

Role of chemokines and cytokines in the neuropathogenesis of African trypanosomiasis

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Abstract

Trypanosoma brucei spp. cause human African trypanosomiasis (HAT) or sleeping sickness in humans and nagana in animals. The early stages of the disease have no specific symptoms; however, the late stage of the disease involves neurological signs of the disease, including disturbance of sleep patterns from which the disease derives the name sleeping sickness. During the late stage of African trypanosomiasis parasites, increased numbers of white blood cells and levels of cytokines and/or chemokines are found in the brain parenchyma and/or cerebrospinal fluid of animal models and HAT patients. In this mini review, contemporary findings on how chemokines and cytokines are thought to play an important role in the central nervous system invasion by the parasites, inflammation and the neuropathology of the disease are discussed. The levels of various cytokines and chemokines, such as interferon-gamma (IFN- γ), interleukin-1 beta (IL-1 β), IL-6, IL-10, tumor necrosis factor-alpha (TNF- α), C-C motif chemokine 2 (CCL2), CCL3, C-X-C motif chemokine 8 (CXCL8, IL-8) and CXCL10, in the cerebrospinal fluid (CSF) of HAT patients correlate with the severity or stage of the disease. Thus, these molecules are possible candidates for differentiating between early and late stage HAT. The role of cytokines and chemokines in parasite invasion of the central nervous system is also being eluci-

dated. IFN- γ , TNF- α and CXCL-10 are some of the cytokines and chemokines now known to facilitate parasite penetration of the brain parenchyma. Interestingly, they also constitute some of the candidate molecules with potential to differentiate between stage 1 and 2 of HAT. The increased levels of cytokines, such as IL-1 β , IL-6, IFN- γ and TNF- α , as well as prostaglandins, during African trypanosomiasis might contribute to the neurological dysfunctions that occur during HAT.

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Key words: African trypanosomiasis; Chemokine; Cytokine; Central nervous system; Brain parenchyma; Cerebrospinal fluid; Neuroinvasion; Neuroinflammation; Neurological disturbances

Core tip: Human African trypanosomiasis (HAT) or sleeping sickness, caused by *Trypanosoma brucei* spp., is staged into an early hemolymphatic stage and a late meningoencephalitic stage. During the late stage parasites, increased numbers/levels of white blood cells, cytokines and/or chemokines are found in the cerebrospinal fluid of patients. In this mini review, contemporary findings on how chemokines and cytokines, such as interferon-gamma (IFN- γ), TNF- α , C-X-C motif chemokine 8 (CXCL8) and CXCL10, are thought to play an important role in the central nervous system invasion by the parasites, inflammation and the neuropathology of the disease and what might be candidates to differentiate between early and late stage HAT are discussed.

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INTRODUCTION

Three morphologically identical subspecies of the hemoflagellate protozoan parasite *Trypanosoma brucei* (*T. b.*), *T. b. brucei*, *T. b. gambiense* and *T. b. rhodesiense*, cause African trypanosomiasis, the latter two species are human infective. The disease is endemic to sub-Saharan Africa and is transmitted through a bite of a tsetse fly (*Glossina* sp.) during a blood-meal. *T. b. gambiense*, which is found in foci in large areas of West and Central Africa, causes a chronic form of human African trypanosomiasis (HAT) that lasts for several months to years. On the other hand, *T. b. rhodesiense*, with a much more limited distribution, is found in East and Southeast Africa and causes an acute form of the disease that lasts for several weeks to months^[1,2].

