The meteorology of cytokine storms, and the clinical usefulness of this knowledge

Ian A. Clark1 · Bryce Vissel2,3

Received: 31 October 2016 / Accepted: 10 April 2017 / Published online: 27 April 2017
© The Author(s) 2017. This article is an open access publication

Abstract The term cytokine storm has become a popular descriptor of the dramatic harmful consequences of the rapid release of polypeptide mediators, or cytokines, that generate inflammatory responses. This occurs throughout the body in both non-infectious and infectious disease states, including the central nervous system. In infectious disease it has become a useful concept through which to appreciate that most infectious disease is not caused directly by a pathogen, but by an overexuberant innate immune response by the host to its presence. It is less widely known that in addition to these roles in disease pathogenesis these same cytokines are also the basis of innate immunity, and in lower concentrations have many essential physiological roles. Here we update this field, including what can be learned through the history of how these interlinking three aspects of biology and disease came to be appreciated. We argue that understanding cytokine storms in their various degrees of acuteness, severity and persistence is essential in order to grasp the pathophysiology of many diseases, and thus the basis of newer therapeutic approaches to treating them. This particularly applies to the neurodegenerative diseases.

Keywords Cytokine storm · TNF · IL-1 · Physiology · Innate immunity · Disease pathogenesis · Neurodegenerative diseases

Introduction

As previously discussed [1, 2], the term cytokine storm appears to have been first used to describe the chaotic pathophysiological state encountered during an acute graft-versus-host disease [3]. The term has caught the popular imagination, with >160,000 hits on a search engine. A flood of harmful polypeptides bursting forth from our cells making us very ill, as if we had severe influenza, is a powerful and accurate image, one clearly worth understanding. Over the intervening 24 years the activity of these cytokines has encompassed a much wider array of biology than dreamed of in 1993, and it is now timely to step back and examine the concept again. In order to provide a wider understanding of the phenomenon of a cytokine storm, we have recounted the history of researchers’ awareness of the main mediators whose release initiates the process. Although the popular concept of a cytokine storm is about dramatic illness and disease, these mediators also have essential roles in normal physiology and innate immunity. The principles are the same throughout, but site of production, cytokine concentration and persistence, as well as generation of countering cytokines, determine outcome. The perspectives now possible thus allow us to develop a better understanding of both of these aspects in health and in sickness, as well as focus on the therapeutic possibilities of this knowledge, which is a main theme of this text. We also extend the concept of a cytokine storm into the chronic neurodegenerative states. These diseases remind us that unrelenting moderate rain can destroy, just as surely as a massive storm that causes a flash flood.
Cytokines, the raw material of a cytokine storm

Some 50 years ago the idea of unsuspected secreted polypeptides, mediators akin to hormones but arising throughout the body from cells with other primary functions rather than from specialized secretory organs, and communicating with many other cells, was quite new. The word cytokine became a generic term for these molecules once immunologists realized that classifying them according to their cell of origin, such as lymphocytes releasing lymphokines [4] and monocytes releasing monokines [5] was quite inadequate, particularly since a single mediator could have many cellular origins, as well as pleotropic activity. By 1991, for example, tumor necrosis factor (TNF) had been documented to possess, or at least initiate, 50 biological functions, most demonstrated quite soon after it had been cloned and made available in a recombinant form [6]. TNF [7] is one of the cytokines that kept its original function-based name. Others include interferons (IFNs) [8] – IFN-γ [9] being particularly relevant – lymphotoxins (LTs) [10] and the transforming growth factors (TGFs) [11]. We should acknowledge here the insight of the authors of a 1979 Letter-to-the-Editor in the Journal of Immunology [12] who proposed the interleukin (IL) form of nomenclature as a way to rescue order out of chaos by suggesting that a number of acronyms describing observed activities could be grouped under a numerical system, beginning with IL-1 and IL-2. This suggestion proved its worth with the increased molecular definition of entities previously known only as activities. Currently IL-1 to IL-37 are recognized, and most, if investigated, are likely to be released in a severe cytokine storm. From what is known of their proinflammatory links to TNF, the cytokines IL-1, IL-12 [13] and IL-17 [14] are particularly likely to contribute to the dramatic outcome of a full-blown storm, but this is the topic of a much wider ranging review. This text is largely restricted to TNF and IL-1, cytokines that conspicuously are released early, and readily induce others. A broad canvas of the array of mediators that can, in excess, form a cytokine storm can be impressive, as can the mathematical models of its dynamics [15], but their known interactions are still in a state of flux. In order to tell the story of the storm rather than the raindrops, we focus here on studies that have contributed to allowing the master initiators, which are released early and set the process going, to be understood, and thus become therapeutic targets.

The biological antiquity of two main players, TNF and IL-1

When a molecule present in mammals proves also to be found in earlier, particularly very early, life forms it is generally taken to denote that it has been conserved in the biological repertoire because it is essential to life. Cytokines can be good examples. For instance, although TNF is large in the mammalian literature it is also found in the marine sponge, Chondrosia reniformis [16], and the reef-building corals, Acropora spp. [17]. Remarkably, these authors found that coral TNF has a mutual receptor cross-reactivity with human TNF. Similarly, IL-1 is present in the starfish, Asterias forbesi [18]. Among insects, cells from at least two genera of moths contain IL-1 and TNF [19], so conceivably all Lepidoptera are similarly endowed. Lower vertebrates such as fish also generate both of these cytokines [20, 21], as well others such as IL-6 [22], IL-8 [23], IL-12 [24] and IL-17 [20].

