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The roles of TNF in brain dysfunction and disease

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ABSTRACT

Certain cytokines, the prototype being the highly pleiotropic TNF, have many homeostatic physiological roles, are involved in innate immunity, and cause inflammation when in excess. These cytokines have long been accepted to have central roles in the pathogenesis of systemic or local non-cerebral disease states, whether acute or chronic, and whether or not caused by infectious agents. Over the last decade they have also been appreciated to be broadly important in brain physiology. As in other organs, excessive levels in brain are harmful, and its physiological complexity leads to correspondingly complex dysfunction. This review summarizes the burgeoning literature on this topic, and how the functions of these molecules, particularly TNF, are influencing the outlook of researchers on the pathophysiology of these diseases. Basic brain physiology is thus informing knowledge of the brain dysfunction that characterizes such apparently diverse states as Alzheimer's disease, trauma (mostly, but not only, to the brain), Parkinson's disease, and severe systemic infectious states, including malaria, sepsis, viral diseases and major depression. The implication is that the anti-cytokine therapies now in use, typically directed at TNF, warrant testing in these diseases in circumstances in which the therapeutic agent enters the cerebrospinal fluid. Routinely administering such drugs to patients exhibiting the neurological changes discussed in this review would simply add another organ system to what is already a very successful strategy in the treament of inflammatory disease at other sites, such as joints, skin and gut. Clearly, the most relevant research is focussed on Alzheimer's disease, but the principles may also apply to other encephalopathies.

Contents

Abbreviations: Aβ, amyloid beta; AGE, advanced glycation end products; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid β (A4) precursor protein; CO, carbon monoxide; CORM-3, tricarbonylchoro(glycinato)ruthenium (II); CSF, cerebrospinal fluid; GABA, gamma-aminobutyric acid; H_2S, hydrogen sulfide; HMBG1, high mobility group box 1 protein; HO-1, hemoxygenase-1; i. c. v., intracerebroventricular; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; LPS, lipopolysaccharide; LTP, long-term potentiation; LTs, lymphotoxins; NMDA, N-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; mtDNA, mitochondrial DNA; RAGE, receptor for advanced glycation end products; SIRT, sirtuin; TAPI-2, TNF protease inhibitor-2; TACE, TNF converting enzyme; TGFs, transforming growth factors; TLR2, toll-like receptor 2; TNF, tumor necrosis factor.

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1. Introduction – why link cerebral malaria and Alzheimer's disease?

Several years ago, driven by the conflict between the traditional mechanism in the literature on human cerebral malaria and the logic of physiology (and therefore pathophysiology), we were searching the outer reaches of its literature for a way to describe the cul de sac the field had entered. This uncovered what we regarded as a particularly clear article (Castellani et al., 2008) on the same problem in Alzheimer's disease: a well-entrenched conventional approach born of an ancient histological observation being argued to have outlived its usefulness – indeed, in Castellani's words, having become

somewhat of a nuisance to what should be the real focus, invisible molecules and subcellular damage that cannot be verified by direct observation.

This sounded familiar for some of us in the human cerebral malaria world. This form of encephalopathy rivals Alzheimer's disease in the scale of the problem, either condition being much more common than other similar diseases. Untreated malaria infection in naive individuals can best be described as fitting in with the systemic infectious diseases that are liable to exhibit an associated encephalopathy. Over a hundred years ago, and for want of any other leads, pathologists were attracted to red cells containing parasites often seen in sections from brains of fatal coma cases caused by the parasite *Plasmodium falciparum* (Marchiafava & Bignami, 1894) when seeking a mechanism for the neurological aspects of malaria, and mechanical blockage of micro-cerebral vasculature soon became the accepted explanation for this condition. Thus in the disease caused by this species of malaria, which dominates most of the malarial world, parasitized red cells adhering to the walls of small cerebral blood vessels became the primary cause of abnormal brain function. This is referred to as the parasite sequestration argument of malarial disease, in which physically restricted blood flow is believed to deprive brain cells of oxygen and nutrients. It is still commonly championed as the primary cause of the encephalopathy seen in human malaria, although, as discussed later, emerging information on vivax malaria is making this allegiance difficult to sustain.

As reviewed (Castellani et al., 2008), those searching brain sections from cases that included what is now called Alzheimer's disease described neurofibrillary tangles (NFTs) (Fuller, 1907) – later found to be comprised of tau protein – and plaques, later realized to be formed of amyloid beta (Aβ). As with adherent parasitized red cells in malaria, these obvious physical structures became the centre of attention for investigators trying to understand Alzheimer's. The earlier literature on the apoE4 association with Aβ (Section 5.2.5.) undoubtedly reinforced the case for amyloid being the primary cause of this disease. Assumed to be directly harmful, NFTs, plaques, and the molecules that formed them became the target of science-based interventions. It seems that in both fields, therefore, histological hallmarks have somehow been allowed to evolve into primary mechanisms that researchers were comfortable with, perhaps, in part, because they could point them out with the aid of a microscope.