Clinically, HAT is divided in to two stages: an early hemolympathic stage (stage 1) and a late encephalitic stage (stage 2)^[1,3,4]. However, the demarcations between these two stages of the disease are not clear, more so for disease caused by *T. b. rhodesiense* where there is rapid transition from stage 1 to stage 2^[3]. In the early stage of HAT, a chancre might develop at the site of inoculation, followed by involvement of blood and lymphatic systems, which presents with general signs and symptoms of infection, chronic intermittent fever, headache, lymphadenopathy, splenomegaly and pruritus. In the late stage of the disease, there are signs of nervous system involvement, which present as sleep disorders, *i.e.*, dysregulation of the circadian rhythm of the sleep-wake cycle and a fragmentation of the sleeping pattern, neurological symptoms, including confusion, tremor, fasciculations, general motor weakness, hemiparesis, akinesia or dyskinesia, sensory disturbances with diffuse hyperpathia, abnormal movements and speech disorders, and psychiatric symptoms. If untreated, the disease will lead to coma and death in most cases. The patients die in a state of cachexia and also because of opportunistic infections^[4]. Clinical symptoms of HAT are of a non-specific nature; thus, its diagnosis is confirmed by finding trypanosomes in the blood and lymph nodes or in the cerebrospinal fluid (CSF) using microscopy, the latter during the late stage of HAT. The serological test card agglutination trypanosomiasis test is used to screen for *T. b. gambiense* infections. The World Health Organization criteria for diagnosing stage 2 HAT is the finding of trypanosomes and/or a white blood cell (WBC) count of $> 5/\mu\text{L}$ in the CSF^[1,4].

Differentiating between the two stages of the disease is imperative before treatment can be begun^[1] because of the differences between the drugs used to treat early and late stages of HAT in terms of ability to cross the blood-brain barrier (BBB) and toxicity. The drugs which are used to treat the late stage of the disease, melarsoprol, eflornithine and the nifurtimox-eflornithine combination treatment, permeate the BBB better but are more toxic than the drugs used to treat the early stage of the disease, suramin and pentamidine^[3,4].

In this mini review, the role of chemokines and cytokines in the invasion of the central nervous system (CNS)

Table 1 Cytokines and chemokines with increased expression in the brain parenchyma of rodents and cerebrospinal fluid of human patients, more during late than early stage African trypanosomiasis

Site	Cytokine/chemokine	Ref.
Chemokines		
Rodent brain parenchyma	CCL2 ¹ , CCL4, CCL5, CCL7, CCL9, CCL12, CCL19, CCL28, CXCL1, CXCL5, CXCL9, CXCL10 ¹ , CXCL12, CXCL13 ¹ , CXCL14, CXCL16,	[5,19]
HAT patient CSF	CCL2 ¹ , CCL3, CXCL8 (IL-8), CXCL10 ¹ , CXCL13 ¹	[5,7,8,20-25]
Cytokines		
Rodent brain parenchyma	IFN- γ ¹ , IL-1 α , IL-1 β ¹ , IL-6, IL-10 ¹ , TGF- β , TNF- α ¹	[10,19,26-28,30]
HAT patient CSF	IFN- γ ¹ , IL-1 β ¹ , IL-6 ¹ , IL-10 ¹ , TNF- α ¹	[5,7,8,20,22,32-34]

¹Expressed in both late stage rodent brains and HAT patients' CSF. CCL: C-C motif chemokine; CSF: Cerebrospinal fluid; CXCL: C-X-C motif chemokine; HAT: Human African trypanosomiasis; IFN: Interferon; IL: Interleukin; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

by the parasite and the ensuing inflammation and neuropathology which makes the disease intractable and fatal in most cases will be discussed. Cytokines are a large group of immunoregulatory molecules. They play an important role in the control and pathogenesis of infectious diseases. Chemokines are involved in recruitment and retention of immune cells during inflammation and infection.

CHEMOKINE AND CYTOKINE EXPRESSION IN THE CNS

Trypanosome infection results in activation of the immune system and induction of expression of various cytokines and chemokines in both HAT patients and animal models of the disease^[5-11]. However, eventually the infection results in immunosuppression^[12-14]. The cytokines and chemokines that are induced, both in the periphery and the CNS, play an important role in the control of the parasites but they also contribute to the inflammation and immunosuppression which occurs during the disease^[6-11,15-17].

Increased expression of chemokines in the CNS has been observed during African trypanosomiasis. The expression of the chemokines C-X-C motif chemokine (CXCL) 1, CXCL2 (macrophage inflammatory protein-2, MIP-2), CXCL5, CXCL9, CXCL10, CXCL12, CXCL13, CXCL14, CXCL16, C-C motif chemokine (CCL) 2 (MCP-1), CCL3 (MIP-1alpha), CCL4, CCL5 (RANTES), CCL7, CCL9, CCL12 and CCL28 was found to be up-regulated in the brains of rodents infected with *T. b. brucei*^[5,9,18,19]. Some of these chemokines are expressed at higher levels during late than early stage African trypanosomiasis (Table 1). CXCL9 and CXCL10 were the most highly up-regulated cytokines in the brain at later stages when parasites had invaded the CNS, compared to early stages of the disease before CNS invasion. The