The discovery of TNF and IL-1 arose from investigating endotoxicity

The earliest published record relevant to this story seems to have been the observation by Maegraith in his 1948 monograph [25] that the functional effects of parenteral bacterial endotoxin, in the form of the typhoid vaccine of the day [26], can be equated with the range of clinical changes observed in falciparum malaria. The clinical non-specificity of malaria, which can mimic rickettsial, bacterial, viral, and non-infectious diseases, carrying it implications of equal non-specificity of disease mechanism, has been documented for many decades [27]. Predictably, therefore, whatever mediates the complex illness seen in endotoxicity is acting in these other diseases as well. This conceptual framework has persisted, and continues to be strengthened. The circumstances to which it has now been extended go far beyond its conceptual origins, where gram-negative bacteria, the walls of which contain endotoxin, are present. A crucial next advance was the argument, in 1957, that the pathophysiology of endotoxicity, traumatic shock and hemorrhagic shock are remarkably identical, even to the point of experimentally inducing tolerance to any one of these states protecting against all three [28, 29]. The first arises in bacterial infection, but the other two are decidedly non-infectious.

Although cytokines now loom large in immunology, awareness of them emerged from curiosity about the useful and harmful (endotoxic) effects of bacterial endotoxin. Originally found, as noted above, in cell walls of gram-negative bacteria, endotoxin proved to be a form of lipopolysaccharide (LPS). The term was used interchangeably with LPS for many years, the later taking precedence in recent times. Endotoxin/LPS influences larger life forms in what can seem a bewildering number of ways. Intriguing early phenomena included the in vivo tolerance to its effects observed after a second and subsequent injections [30]. Another major development in 1955 was the capacity of typhoid vaccine, inevitably, we now know, containing LPS, to generate a
mediator termed endogenous pyrogen in the serum of rabbits [31]. This was argued to be of leukocyte origin, to be transferable to other rabbits, and not to cross-tolerize with typhoid vaccine [32]. In due course this was one of the paths that led to the recognition of IL-1, as discussed below.

Further complexity arose from the long history of experimental anti-tumor activity [33] of bacterial LPS implying a biological relevance beyond bacterial disease. Others [34] had achieved similar outcomes with an attenuated form of Mycobacterium bovis termed Bacillus Calmette-Guérin (BCG), which greatly sensitizes mice to LPS [35]. Combining these anti-tumor approaches eventually led, in 1975 [7], to the term tumor necrosis factor (TNF), currently with over 135,000 PubMed hits, far more than any other cytokine, entering the scientific lexicon. Until the insights that arose from this work, endotoxin/LPS had been assumed to be directly responsible for its tumor-killing activities. The next year the hypoglycemia induced by LPS [36] proved to arise, as did TNF, through the actions of a macrophage-origin, LPS-induced, polypeptide the authors termed glucocorticoid antagonizing factor (GAF) [37]. As far as its purification was taken, GAF mirrored TNF [38]. These two lines of research pointed the way to appreciating that endotoxin, of itself, is not, as had been thought, directly active against tumors or has the ability to change blood glucose levels, but induces soluble mediators of host origin that have these properties. In other words, mice exposed to parenteral endotoxin generate molecules with anti-tumor and hypoglycemic activity. This opened minds to wondering how many of these mediators existed, and what they did.

Work on the identity of endogenous pyrogen (see [31], above) lay dormant for many years, until 1979, when LPS was appreciated to induce serum amyloid A (SAA) from macrophages indirectly, through the action of another macrophage-origin mediator the authors appropriately termed SAA-inducer [39]. Soon after, this product was found to be identical to both endogenous pyrogen and lymphocyte activating factor (LAF) [40, 41], one of the many names subsumed into the term IL-1 [12]. Hence endogenous pyrogen was evidently identical to IL-1.

What controls TNF increases in innate immunity and disease?

As we have recently reviewed in this context [42], from the late 1980s interest in the evolution of the immune system fostered ideas on how the cytokines that caused innate immunity and disease pathogenesis could arise, and be controlled, in non-infectious as well as infectious disease states. The models that this era generated [43, 44] are still in place. In brief, pathogen-associated molecular patterns (PAMPs) are released by pathogens, and damage-associated molecular patterns (DAMPs) by tissue damaged by trauma, hypoxia, and metals such as lead, which hypomethylate host DNA. This has the same PAMP activity as do mitochondrial DNA and bacterial DNA, which are innately hypomethylated. Both PAMPs and DAMPs are agonists for non-specific pattern recognition receptors (PPRs) on or inside most cell types, the best described of which are the toll-like receptors, or TLRs [45]. In this way, a disparate collection of signals triggering the same functional outcome fits within a framework that provides these signals with the ability to trigger the release of proinflammatory cytokines. For instance, within this now widespread terminology the LPS discussed in the previous section is one of the PAMPs that are agonists for TLR4 [46]. These cytokines, through the processes of innate immunity, have the capacity to kill the pathogen that provided the PAMP. Also, when in excess, these cytokines initiate pathological processes shared by both infectious and non-infectious diseases.