Over 60 years ago, a malaria researcher with sepsis research experience summarized the accumulated scepticism in the malarial literature, and suggested that inflammation was a more likely explanation for the mechanism of the disease (Maegraith, 1948). The parallels with the scientific challenge at the core of cerebral malaria and Alzheimer's disease are striking, not least because the key inflammatory cytokine, tumor necrosis factor (TNF), is appearing with increasing frequency in both literatures. The link between TNF and any non-tumor disease actually began with malaria.

In the late 1970's, when TNF had a small new literature restricted to tumor killing, one of us (IAC) began collaborating with the group who first described TNF (Carswell et al., 1975). This original TNF-systemic disease link thus made has been reviewed recently (Clark, 2007). Our joint research was directed at understanding host protection against malaria parasites as well as malarial pathology. By 1995, these same inflammatory mediators were argued to be relevant to the pathogenesis of Alzheimer's and other neurodegenerative diseases (McGeer & McGeer, 1995). Some years later, tissues from malaria brains were stained for amyloid β (Aβ) precursor protein (APP) (Medana et al., 2002) and cerebral malaria CSF was assayed for tau (Medana et al., 2005). In the same year it was reported that excess Aβ would not alter an important neurological function in mice lacking the gene for TNFR1 (Wang et al., 2005), and later cerebral malaria severity was correlated with CSF levels of TNF (John et al., 2008b). In the following year it was reported that TNF induces tau accumulation (Gorlovoy et al., 2009). Clearly, acquiring a decent working knowledge of the science behind Aβ and tau, the histological hallmarks of Alzheimer's disease, is necessary for research into malarial disease, and competence in Alzheimer's research increasingly requires reasonable literacy in TNF. Only then can the considerable congruency between cerebral malaria and Alzheimer's disease be appreciated. Indeed, such an interaction was the genesis of the collaboration represented by this review, with a TNF researcher with a cerebral malaria background reading a review on the link between neurogenesis and cytokines (Abdipranoto-Cowley et al., 2009).

The major theme developed in this review is that the development of the basic literature on TNF and neurophysiology (and hence neuropathophysiology) appears to apply to cerebral malaria and Alzheimer's disease. Although these two diseases differ greatly in the age group affected and rapidity of onset and duration of clinical change, Alzheimer's might be usefully viewed, in pathophysiological terms, as a much less acute, but more insidious, version of cerebral malaria and its sequelae. This contrast should not deter us from this view, any more than should the chronicity of AIDS dementia conceptually separate it from the more acute viral encephalopathies. All encephalopathies discussed here show evidence of the same pattern of events, albeit with different severities and durations. Cytokine-mediated diseases in particular are inevitably multifactorial, and much can be lost if each is considered in isolation. Our hope in this review is that by considering these diseases together perspectives that might have otherwise lain dormant will surface, and bring about a consensus that leads to useful treatment.

2. Tumor necrosis factor TNF and the other cytokines, and the innate immune system

As well as discussing the inflammatory cytokines themselves, a brief overview of the innate immune system, which is evolutionarily older than adaptive immunity, is warranted here. Activation of the innate immune system leads to the production of TNF and similar cytokines, and depends on them. The past decade has witnessed considerable conceptual advances in our understanding of how innate immune responses, which dominate the CNS (Section 4.5), are initiated. New inclusive terminologies have accompanied this. PAMPs, or pathogen-related molecular patterns (Janeway, 1992), on viruses, bacteria and fungi are now joined by DAMPs, (danger-associated molecular patterns) found on proteins, released from damaged cells (Matzinger, 2002) as entities recognized, or sensed, by pattern recognition receptors (PRRs). Gram-negative bacterial cell wall lipopolysaccharide (LPS), also called endotoxin, and discussed variously throughout this review, is an example of a PAMP, and HMGB1 (Section 4.3) can be regarded as a DAMP. The most intensely studied PRRs are the Toll-like receptors (TLRs) comprising a superfamily of at least 11 members expressed by a wide range of cells. As reviewed, (Beutler & Poltorak, 2001), the Drosophila Toll protein has a fascinating lineage stretching from insect dorso-lateral polarity, through insect innate immunity, to its homologs being important for mammalian innate immunity. Once activated, TLRs induce signalling cascades that predominantly lead to release of inflammatory cytokines, chemokines, and anti-microbial peptides (AMPs). This is discussed in more detail in Section 5.2.3).

More recently, other families of PRRs have been described. Unlike most TLRs, which are membrane-bound, the newer PRR families consist of soluble proteins that provide cytoplasmic surveillance in order to detect intracellular invaders. They include NLRs, or NOD-like receptors. NLRs, and other proteins such as NALP3, form cytoplasmic complexes termed inflammasomes that activate caspase-1, thus generating IL-1β and IL-18 from their precursor proteins (Martinon et al., 2002, 2009). IL-18 is a well-known inducer of TNF (Tsutsui et al., 1997; Dinarello, 1999). TNF in turn promotes activation of caspase-1 induced by other agents, such as ATP (Franchi et al., 2009), logically enhancing IL-1β and IL-18 production, and hence reinforcing itself, even in the absence of microbial infection.