Table 2 Cytokines and chemokines involved in *Trypanosoma brucei* spp. neuroinvasion

Cytokine/Chemokine	Trypanosome levels in the brain parenchyma of transgenic mice compared to WT mice	Ref.
Chemokines		
CXCL10	CXCL10 ^{-/-} and CXCR3 ^{-/-} mice had less trypanosomes in the brain parenchyma compared with WT mice.	[5]
Cytokines		
IFN- α / β	IFN- α / β R ^{-/-} mice had slightly less trypanosomes in the brain parenchyma compared with WT mice.	[15]
IFN- γ	IFN- γ ^{-/-} and IFN- γ R ^{-/-} had less trypanosomes in the brain parenchyma compared with WT mice. Trypanosomes accumulated in the perivascular compartment, confined between the endothelial and the parenchymal basement membranes, in certain areas of the brains of both transgenic mice	[10]
IL-12	IL-12P40 ^{-/-} mice had less trypanosomes in the brain parenchyma compared with WT mice.	[10]
TNF- α	TNFR1 ^{-/-} mice had less trypanosomes in the brain parenchyma compared with WT mice.	[15]

CXCL: C-X-C motif chemokine; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor; WT: Wild type.

increased expression of both chemokines was found to be dependent on interferon (IFN)- γ ^[5]. CXCL10 was found to be predominantly up-regulated in parenchymal astrocytes of hypothalamic regions, optic chiasm and optic tracts at later stages of the disease^[5]. Of these chemokines, CCL2, CCL3, CXCL8 (IL-8), CXCL10 and CXCL13 have been found to be increased in the CSF of patients with late stage HAT infected with either *T. b. gambiense* or *T. b. rhodesiense* more than non-infected control patients or patients with early stage HAT (Table 1)^[5,7,8,20-25].

Several studies have reported the increased expression of cytokines in the CNS during trypanosome infection. The cytokines IFN- α / β , IFN- γ , interleukin (IL)-1 α , IL-1 β , IL-4, IL-6, IL-10, IL-13, transforming growth factor (TGF)- β and tumor necrosis factor (TNF)- α were found increased in the brains of rodents infected with *T. b. brucei*^[10,18,19,26-30]. Some of these cytokines are also expressed at higher levels during late than early stage African trypanosomiasis (Table 1). It has been suggested that astrocytes might be the source of some of these cytokines since the levels of these cytokines were found to correlate with astrocyte activation^[19]. Lymphocytes are the major source of IFN- γ in the brains of *T. b. brucei* infected mice^[10]. *T. b. brucei* CpG-DNA stimulates macrophages to increase the production of IL-12 and TNF- α ^[31], thus, macrophages and possibly microglia might be some of the major producers of these cytokines in the brain during *T. b. brucei* infections. Of these cytokines, IFN- γ , IL-1 β , IL-6, IL-10 and TNF- α have been found to be increased in the CSF of patients with late stage HAT infected with either *T. b. gambiense* or *T. b. rhodesiense* more than non-infected controls or patients with early stage HAT (Table 1)^[5,7,8,20,22,32-34]. On the other hand, the level of TGF- β was decreased in the CSF of patients with late stage HAT infected with *T. b. rhodesiense* compared to patients with early stage HAT but was higher than a non-infected control, where it was not detected in the latter^[34].

CYTOKINES, CHEMOKINES AND TRYPANOSOME BRAIN INVASION

Taking into consideration that the expression of various chemokines and cytokines in the CNS correlate with

presence of trypanosomes in the brains of animal models of the disease and CSF of HAT patients, there is a possibility these molecules play a role in the recruitment, mobility and retention, and also in the control of the levels, of the parasites in the CNS. The role which some of these molecules play in trypanosome invasion of the brain have been studied using transgenic animal models (Table 2)^[35].