Some physiological roles of TNF and IL-1 outside the brain

While the principles governing cytokines in innate immunity and disease pathogenesis were being elucidated it was not yet appreciated that TNF and IL-1 are crucial for physiological homeostasis [47]. IL-1 is generally less reported in this context than is TNF, arguably because IL-1-specific reagents are less freely available. Nevertheless, normal hematopoiesis is known to depend on these two cytokines [48, 49], as does normal sleep regulation [50]. Mitochondrial function depends on TNF [51], and it has, as we have reviewed, homeostatic effects on the normal reproduction rate of various progenitor cells, of particular clinical importance those of endothelial cells in severe malaria and sepsis [52]. Clearly, much physiology is controlled by small fluctuations in TNF and IL-1 acting as signaling molecules. The above examples suffice to demonstrate the now established principle that the key cytokines mediating innate immunity and disease pathogenesis are, as next discussed, normally present, and indeed necessarily present, in healthy individuals, fulfilling physiological roles unrelated to inflammation. Thus we advocate not routinely referring to TNF and IL-1 as proinflammatory cytokines, since this terminology often leads this closely linked pair to be regarded simply as biomarkers for the presence of inflammation, a link not made until over 10 years after TNF had been first described [53], and in any event relatively minor within the range of broad biological effects of these cytokines.

Roles of TNF and IL-1 in innate immunity and disease pathogenesis

As has been reviewed [54], in the mid-1970s our laboratory had been seeking a plausible explanation for our observation
that mouse hemoprotozoan parasites die inside circulating erythrocytes during the immune response [55], an unpopular finding in certain quarters, since it was inconsistent with antibody-based dogma on which malaria vaccine research was then based. We were also wondering why a two week prior infection of mice with BCG, administered on the advice of a colleague, Jean-Louis Virelizier, created a milieu inimical to these parasites, causing their death, in the same intra-erythrocytic location, some 12 h after their injection into the mice [56]. An additional puzzle was why the illness and pathol- ogy caused by these organisms, was, as Maegraith had argued in human malaria decades earlier [25], so similar to endotoxicity. Importantly, we had found we could mimic the mouse disease as well as the death of parasites inside erythrocytes by injecting small amounts of endotoxin/LPS [57]. Remarkably, these changes happened of their own accord in undisturbed self-limiting infections, arguably induced by a stimulus functionally similar to LPS that was provided by the increased parasite load as the infection progressed. Thus we began to search for explanations based on LPS-induced macrophage products that might make sense of these obser-
vations. The essential revelation that awakened us to the poss-
ibility of TNF being responsible came from reading the then new1975 Sloan Kettering paper [7] on the use of BCG and LPS, reagents we had been using with the same timing, but in our case to understand the relationship between an infectious agent and its host rather than tumor killing. With their collabor-
oin in assaying TNF, we began to develop our then novel view that infectious disease is caused not directly by the invading pathogen, but by what were effectively the side effects of the host’s over-exuberant innate immune response to it. We had evidence, albeit now regarded as rudimentary because of the pre-recombinant assays of the day, that TNF and lymphocyte activating factor (LAF), an old name for IL-1, could be involved [58].

This proposal could not, of course, be properly tested until peptides such as cytokines became available in recombinant form, and in sufficient quantity for in vivo use. Since TNF was first recognized for its tumor killing properties, ambitions were high in the late 1980s that rTNF [59] would be therapeu-
tically valuable to cancer patients. In hindsight, we know that severe side-effects [60–62] of the type now attributable to a cytokine storm, were inevitable. To these researchers’ minds the side effects of rTNF they produced resembled an influenza-like disease [63], but to us, with our malaria background, they were also profoundly malaria-like. This generally unanticipated outcome of treatment with rTNF was extremely instructive for our theories on the cytokine origins of the illness of malarial disease and bacterial sepsis [58, 64], and we and others had already been injecting rTNF into animal models for this purpose [65, 66]. In the next year, 1988, these principles were incorporated into the original description of sickness behavior [67], which we subsequently described, in its extreme form, as being the basis of the syn-
drome seen in severe systemic protozoal, bacterial, viral dis-
ease, as well as post-trauma [68].

Thus developed the view that infectious disease is caused not directly by the invading pathogen, but by the host’s exces-
sive innate immunity to it. The concept eventually spread across the board to include both innate immunity and disease pathogenesis in, for example, infection with Mycobacterium spp. [69, 70], Brucella abortus [71, 72], Salmonella spp. [73, 74], Listeria monocytogenes [75, 76], Leishmania spp. [77, 78], Toxoplasma gondii [79, 80], and influenza [81, 82]. This pattern of cytokines being useful in low concentrations but harmful in high, first reviewed in 1987 in a malaria context [83], is now generally accepted in infectious disease. It is not, however, at all restricted to pathogen-induced conditions, as discussed below.

