DC migration is essential for the host to control infection and may rely on additional chemokine receptor signaling. For example, skin DCs rely on expression of ligands for both CCR2 and CCR7 to migrate to the lymph node during cutaneous Leishmaniasis [80, 81]. Although CCR7/CCL21 signaling is a ubiquitous process, it is not always required to mount protective immune responses. In many non-parasitic infections and in the presence of a large antigenic challenge, CCR7-CCL21 interactions are dispensable [82–86]. However, it is absolutely essential to prime T cells during the onslaught of *Toxoplasma* infection [15]. Without such signaling there is insufficient activation of T cells, poor production of IFN- γ and failure to control parasite replication.

B cell responses are equally critical during the transition to adaptive immunity, not only against helminth infection but also against protozoans, including *Toxoplasma*, *Plasmodium* and *Trypanosomes* [87–89]. Ligands for CXCR4, CXCR5, and CCR7 all cooperate to position B cells to mount appropriate antibody responses. High expression of CXCR5 in naïve B cells keeps them confined to the B cell follicles that are lined with CXCL13 [13, 90]. Upon activation with antigen, B cells upregulate CCR7 facilitating migration toward the T cell zone to receive T cell help [11, 12, 91]. During *T. cruzi* infection, CCL5 plays an important protective role in mobilizing B cell populations and is directly able to induce B cell proliferation and IgM secretion [92]. In contrast, increased CCR9 expression on circulating B cells during human filarial infections is associated with increased disease characterized by lymphedema [93]. Significantly, recent studies have demonstrated a role for B cells in limiting hepatic pathology during chronic schistosome infection [94, 95]. Most relevant is that these B cells are recruited to the liver from the hepatic lymph nodes in a manner requiring IL-10-dependent production of CXCL9 and CXCL16 [95]. Thus, it seems that CXCR3, CXCR6 expressing B cells, generated only after lengthy exposure to antigen, are regulatory lymphocytes required for long-term control of liver pathology. Whether or not there is other organ-specific chemokine-dependent recruitment of regulatory cell populations, as has been demonstrated here for CXCL16 and B cells, may provide fruitful avenues of research.

Parasite Dissemination and Cell Recruitment to Other Organs

The initial infection site is not the only source of antigen for DCs. Once *Plasmodium* leaves the skin via the bloodstream they traffic to the liver where they traverse Kupffer cells and invade hepatocytes before infecting red blood cells [96–98]. Splenic macrophages are particularly important in the clearance of infected red blood cells through opsonization [99], NK cells remain an important source of IFN- γ [100] and DCs are again essential for T cell priming and the generation of an adaptive immune response [101]. In contrast, *T. cruzi* amastigotes can replicate in a variety of cells including adipose, endothelial, epithelial, muscle, and neuronal cells as well as macrophages and DCs. Although DC populations are required for mounting an adaptive immune response, it is CCL3 dependent recruitment of

macrophages that is necessary to control parasite replication. Blockade of CCL3 leads to increased immunopathology and higher parasite burden in the heart [102]. Once antigen has been acquired, DCs migrate toward the lymph node in a CCR7 dependent manner [15, 76, 103] to initiate the T cell response. *T. gondii*'s host cell range is the most broad as it is able to replicate within any nucleated cell. *T. gondii* dissemination has been extensively studied by Barragan and colleagues. They have demonstrated marked changes in DC behavior following infection with *Toxoplasma* tachyzoites. Infected DCs become highly migratory associated with an increase in speed, upregulation of CCR7 and enhanced migration to CCL19 [63, 64, 104, 105]. This results in increased parasite burden and quicker dissemination from the initial site of infection to the brain.

During protozoan infections, including *Plasmodium*, *Leishmania*, *T. cruzi*, and *T. gondii*, mature CD4⁺ Th1 T cells producing the essential effector cytokine IFN- γ migrate to replication sites. These cells are high expressers of CXCR3 and their trafficking is dependent on the CXCR3 ligands, CXCL9 (MIG) and CXCL10 (IP-10) [106–109]. These cells are required for activating inflammatory monocytes in the gut during *Toxoplasma* infection [110] and T cells targeting *Plasmodium* and *Leishmania* home to the liver where increased concentrations of CXCL10 are expressed during infection [111]. In contrast to *Plasmodium*, during *Leishmania* infection CXCL10 mediated T cell infiltration in the liver leads to parasite clearance [112]. In the spleen however, Th1 associated CXCL10 expression competes with a Th2 response perhaps helping to explain why parasites remain there after being cleared in the liver [112, 113].

