Review

Tumor necrosis factor α in the pathogenesis of cerebral malaria

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Physiologically in the brain, cytokines such as tumor necrosis factor-alpha (TNFα) are released by the immune system and can modulate neurological responses. Conversely, the central nervous system (CNS) is also able to modulate cytokine production. In the case of CNS disorders, cytokine release may be modified. Cerebral malaria (CM) is a complication of Plasmodium falciparum infection in humans and is characterized by a reversible encephalopathy with seizures and loss of consciousness. Central clinical signs are partly due to sequestration of parasitized red blood cells in the brain microvasculature due to interactions between parasite proteins and adhesion molecules. TNFα is produced and released by host cells following exposure to various malarial antigens. The increase of TNFα release is responsible for the overexpression of adhesion molecules. This article reviews the involvement of TNFα in cerebral malaria and the relation with all the processes involved in this pathology. It shows that (i) TNFα levels are increased in plasma and brain but with no clear correlation between TNFα levels and occurrence and severity of CM; (ii) TNFα is responsible for intercellular adhesion molecule-1 upregulation in CM, the relation being less clear for other adhesion molecules; (iii) TNFα receptors are upregulated in CM, with TNF receptor 2 (TNFR2) showing a higher upregulation than TNFR1 in vivo; (iv) in murine CM, low doses of TNFα seem to protect from CM, whereas excess TNFα induces CM and anti-TNFα therapies (antibodies, pentoxifylline) did not show any efficiency in protection from CM. Moreover, the involvement of lymphotoxin α, which shares with TNFα the same receptors with similar affinity, appears to be an interesting target for further investigation.

Key words. Cerebral malaria; tumor necrosis factor-α; TNF receptor; cytokine; adhesion molecules; blood-brain barrier.

Introduction

Cerebral malaria (CM) is a major life-threatening complication of Plasmodium falciparum infection in humans. Although the physiopathology has been extensively investigated, cellular and molecular bases of the neurological pathology are still unclear, particularly the intricacy of the different factors involved in pathogenesis: secretion of cytokines; sequestration of parasitised red blood cells (PRBCs) leading to mechanical blockage of microvessels; modifications of the T cell repertoire; immune status and genetic background of the host; parasite factor [1]. Sequestration of PRBCs to the surface of the microvasculature of various organs including the brain and the lungs is mediated by different endothelial cell surface receptors, including thrombospondin (TSP), CD36,
TNFα

TNFα is a pro-inflammatory cytokine principally produced by activated immune cells, such as macrophages, T and B cells, and mast cells. TNFα is produced mainly as a soluble 17-kDa secreted protein and also in transmembrane form at the surface of macrophages and activated T cells [6–8]. TNFα may have both beneficial and detrimental functions. It can activate host defense and promote resistance to infectious diseases, and it can also be involved in toxicity and inflammatory processes [9, 10]. It plays an important role in inflammatory reactions by:

- promoting extravasation of neutrophils, lymphocytes and monocytes, and enhancing their adhesion to endothelial cells [11]
- affecting immune responses by controlling T cell activation, which stimulates cell surface expression of major histocompatibility complex (MHC) class I and II molecules on a variety of cell types [12]
- inducing the synthesis of numerous pro-inflammatory cytokines [interleukin (II)-1, II-6, …] and TNFα itself [13]
- inducing apoptosis of different cell types, including endothelial cells [14].

Contradictory data indicate that TNFα has multiple physiological effects in the brain:

- in the embryonic development of the brain, the role of TNFα is controversial. High levels of TNFα have been reported in the embryonic brain [15], while no alteration of the brain has been described in mutant mice lacking TNFα receptors (TNFR1 and TNFR2) or in TNFα knockout mice [16]
- TNFα is implicated in CNS homeostasis and is involved in the proliferation and survival of CNS cells. It induces proliferation of astrocytes and glioma cells [17]
- it also has pro-inflammatory effects through modulation of MHC class I expression in astrocytes and neurons [17].

TNFα binds to two types of TNF receptors: TNFR1 (55–60 kDa) and TNFR2 (75–80 kDa) with similar affinity. TNFα actions mediated by binding to TNFR1 are mainly cytotoxic, while those mediated by binding to TNFR2 are proliferative. In most cells, both receptors are coexpressed, and some data suggest that TNFR1 mediates most of the actions of soluble TNFα, while TNFR2 mediates most of those of transmembrane TNFα [7].

Astrocytes, microglia and neurons are able to locally produce TNFα after physiological and pathological stimuli [18].

The overproduction of TNFα is related to brain damage in pathological situations, such as bacterial meningitis, multiple sclerosis, Alzheimer’s disease and CM. Brain damage has been evidenced in transgenic mice overexpressing TNFα and has been prevented by pretreatment with antiserum TNFα antibody [19].

Different data suggest that the toxic role of TNFα in inflammatory pathologies is more targeted at the blood-brain barrier (BBB) (astrocytes) rather than the central nervous system (CNS) (neurons) itself. Transgenic mice overexpressing noncleavable transmembrane human TNFα in astrocytes develop CNS inflammation, while transgenic mice overexpressing transmembrane TNFα in their neurons do not [17].

Production of TNFα in malaria and CM

In humans, TNFα is synthesised as a transmembrane molecule and can be released by metalloproteinases from the immune cells into biological fluids. TNFα is produced and released by immune host cells following exposure to various malarial antigens at different steps of the life cycle of Plasmodium species [20, 21]:

- At the preerythrocytic phase, when parasites enter the host via the saliva of an infected female Anopheles mosquito during feeding, the sporozoite circulates in the blood stream before invading the liver. During this brief sporozoite phase, sporozoite antigens stimulate TNFα release in a short period of time [21].
- At the liver stage, parasites invade the host’s hepatocytes, where they multiply. Very few studies have reported the involvement of TNFα at this stage [22, 23].
- After multiplication in the liver, merozoites are released in the bloodstream and infect red blood cells by...