Many reports link high circulating levels of TNF and IL-1, arguably the original hallmarks of a cytokine storm, with the biochemical details of the pathogenesis of clinical markers of critically ill patients. A random illustration is hypoalbumin-
emia, an independent marker of poor outcomes in severely ill patients with various diagnoses [84], as recently investigated in critically ill children in intensive care [85]. As reviewed [68], hypoalbuminemia is also a characteristic of malaria, sep-
sis, acute viral diseases, and severe trauma, all conditions with high TNF. They are, indeed, prototype examples of the effects of a cytokine storm. Reduced albumin is to be expected in all these circumstances, since the liver-specific albumin gene is positively regulated by Dbp [86], one of the circadian genes that TNF and IL-1 suppress [87]. Picomolar concentrations of TNF have been demonstrated to reduce albumin production by human hepatocytes [88]. Whether it does so by inducing IL-1, or independently, or whether they act synergistically, appears, as in too many other circumstances, yet to be determined.

**Persistent cytokine storms in the ill brain**

Moderate, but persistent, cytokine storms are typical of the chronic neurodegenerative states, including post-stroke, post-traumatic brain injury, and Alzheimer’s disease (AD). In the weather analogy, cytokines are what water is to life. Light falls of rain, like low levels of TNF and IL-1, keep physiology ticking over and organisms alive. In moderate amounts rain improves outcome, as does self-limiting innate immunity, but in acute excess, or unrelenting moderate amounts, both rain and cytokines can kill. Both the acute and unrelenting patterns are valid cytokine storms. Acute systemic cytokine excesses, ie those outside the central nervous system (CNS), typically arise from the effects from bacterial or viral PAMPs, and are, if not acutely fatal, generally tran-
sient. In contrast, when excess cytokine is generated within
the brain in sufficient quantities, as distinct from entering from outside, the usual type of cytokine storm is an unrelenting moderately raised activity that leads to non-resolving inflammation.

This non-resolving pattern of inflammation in the brain is consistent with the consequences of injecting LPS, the prototype TNF inducer, and a TLR4 agonist, in order to generate models of neurodegenerative disease in rodents [89]. Following a single systemic LPS injection, TNF production in mouse brain remains high for at least ten months [90]. In contrast, serum TNF levels peaked at the expected nine hours. Why this difference? These authors argue that an acute systemic injection of LPS activates brain microglia through TNF receptors that initiate sustained activation of brain cytokine synthesis and neuroinflammation. These studies are consistent with earlier work in which the TNF switch-off that occurs systemically after a second LPS injection, which demonstrates the presence of LPS tolerance, proved to be absent in the intracisternal space [91]. Evidently TNF generation is inhibited differently systemically and cerebrally, conceivably mediated either through failure of the anti-inflammatory cytokines IL-4 or IL-10 to increase as they do systemically, and, as noted above, LPS tolerance being weak or absent inside the blood brain barrier (BBB). It is also consistent with the activated state of microglia many years after brain ischemia [92] or brain trauma events [93, 94], as well as with evidence for a positive feedback loop for microglial activation via TNF [95].

Thus the central nervous system is especially vulnerable to cytokine storms that arise when TNF is generated within the brain, from many cell types, particularly microglia and astrocytes but also including neurons [96], and leads to loss of homeostasis in such vulnerable sites as synapses. One predictable consequence is the loss of the subtle homeostasis we depend on for learning, memory, and normal behavior, as seen in chronic neurodegenerative states. As discussed below, severe changes include neuronal death through excitotoxicity.

Since brain function determines subtleties such as personality, behavior, executive function, mood, willpower, learning and memory, we can expect the effects of brain TNF excess to be much more nuanced than the same change in the rest of the body. This is indeed what happens. For example, mice without certain TNF receptors do not become aggressive [97]. The origins of delirium, in which a seriously ill patient shows transient disorientation, confusion and memory loss as part of an exaggerated sickness behavior, remain controversial [98], but it is certainly part of a cytokine storm. It is now considered to be best understood in terms of peripheral TNF being increased sufficiently for enough to cross the BBB for a limited period [99]. Dementia, in contrast, reflects continual TNF production within the brain. Likewise, the coma that is often part of an encephalopathy accompanying sepsis, influenza or malaria can also be rationalized in cytokine terms, with associated coma argued to arise through increased cerebral TNF reducing orexin levels [100]. See reference [101] for a review.

Some key physiological roles of TNF and IL-1 inside the brain

As we have noted [42], physiological roles of TNF and IL-1 inside the brain include their release during physiological neuronal activity and, as has been reviewed [102], playing a crucial role in regulating the strength of normal synaptic transmission. TNF, of itself rather than through the inflammatory cascade it can trigger, is also involved in normal transmission via modulating excitatory neurotransmission [103], trafficking of AMPA receptors [104], homeostatic synaptic scaling [105], long-term potentiation [106], and maintaining normal background levels of neurogenesis [107]. As noted earlier, and of particular relevance in the brain, which requires much oxygen, mitochondrial function depends on TNF [51]. So too does regulation of the neurotransmitter orexin [100], which, as we recently reviewed in a brain disease context [101], controls sleep, motor control, focused mental effort, appetite and water intake. TNF also regulates neuronal type-1 inositol trisphosphate receptors (IP3R), which are central to neuronal Ca ++ homeostasis, and thus the ionic signaling cascades on which normal function of these cells depends [108]. Likewise, glycine receptors, which are structurally related to γ-aminobutyric acid (GABA) receptors and have a similar inhibitory role, are influenced by proinflammatory cytokines [109].