While protection against protozoa is dependent on the generation of Th1 immune responses, a Th2 profile is required for protective immune responses to helminths. IFN- γ producing T cells are reliably CXCR3 high and consistently migrate towards CXCR3 ligands. Th2 cells are not as monogamous. CCR3, CCR4 and CCR8 are all expressed by Th2 cells. However, *in vitro* polarized Th2 cells migrate most specifically to the CCR4 ligand, CCL17 [114]. Yet during *Nippostrongylus* infection, analysis of IL-4 producing T cells revealed reduced migration towards CCL17 in an *ex vivo* chemotaxis assay. Indeed, T cells isolated from the infected lung were more likely to express the Th1 associated receptor, CXCR3 and the more ubiquitous CXCR4, than CCR4 [114]. This less defined role for specific Th2 chemokine responses is also seen in schistosome granuloma formation where *in vivo* neutralization of CCL17 increased Th1 and Th2 cytokines and resulted in little physical change in the Th2 dependent granuloma response [115]. However CCL22, another CCR4 ligand, was much more intrinsic to the generation of the Th2 based granuloma response. Many of these experiments suggest that our desire to tidily box chemokines and their receptors into Th1/Th2 responses may not be appropriate. They also point to a need for more sophisticated techniques for measuring cell recruitment *in vivo* that may take into account receptor desensitization while still measuring functional phenotype.

Independent of whether it is a protozoan Th1 or helminth induced Th2 response, insufficient control of inflammation can cause profound and often fatal pathology. For instance, *Plasmodium* can cause the development of cerebral malaria where infected red blood cells aggregate in the vasculature of the brain. Subsequent recruitment of immune cells exacerbates inflammation at this site with CCL2 dependent recruitment of monocytes

followed by CXCR3 dependent T cell trafficking [116, 117]. Further pathology occurs with secretion of CCL3 and CCL4, which augment lymphocyte migration to the brain and facilitate the breakdown of the blood-brain barrier [118]. CXCR3 dependent migration is required during *T. cruzi* infection [119–122], while *T. brucei* invasion of the central nervous system (CNS) occurs with elevated production of CCL2, CCL3, CCL5, CXCL2, CXCL8, and CXCL10 [123–125], facilitating widespread mononuclear cell infiltration within the brain parenchyma surrounding the blood vessels [123]. Control of inflammation during parasitic infection is achieved mostly by Treg cells, IL-10 producing CD4⁺ T cells, and IL-27R signaling [126–128]. Recently, Couper and colleagues have demonstrated that IL-27 is responsible for inhibiting the CCL4 and CCL5 responding CD4⁺ T cells that migrate to *Plasmodium* infection in the liver and does so by directly downregulating CCR5 expression [129]. Surprisingly, considering the significant volume of studies investigating many of these immunomodulatory pathways, there is little understanding of chemokine recruitment of regulatory cell populations during parasitic infection [95]. The best characterized is the expression of CXCR3 by Treg cells and their reliable migration to CXCL10 [114]. With CXCR3 being one of the most widely expressed chemokine receptors on activated T cells, this would fit with a regulatory T cell population being recruited by similar chemokine gradients as the proinflammatory populations they are trying to control. However, CXCR3 as will be discussed later may, in addition, have more fundamental roles to play in cell migration.