Of these molecules, the role of IFN- γ in trypanosome invasion of the brain was the first to be studied using transgenic mice^[10]. Mice deficient of IFN- γ or its receptor had higher parasites in the blood but had less parasites and lymphocytes in the brain parenchyma compared to wild type (WT) mice. In these transgenic mice, the parasites accumulated in the perivascular space between the endothelial and parenchymal basement membranes of the post-capillary venules^[10], suggesting that IFN- γ or factors induced by it are important for parasite crossing of the parenchymal basement membrane. The source of the IFN- γ was most likely lymphocytes since the levels of IFN- γ did not increase in recombination activating gene deficient mice (lacking mature B and T lymphocytes) and parasite penetration into the brain parenchyma was reduced in these mice. Mice deficient of IL-12 have reduced IFN- γ levels^[36] and also have less parasites penetrating the brain parenchyma^[10].

IFN- γ induces the production of the chemokine CXCL10, also known as IFN- γ -induced protein 10 (IP-10). Mice deficient of IFN- γ have reduced expression of CXCL10 compared to WT mice during trypanosome infection^[5]. Transgenic mice lacking CXCL10 or its receptor CXCR3 also showed reduced parasites penetrating the brain parenchyma, although they had similar parasites in the blood compared to WT mice^[5]. CXCL10 deficient mice did not have accumulation of parasites in the perivascular space, suggesting that other IFN- γ -induced molecules instead of CXCL10 play a role in IFN- γ dependent passage of parasites across the parenchymal basement membrane.

The role of TNF- α in trypanosome invasion of the brain was also studied using transgenic mice^[15]. Mice deficient of TNF- α receptor 1 had higher parasites in the blood but had less numbers of both parasites and T lymphocytes in the brain parenchyma compared to WT mice^[15]. *T. b. brucei* infected mice deficient of TNFR1

Table 3 Selected cytokines and associated neurological and neuroendocrine features of African trypanosomiasis

Cytokine	Possible neurological and neuroendocrine features associated with	Ref.
IFN- γ	Sleep pattern disruptions, hyperalgesia/hyperesthesia and pain	[41,60]
IL1 β	Hyperalgesia/ hyperesthesia and pain, neurodegeneration	[28,29,61]
IL-6	Hypopituitarism and endocrine dysfunctions, sleep pattern disruptions, hyperalgesia/ hyperesthesia and pain	[38]
TNF- α	Hypopituitarism and endocrine dysfunctions, sleep pattern disruptions, hyperalgesia/hyperesthesia and pain, neurodegeneration	[28,29,38,41]

IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor.

had less adhesion molecules, vascular cell adhesion protein 1 and intercellular adhesion molecule 1 compared to WT mice, suggesting that the induction of adhesion molecules through TNF- α signalling might play a role in the TNF- α facilitated parasite and T cell invasion of the brain parenchyma. Mice deficient of IFN- α/β R had reduced numbers of T lymphocytes and parasites in the brain parenchyma compared to WT mice, but the magnitude was not as pronounced as mice deficient of IFN- γ , TNF- α or CXCL-10 signalling^[15]. Mice lacking the receptors of two other cytokines, IL-1R and IL-18R, had similar parasites in the blood, as well as parasites and T lymphocytes in the brain parenchyma, as WT mice^[15], suggesting that these cytokines do not play a significant role in parasite penetration in to the CNS.

CYTOKINES, CHEMOKINES AND NEUROPATHOLOGY DURING AFRICAN TRYPANOSOMIASIS

Chemokines such as CXCL10 play a role in the attraction, mobility and/or retention of inflammatory cells into the CNS during African trypanosomiasis^[5] and thus contribute to the neuroinflammation and morbidity seen in the late stage of the disease. High levels of CCL2, CCL3, CXCL8 and CXCL10 in the CSF were found to be associated with the severity of the disease and neurological signs which are characteristic of late stage HAT^[5,7].

High levels of cytokines, such as IL-1 β , IL-6, IFN- γ and TNF- α , in the plasma or CSF have also been found to be associated with the severity of the disease and neurological signs which are characteristic of late stage HAT^[7,8,22,36,37]. However, as well as neuroinflammation, the role of cytokines in causing brain dysfunctions which result in neuroendocrine dysfunctions, neurological symptoms and/or sleep disorders (Table 3) have also been studied. In HAT patients, high plasma concentrations of IL-6 and TNF- α have been found to correlate with hypopituitarism and endocrine dysfunctions^[38].