Some key pathophysiological roles of TNF and IL-1 inside the brain

As we have recently reviewed [110], high brain TNF levels increase harmful cerebral glutamate concentrations through enhancing both glutaminase activity and glutamate re-entry proteins, but evidence implies that IL-1 does not [111]. Clearly, these brain functions are susceptible to TNF and/or IL-1 being above their homeostatic range during a cytokine storm, and consequent change can be expected in the subtleties as well as the gross consequences of excitotoxicity in circumstances when the proinflammatory cytokine load is high and prolonged. Neurogenic pain [112] and insulin resistance in AD brains [113] are examples.

Much relevant material on TNF and the brain that space considerations preclude here is contained in our 2010 review [114]. This text developed from our view that the riddle of malarial encephalopathy (cerebral malaria, (CM)) could be understood only by getting engrossed in understanding how TNF influences brain function in other states, such as AD [115]. We felt that in both of these conditions the historical
histological hallmarks – sequestered parasitized erythrocytes in CM, and amyloid (Aβ) plaques in AD – had somehow been allowed, in the absence of other contenders, to evolve into primary mechanisms that researchers were comfortable with, conceivably because they could point them out under a microscope. Increasingly, each hallmark has fallen from the spotlight because of developments in the cytokine storm literature. Importantly, CM has been reported recently to respond dramatically after treating affected mice with the glutamine analog 6-diazo-5-oxo-L-norleucine (DON) [116], lowering the brain glutamate and thus excitotoxicity, that excess brain TNF generates [110].

Likewise, developments in cytokine biology have meant that Aβ, for decades almost universally argued to be central to understanding AD, has lost momentum as the key to this disease as well as its proposed importance in post-stroke syndromes [117] and traumatic brain injury [118]. Over two decades ago TNF was reported to alter synaptic transmission in hippocampal slices [119]. Five years later [120] it was shown that this earlier observation explained the ability of Aβ, through TNF, to do the same. Other laboratories expanded the roles of TNF in this context [103]. The capacity of Aβ to act as a ligand for CD14 and TLR2 indicates that these findings with Aβ [120] are consistent with basic immunology, since occupancy of CD14 and TLRs is how the usual bacterial and protozoal-origin inducers of TNF operate [121]. Key support for this concept has been provided by the recent demonstration that the release of pro-inflammatory cytokines from astrocytes is necessary for either Aβ to be neurotoxic or tau phosphorylation to be initiated [122]. Importantly, a recent large epidemiological study, in which administering regular subcutaneous etanercept, a specific anti-TNF biological agent in common clinical use, over an extended period in treatment of rheumatoid arthritis (RA), was reported to reduce incidence of AD [123] in these patients. This further greatly enhances the likelihood of TNF, and correspondingly decreases the likelihood of Aβ, being the key to AD pathogenesis. These and related arguments are discussed in our reviews [42, 52, 110, 124–128].

More recently a technically impressive study [129] has identified changes in the dynamics of re-uptake proteins, and thus of glutamate, in the extracellular microenvironment near Aβ plaques in the brain of a high Aβ mouse model of AD. Unfortunately, presenting these data as evidence for a direct functional link between Aβ and cognitive impairment and neuronal loss through excitotoxicity, as these authors do, ignores the literature on the essential intermediary role of TNF in these observations [120, 130]. The outcome is actually a strong case for AD arising through a chronic cerebral cytokine storm, since TNF, as well as being induced by many TLR agonists, including Aβ, is well known [110] to influence glutamate dynamics in the way described above [129].

Clinical usefulness of this knowledge

The obvious inference from the literature reviewed here is that patients suffering from cytokine storms should be treated by neutralize the offending cytokines, mainly TNF. It was, however, established quite early in mice [131] and baboons [132], when knowledge of post-TNF pathways was in its infancy, that specific anti-TNF neutralizing agents have to be administered 1–2 h before TNF induction, while animals are still perfectly healthy, in order to save them. An example of a useful application of this principle has been the successful treatment of the life-threatening Jarisch-Herxheimer reaction that can be induced by the PAMPs released from damaged and dead Borrelia duttonii, the cause of African East Coast Relapsing Fever, as a consequence of treating patients with penicillin [133]. Treatment consisted of pre-penicillin exposure to a polyclonal Fab antibody fragments against TNF-alpha (anti-TNF-alpha Fab). In contrast, when someone is acutely ill from sepsis the TNF that made them ill has largely come and gone, having set in train many harmful pathways. This is presumably what prevents specific anti-TNF neutralizing agents from being clinically useful in patients who are acutely ill from sepsis [134]. There is also the practical consideration of anti-TNF agents reducing the efficacy of innate immunity in acute infections, albeit first recognized in treatment of RA patients harboring chronic infections such as tuberculosis, in which innate immunity is an important component [135].