Chronic Infection

One common aspect of parasitic infection is that they cause morbidity rather than mortality due to persistent and chronic infections characterized by a contraction of the immune response. Parasites persist in a particular organ or cell type, and chemotactic signals facilitate continuous cell infiltration to keep parasites sequestered or replication under control. Adult *Schistosoma* worms persist, in the hepatic portal or mesenteric vessels of the small intestine, or in the vesical and pelvic plexuses for the lifetime of the host. A time course study of schistosome infection reveals an early Th1 mediated response that wanes as eggs are produced [130]. It is the eggs that cause pathology in this disease, as during circulation they become trapped in visceral organs and induce a strong Th2 response, resulting in granuloma formation. CCL3, CCL5, CCL17 (VCC-1, DMC), and CCL11 are all secreted to orchestrate the recruitment of basophils, eosinophils, mast cells, T cells, and macrophages to form the layers of a persistent granuloma [115, 131, 132]. CXCL9 and CXCL16 expression also increases in the schistosome infected liver to mediate parasite specific B cell migration in a CXCR3 and CXCR6 dependent manner [95].

Infection with *T. cruzi* is a classic case of chronic parasitic disease. After the acute and relatively asymptomatic blood stage of *T. cruzi* infection, parasites are primarily confined to myocytes and adipocytes [133]. Anti-parasitic drugs become ineffective and control of Chagas disease becomes all about treating the chronic symptoms including cardiac and gastrointestinal problems. These potentially fatal symptoms are likely a result of not simply chronic parasitemia, but considerable chronic inflammation at these sites. A continuous recruitment of T cells, mediated by CCL5, CXCL9, and CXCL10 is required to control parasite replication and expression of these chemokines remain elevated even when parasite

burden is low [120]. Several additional chemokines have been implicated in the recruitment of this inflammatory response including CX3CL1 and endothelin-1 [134]. Studies of patients with chronic cardiac disease demonstrate a significant positive correlation with the production of macrophage inhibitory factor (MIF) and disease severity. MIF can recruit a vast array of cells, can exacerbate cytokine production and probably plays a role in the continuous recruitment of T cells to the inflammation site [135].

Other parasites establish chronic infections by invading areas that are generally considered “immune-privileged” such as the CNS. In the case of *T. gondii*, parasites persist in the brain after trafficking to the CNS as free parasites [136] or inside infected cells [137, 138]. Parasites can appear in the brain as early as 10 days after initial exposure [139] and remain there for the lifetime of the host [140]. Control of parasite replication and maintenance within cysts depends on IFN- γ production by infiltrating T cells [74, 141–143]. Two major chemokine ligand/receptor systems are important for T cell recruitment and behavior within the chronically infected brain: CCL21/CCR7 and CXCL10/CXCR3. Both CCL21 and CCL19 are upregulated in the brain during infection and linear strands of CCL21 can be observed within the brain parenchyma associated with migrating CD8+ T cells [15, 144]. In addition, CCL21 is required for efficient CD4+ T cell migration from extraparenchymal sites into the brain parenchyma [145] (Figure 2C). This was demonstrated in *plt/plt* mice (deficient in CCL19 and CCL21-ser) and transgenic GFAP-CCL21 mice (where CCL21 is constitutively over-expressed under the astrocyte specific promoter, GFAP). In wild type mice chronically infected with *T. gondii*, immune infiltrates can be observed in the perivascular spaces and meninges, in addition to the tissue parenchyma [145]. In mice lacking CCL19/CCL21, significantly higher numbers of CD4+ T cells are recruited to the brain. However, these cells accumulate in the extraparenchymal spaces. In contrast, mice overexpressing CCL21 displayed little accumulation of CD4+ T cells in extraparenchymal spaces and instead were found dispersed throughout the brain instead of focused in the frontal cortex where *T. gondii* primarily resides [145].

Ligands for CXCR3, CXCL9 and CXCL10, are significantly upregulated in the brain upon infection [146]. CXCL10 is required for a protective antigen specific CD8+ T cell population within the CNS. Whether this is through recruitment or retention of these cells is not known, however in the absence of CXCL10 there is a 60% reduction in the T cell population at this site [146]. CXCL9 and CXCL10 are found at perivascular areas in the brain, suggesting a role in recruitment across the blood brain barrier [147]. However, the role of CXCR3/CXCL10 signaling in the *Toxoplasma* infected brain seems more fundamental than trafficking across this barrier. Recent mathematical modeling of CD8+ T cell behavior demonstrates that these cells undergo a Lévy random walk, characterized by sudden long ‘flights’. This is an optimal search strategy conserved throughout the animal kingdom and at the cellular level [146], and suggests that these cells are not undergoing gradient-guided migration. However CXCR3 signaling is required for CD8+ T cell migratory speed [146], as blockade of CXCL10 signaling leads to a significant reduction in cell velocity without changes in the search strategy of the cell. Ultimately more work is needed to determine if or when guided migration within infected tissue occurs, how local

such gradients act, and the effect differential downstream signaling of competing chemokines may have on cell behavior and optimal parasite control.