Endocrine dysfunctions result in some of the signs and symptoms of HAT, such as impotence, amenorrhea, infertility and lethargy. Chronically elevated concentrations of IL-6 and/or TNF- α during HAT might have a direct inhibitory effect on the hypothalamus-pituitary-thyroid or adrenal axis, resulting in reduced thyroid hormone and cortisol secretion^[38]. TNF- α inhibitors have been shown to restore the hypothalamic-pituitary-adrenal axis in other chronic inflammatory diseases, such rheumatoid arthritis^[39].

IL-6, IFN- γ and TNF- α can alter synaptic functions and are implicated in causing sleep pattern disruptions^[40-45]. IFN- γ alters clock gene expression and circadian rhythms in the suprachiasmatic nucleus (SCN)^[41,46]. The SCN is essential for the generation and maintenance of daily rhythms in physiology and behavior^[47-49]. IL-1 β , TNF- α and IFN- γ also affect hypothalamic and brainstem neurons which are involved in sleep-wakefulness regulation^[41,50,51]. Apart from HAT, IL-6 and/or TNF- α are elevated in other disorders associated with excessive daytime sleepiness, such as sleep apnea, narcolepsy and idiopathic hypersomnia^[43,44,52].

Cytokines and chemokines can sensitize and stimulate nociceptors in the periphery and/or synaptic targets in the CNS, which can result in neuropathic pain^[53]. Administration or up-regulation of IL-1 β , IL-6, IFN- γ and TNF- α can induce neuropathic pain in rodents^[40,54-59]. It has been suggested that IL-1 and IFN- γ might be implicated in the thermal hyperalgesia observed in *T. b. brucei* infected rats^[60,61]. Hyperesthesia is one of the clinical features reported in HAT patients^[3,4]. Thus, these cytokines, together with other inflammatory molecules, most likely contribute to the hyperalgesia/hyperesthesia and pain observed in HAT.

In rats infected with *T. b. brucei*, apoptosis of some cells and degeneration of some nerve fibres, although modest, in the brain have been found to be spatially associated with mRNA expression of the cytokines IL-1 β and TNF- α ^[29]. Intraventricular infusion of an antagonist of TNF- α , but not IL-1, was found to reduce trypanosome-induced neurodegeneration^[28]. Infusion of antagonists of both cytokines further reduced the trypanosome-induced neurodegeneration; thus implying that TNF- α is a principle mediator of trypanosome-induced neurodegeneration and its effects are augmented by IL-1^[28].

CONCLUSION

The expression of cytokines and chemokines in the brain and/or CSF is increased in animal models of African trypanosomiasis and HAT patients and the levels of these molecules correlate with the severity or stage of the disease. The high levels of chemokines and cytokines in the brain and CSF during late compared to early stage African trypanosomiasis are most likely due to the invasion of the CNS by trypanosomes and/or WBCs in the late stage, resulting in neuroinflammation. Thus, these molecules are possible candidates for differentiating between early and late stage HAT. In the future,

clinicians could utilize this knowledge to treat patients with high levels of these molecules in the CSF as late stage patients; thus, possibly reducing the occurrence of relapses in late stage HAT patients who might have been wrongfully diagnosed as early stage and treated as such using the current staging criteria. Recently, extensive research has been undertaken to evaluate the suitability of these molecules as stage biomarkers and also as markers for treatment outcome in HAT patients^[5,7,8,20-25,32-34]. The role of cytokines and chemokines in parasite invasion of the CNS is also being elucidated. IFN- γ , TNF- α and CXCL-10 are some of the cytokines and chemokines now known to have a facilitative role in parasite penetration of the brain parenchyma. Interestingly, they also constitute some of the molecules with potential to differentiate between stage 1 and stage 2 of HAT^[5,20,22]. Moreover, neopterin, a stable product produced by IFN- γ activated immune cells, has been suggested to have potential to differentiate between these two stages of HAT^[24]. The increased levels of cytokines, such as IL-1 β , IL-6, IFN- γ and TNF- α , during African trypanosomiasis contribute to the neurological dysfunctions that occur during HAT. Thus, studying cytokines and chemokines during African trypanosomiasis not only aids in understanding the neurobiology of the disease, but also provides candidate diagnostic markers and possible therapeutic targets to reduce the neurological sequelae in surviving patients.

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