Chronic inflammation is quite another story. Some 5 years ago Karl Nathan reviewed the therapeutic challenge represented by resolving compared to non-resolving inflammatory diseases [136]. Specific anti-TNF biologicals have made their mark in a number of these non-resolving inflammatory states, and their influence is set to expand. They are well-established in the treatment of RA, psoriasis and Crohn’s disease, three non-resolving conditions affecting different anatomical sites in the periphery. Although for historical reasons these three diseases are the province of three different medical specialties, this has not prevented a common approach to treatment. Moreover, treating the non-resolving inflammatory states that constitute the neurodegenerative diseases by this same approach has, for some time now, awakened great interest in some quarters. Unfortunately, this enthusiasm for treating the brain for excess TNF is, to date, largely restricted to neuroscientists and medical specialists with prior anti-TNF experience in their field [123, 137–139]. It has yet, it seems, to extend to neurologists [128], conceivably in part for commercial-in-confidence reasons [140]. Nevertheless, the value for patients in bridging this knowledge gap has been compelling for some years, particularly with recent awareness that brain TNF levels are a main cause of variation in synaptic activity of glutamate, which, across the neurodegenerative diseases, is manifested when in excess as excitotoxicity.
report that TNF induces production of IL-1. This is consistent with later studies surrounding the first demonstration of clinical success of infliximab [144], the original specific anti-TNF biological agent, being reported to reduce IL-1 as well as TNF levels [145–147]. It also reduced IL-6 [146, 148], and IL-8 [146]. During these studies this group appears to have been the first to described the concept of a cytokine cascade [146, 148].

Nevertheless, while this literature provides an excellent rationale for the therapeutic use of specific anti-TNF biological agents, there may be an opportunity, particularly regarding IL-1, that is still relatively neglected. There is ample evidence that in certain circumstances IL-1, induced by TNF [143], can itself induce TNF, and the shared and unshared functions of these two cytokines have been discussed at length [149]. These include the membrane-associate IL1 (IL-1α) [150], as well as circulating IL-1, or IL-1β [151, 152]. In addition, TNF and IL-1 can synergize [153–155], for example in causing illness and pathology [156, 157]. Thus, although neutralizing excess TNF has become the dominant pharmacological approach in this field, excess IL-1 is receiving, and certainly warrants, further attention as a target molecule.

TNF and IL-1 received roughly equal prominence in the earlier literature, but neutralizing the effects of TNF has largely dominated the therapeutics literature. In part this may be because specific anti-TNF biologicals have been freely available laboratory and clinical tools, since the mid 1980s and mid 1990s respectively. Two specific anti-IL-1β biologicals, canakinumab [158] and another termed P2D7KK [159], as well as a recombinant form of a naturally occurring antagonist to IL-1 receptor, Anakinra [160, 161], are available. We feel it can fairly be said to date, however, that these agents have proved to be less potent in treating inflammatory disease than are the specific anti-TNF biological agents. In 2013 Dinarello [162] extensively reviewed why this was apparently so. Nevertheless, various applications are still vigorously explored. For example one group has been capitalizing on their finding that IL-1 receptor antagonist (IL-1ra) is an endogenous neuroprotectant that is increased rapidly in a rat model of focal ischemia. This has led them to enhance this antagonist by supplementing its in vivo levels with the recombinant form, Anakinra [163]. They have since reported that, despite a large molecular weight that would preclude its passage through the normal BBB after subcutaneous injection in the rat, Anakinra entered the CSF for a therapeutic window of up to 24 h after the stroke event, and prevented subsequent damage by a reported 33% [164]. This delivery method was also successful after a range of intravenous injection protocols in patients, although clinical outcomes were not measured [165]. An initial controlled trial produced no harm, and was considered too underpowered to achieve positive outcomes [166]. The most likely target for this treatment has been considered to be to increase cerebral blood flow. As noted previously, this group had earlier reported that IL-1ra did not influence glutamate release into synaptosomes [111].

In conclusion, we note that these recent implications of cytokine storms for understanding encephalopathies usefully allow disease pathogenesis to be appreciated as a single entity through bridging the gap between TNF in systemic disease and the brain, as well as encompassing infectious and non-infectious disease on both sides of the blood-brain barrier. This promises new therapeutic perspectives for important cerebral disorders, particularly chronic neurodegenerative states, as exemplified by new data linking cerebral TNF and extracellular glutamate referred to earlier in this text. As we have summarized [110], cerebral TNF and consequently extracellular cerebral glutamate are both chronically increased in Alzheimer’s disease, post-stroke syndromes, traumatic brain injury, and Parkinson’s disease, Huntingdon’s disease, Amyotrophic lateral sclerosis, septic encephalopathy, poor post-operative cognition, poor post-irradiation cognition, HIV dementia, cerebral malaria and viral encephalitides. Cerebral palsy also fits this pattern [167, 168]. As noted [110], this relationship between TNF and glutamate is consistent with excitotoxicity and synaptic shutdown being major consequences of chronic cerebral cytokine storms, albeit with different anatomical locations, initiators and kinetics. We suggest that the physiological roles of TNF in the brain are sufficiently diverse to generate, when homeostasis of this cytokine and therefore glutamate are lost, most of the overlapping syndromes encompassed by the above array of disease states. Logical therapeutic approaches include specific anti-TNF or anti-IL-1 agents that enter the CSF, whether through their route of administration [139] or size [110]. With these advances, our understanding of cytokine storms is much closer to coming of age.