Parasite-derived chemokine homologues

Many of the described processes of chemokine guided cell trafficking are highly conserved and necessary for mounting immune responses to non-parasite challenges. However, there is evidence that parasite derived antigens can induce or enhance cell migration by stimulating chemokine receptors [55]. For example, eosinophil migration can be induced with soluble extract from *Strongyloides stercoralis*. By blocking chemokine receptors with specific antagonists, the authors were able to determine nematode induced migration depended on CCR3, CXCR2, and CXCR4 and speculated that although parasite-derived chemotactic factors are biochemically distinct from host chemokines, the host may have evolved to respond to them to ensure a robust response [55]. In contrast, a unique complication of infection with a parasite is the ability of these eukaryotes to divert the immune response by inactivating host-derived chemokines (as discussed earlier [56]) or by producing antagonistic chemokine homologues. For instance, parasite macrophage migration inhibitory factors (MIF) have extraordinary homology to mammalian MIF proteins. The first MIF was identified in *B. malayi* [148] and since that time MIF homologues have been isolated from a number of nematode [149, 150], hookworm [151], and protozoan [152,153] species. By secreting homologues to host factors that ameliorate the immune response, parasites have evolved yet another mechanism to promote their own survival.

Conclusions

While our grasp of immune cell migration to and away from infected tissues is rapidly evolving, gaps in our knowledge still remain. Parasitic infections are particularly complex, but exactly because of this they can teach us much about cell trafficking. Coordinated cell recruitment and maintenance of cell populations is required in all the infections described. Many of these parasites occupy a chronic niche within the host and therefore necessitate sustained chemokine dependent recruitment to specialized organs. Currently chemokines are studied by manipulating them or their receptors one by one. Techniques have to be developed where it is recognized that a cell may be able to detect and/or respond to multiple chemokines simultaneously, a much more realistic situation for cell migration within infected tissue. In addition, immunologists spend a considerable amount of time phenotyping cell populations and demonstrating their heterogeneity. Even the swarming behavior of neutrophils is not a clonal response during parasite infection. Rapid detection of changes in receptor expression, internalization and downstream signaling currently available *in vitro* and being applied to the field of developmental biology [154] need to be utilized *in vivo* to truly understand chemokine dynamics during infection.

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List of Abbreviations

APC	antigen presenting cell
BV	blood vessel
CCL	CC motif chemokine ligands
CCR	CC motif chemokine receptors
CD	cluster of differentiation
CXCL	CXC motif chemokine ligands
CXCR	CXC motif chemokine receptors
DC	dendritic cell
HEV	high endothelial vessels
IFN-γ	interferon gamma
LC	Langerhans cell
LPG	lipophosphoglycan
LV	lymphatic vessel
MIF	macrophage inhibitory factor
NK	natural killer cell
Th1	T helper cell, type 1
Th2	T helper cell, type 2
TNFα	tumor necrosis factor alpha

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Figure 1.

Initial exposure to parasitic infection. A. As a mosquito probes for a blood meal, *Plasmodium* sporozoites are released into the skin (1). Tissue damage from the bite leads to the release of chemokines such as CXCL2 (2), and CCL2 (3), which recruit neutrophils and monocytes to the infection site from blood vessels (BV). B. Upon ingestion and rupture of *Toxoplasma* cysts (1), the parasite invades and replicates within the intestinal epithelium, forming plaques (2). Neutrophils and inflammatory monocytes are recruited to areas of parasite replication (3), while DCs are found surrounding the plaques (4).

Figure 2.