Acknowledgements No funding was received for this work, and the authors have no interests to declare.
Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Clark IA (2007) The advent of the cytokine storm. Immunol Cell Biol 85:271–273
2. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG (2012) Into the eye of the cytokine storm. Microbiol Mol Biol Rev 76(1):16–32. doi:10.1128/mmbrr.05015-11
3. Ferrara JL (1993) Cytokine dysregulation as a mechanism of graft versus host disease. Curr Opin Immunol 5(5):794–799
4. Dumonde DC, Wolstencroft RA, Panayi GS, Matthew M, Morley J, Howson WT (1969) "Lymphokines": non-animal mediators of cellular immunity generated by lymphocyte activation. Nature 224(5214):38–42
5. Kouttab NM, Mehta S, Morgan J, Tannir N, Sahasrabuddhe C, Maizel AL (1984) Lymphokines and monokines as regulators of human lymphoproliferation. Clin Chem 30(9):1539–1545
6. Jäättelä M (1991) Biologic activities and mechanisms of action of tumor necrosis factor-a cachectin. Lab Invest 64(6):724–742
7. Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B (1975) An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A 72(9):3666–3670
8. Issacs A, Lindenmann J (1957) Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 147(927):258–267
9. Hovanessian AG, La Bonnardiere C, Falcoff E (1980) Action of murine gamma (immune)interferon on beta (fibroblast)-interferon resistant L 1210 and embryonal carcinoma cells. J Interf Res 1(1):125–135
10. Ruddle NH, Waksman BH (1967) Cytotoxic effect of lymphocyte-antigen interaction in delayed hypersensitivity. Science 157(792):1060–1062
11. Moses HL, Branum EL, Proper JA, Robinson RA (1981) Transforming growth factor production by chemically transformed cells. Cancer Res 41(7):2842–2848
12. Aarden LA (1979) Revised nomenclature for antigen-nonspecific T cell proliferation and helper factors. J Immunol 123:2929–2929
13. Gately MK, Desai BB, Wolitzky AG, Quinn PM, Dwyer CM, Podlaski FJ, Familletti PC, Sinigaglia F, Chizonitte R, Gubler U (1991) Regulation of human lymphocyte proliferation by a heterodimeric cytokine, IL-12 (cytotoxic lymphocyte maturation factor). J Immunol 147(3):874–882
14. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spiggs MK, Armitage RJ (1995) Human IL-17: a novel cytokine derived from T cells. J Immunol 155(2):5483–5486
15. Yiu HH, Graham AL, Stengel RF (2012) Dynamics of a cytokine storm. PLoS One 7(10):e45027. doi:10.1371/journal.pone.0045027
16. Pozzolini M, Scarfi S, Mussino F, Fernando S, Gallus L, Giovin M (2015) Molecular cloning, characterization, and expression analysis of a prolyl 4-hydroxylase from the marine sponge Chondrosia reniformis. Mar Biotechnol (NY) 17(4):393–407. doi:10.1007/s10227-016-9630-3
17. Quistad SD, Stotland A, Barott KL, Smurthwaite CA, Hilton BJ, Grasis JA, Wolkowicz R, Rohwer FL (2014) Evolution of TNF-induced apoptosis reveals 550 my of functional conservation. Proc Natl Acad Sci U S A 111(26):9567–9572. doi:10.1073/pnas.1405912111
18. Beck G, Habicht GS (1986) Isolation and characterization of a primitive interleukin-1-like protein from an invertebrate, Asterias forbesi. Proc Natl Acad Sci U S A 83(19):7429–7433
19. Wittwer D, Franchini A, Ottaviani E, Wiesner A (1999) Presence of IL-1- and TNF-like molecules in galleria mellonella (Lepidoptera) haemocytes and in an insect cell line Fromestigmene acraea (Lepidoptera). Cytokine 11(9):637–642. doi:10.1016/cyto.1998.0481
20. Gunimaladevi I, Savar R, Sakai M (2006) Identification, cloning and characterization of interleukin-17 and its family from zebrafish. Fish Shellfish Immunol 21(4):393–403. doi:10.1016/j.molimm.2006.01.004
21. Wang T, Bird S, Koussoudasis A, Holland JW, Carrington A, Zou J, Secombes CJ (2009) Identification of a novel IL-1 cytokine family member in teleost fish. J Immunol 183(2):962–974. doi:10.4049/jimmunol.0802953
22. Wang T, Secombes CJ (2009) Identification and expression analysis of two fish-specific IL-6 cytokine family members, the ciliary neurotrophic factor (CNTF)-like and M17 genes, in rainbow trout Oncorhynchus mykiss. Mol Immunol 46(11–12):2290–2298. doi:10.1016/j.molimm.2009.04.003
23. Wang E, Wang J, Long B, Wang K, He Y, Yang Q, Chen D, Geng Y, Huang X, Ouyang P, Lai W (2016) Molecular cloning, expression and the adjuvant effects of interleukin-8 of channel catfish (Ictalurus punctatus) against streptococcus iniae. Sci Rep 6:29310. doi:10.1038/srep29310
24. Wang T, Husain M, Hong S, Holland JW (2014) Differential expression, modulation and bioactivity of distinct fish IL-12 isoforms: implication towards the evolution of Th1-like immune responses. Eur J Immunol 44(5):1541–1551. doi:10.1002/eji.201344273