Role of CCL21 in response to parasitic infection. A. Skin resident LCs (white) and dermal DCs (teal) scavenge antigen at the exposure site. LCs are slow to move in the epidermis, but extend their dendrites to scavenge antigen (black) from their environment. In contrast, dermal DCs constantly patrol their environment and upon antigen uptake, they upregulate CCR7 and migrate to the lymphatic vessels (LV) following gradients of CCL21 (red) produced by the lymphatic endothelium (green). B. Once DCs reach the lymph node, they transverse the walls of the high endothelial vessels (HEVs) and enter the parenchyma of the lymph node (1). There, they migrate randomly along a network of fibroblastic reticular cells (light green) coated with CCL21. The random migration elicited by CCL21 enables DCs to encounter and present antigen to naïve, CCR7+ T cells and initiate an adaptive response (2). C. Both neurons (light blue) and astrocytes (green) produce CCL21 in response to injury or insult. CCL21 is necessary to recruit CD4+ T cells into the brain from the perivascular spaces to keep parasite replication under control. CCL21 co-localizes with astrocytic and neuronal markers, appearing as long strands to which migrating T cells associate.

Table 1

Stage of Infection	Chemokine	Role	Parasite/References
Invasion/Exposure	CCL2	Basophil, monocyte, neutrophil, NK cell recruitment	<i>Leishmania</i> [80, 111]
			<i>Plasmodium</i> [14]
			<i>Trypanosoma</i> [119, 120, 125]
			<i>Toxoplasma</i> [62, 65, 69]
	CXCL1	Neutrophil recruitment	<i>Leishmania</i> [20]
			<i>Trypanosoma</i> [120]
	CCL3	Basophil, eosinophil, neutrophil recruitment	<i>Leishmania</i> [111]
			<i>Trypanosoma</i> [120, 125]
	CCL4	NK cell, monocyte recruitment	<i>Leishmania</i> [34]
			<i>Trypanosoma</i> [120]
	CXCL2	Neutrophil recruitment	<i>Toxoplasma</i> [65]
			<i>Trypanosoma</i> [120]
	CXCL8	Basophil, neutrophil recruitment	<i>Trypanosoma</i> [125]
	CXCL10	NK cell recruitment	<i>Leishmania</i> [20]
		T cell recruitment	<i>Toxoplasma</i> [59, 65, 110]
	CCL11	Basophil, eosinophil recruitment	<i>Brugia</i> [51]
			<i>Schistosoma</i> [155]
			<i>Trichinella</i> [57]
	Vector-derived Chemotactic factors	Cell recruitment to the exposure site	<i>Leishmania</i> [26, 27]
			<i>Plasmodium</i> [25, 28, 44]
Parasite dissemination/ Mounting an Adaptive Response	CCL19 and CCL21	DC and T cell trafficking and priming	<i>Toxoplasma</i> [15]
			<i>Plasmodium</i> [158]
			<i>Leishmania</i> [81, 159]
	CXCL10	Encephalitis	<i>Plasmodium</i> [116, 117]
			<i>Trypanosoma</i> [121, 123]
	CCL3	Basophil, eosinophil, neutrophil recruitment	<i>Trypanosoma</i> [102]
	CCL5	B cell, T cell, eosinophil, and basophil recruitment	<i>Trypanosoma</i> [92, 102, 124]

Stage of Infection	Chemokine	Role	Parasite/References
			<i>Plasmodium</i> [116]
Chronicity	CCL21	T cell recruitment to the brain	<i>Toxoplasma</i> [144, 145]
	CXCL10	T cell behavior	<i>Toxoplasma</i> [146]
	CCL2	Granuloma formation	<i>Schistosoma</i> [132]
		Sustained Macrophage recruitment	<i>Leishmania</i> [112]
	CCL3	Sustained Macrophage recruitment	<i>Schistosomiasis</i> [131, 132, 160]
	CCL17	Granuloma formation	<i>Schistosoma</i> [115]
	CCL22	Granuloma formation	<i>Schistosoma</i> [115]
Pathogen Clearance	CXCL10	T cell recruitment to liver	<i>Leishmania</i> [112]