25. Maegraith B (1948) Pathological processes in malaria and Blackwater fever. In: Blackwell, Oxford, pp 367–369
26. Altschule MD, Freedberg AS, McManus MJ (1957) The relationship between the vascular manifestations of shock produced by endotoxin, trauma, and hemorrhage. I. Certain similarities between the reactions in normal and endotoxin-tolerant rats. J Exp Med 106(403–414
27. Zweifach BW, Thomas L (1957) The relationship between the vascular manifestations of shock produced by endotoxin, trauma, and hemorrhage. II. The possible role of the reticulo-endothelial system in resistance to each type of shock. J Exp Med 106:385–401
28. Biozzi G, Benacerraf B, Halpern BN (1955) The effect of Salm. Typhi and its endotoxin on the phagocytic activity of the reticulo-endothelial system in mice. Br J Exp Pathol 36(3):226–235
29. Atkins E, Wood WB Jr (1955) Studies on the pathogenesis of fever. I. The presence of transferable pyrogen in the blood stream following the injection of typhoid vaccine. J Exp Med 101(5):519–528
30. Atkins E, Wood WB Jr (1955) Studies on the pathogenesis of fever. II. Identification of an endogenous pyrogen in the blood stream following the injection of typhoid vaccine. J Exp Med 102(5):499–516
31. Prigal SJ (1961) Development in mice of prolonged non-specific resistance to sarcoma implant and staphylococcus infection following repository injection of lipopolysaccharide. Nature 191:1111–1112
32. Old LJ, Clarke DA, Benacerraf B (1959) Effect of bacillus Calmette Guérin infection on transplanted tumours in the mouse. Nature 184(4682):291–292
35. Suter E (1964) Hyperreactivity to endotoxin after infection with BCG. J Immunol 92:49–54
36. Shands JW Jr, Miller V, Martin H (1969) The hypoglycemic activity of endotoxin. I. Occurrence in animals hyperreactive to endotoxin. Proc Soc Exp Biol Med 130(2):413–417
37. Moore RN, Goodrum KJ, Berry LJ (1976) Mediation of an endotoxic effect by macrophages. J Reticuloendothel Soc 19(3):187–197
38. Hill MR, McCallum RE (1992) Identification of tumor necrosis factor as a transcriptional regulator of the phosphoehropyruvate carboxykinase gene following endotoxin treatment of mice. Infect Immun 60(10):4040–4050
39. Sipe JD, Vogel SN, Ryan JL, McAdam KP, Rosenreich DL (1979) Detection of a mediator derived from endotoxin-stimulated macrophages that induces the acute phase serum amyloid response in mice. J Exp Med 150(3):597–606
40. Szein MB, Vogel SN, Sipe JD, Murphy PA, Mizel SB, Oppenheim JJ, Rosenreich DL (1981) The role of macrophages in the acute-phase response: SAA inducer is closely related to lymphocyte activating factor and endogenous pyrogen. Cell Immunol 63(1):164–176
41. McAdam KP, Li J, Knowles J, Foss NT, Dinarello CA, Rosenwasser LJ, Selinger MJ, Kaplan MM, Goodman R, Herbert PN, Baussner LL, Nadler LM (1982) The biology of SAA: identification of the inducer, in vitro synthesis, and heterogeneity demonstrated with monoclonal antibodies. Ann N Y Acad Sci 389:126–136
42. Clark IA, Vissel B (2015) Amyloid beta: one of three danger-associated molecules that are secondary inducers of the proinflammatory cytokines that mediate Alzheimer’s disease. Br J Pharmacol 172(15):3714–3727. doi:10.1111/bph.13181
43. Janeway CA Jr (1989) Pillar article: approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb Symp Quant Biol 54(9):1–13
44. Matzinger P (2002) The danger model: a renewed sense of self. Science 296(5566):301–305
45. Pollartak A, Smimova I, He X, Liu MY, Van Huffel C, McNally O, Birdwell D, Alejos E, Silva M, Du X, Thompson P, Chan EK, Ledesma J, Roe B, Clifton S, Vogel SN, Beutler B (1998) Genetic and physical mapping of the Lps locus: identification of the toll-4 receptor as a candidate gene in the critical region. Blood Cells Mol Dis 24(3):340–355
46. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, Akira S (1999) Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide. J Immunol 162(7):3749–3752
47. Tovey MG (1988) The expression of cytokines in the organs of normal individuals: role in homeostasis. In: J Biol Regul Homeost Agents 2(2):87–92
48. Clark IA, Chaudhri G (1988) Tumour necrosis factor may contribute to the anaemia of malaria by causing dyserythropoiesis and erythrophagocytosis. Br J Haematol 70(1):99–103
49. Bagby GC Jr (1989) Interleukin-1 and hematopoiesis. Blood Rev 3(3):152–161
50. Jewett KA, Krueger JM (2012) Humoral sleep regulation; interleukin-1 and tumor necrosis factor. Vitam Horm 89:227–245. doi:10.1016/B978-0-12-394623-2.00013-5
51. Sanchez-Alcazar JA, Schneider E, Martinez MA, Carmona P, Hernandez-Munoz I, Siles E, De la Torre P, Ruiz-Cabello J, Garcia I, Solis-Herruzo JA (2000) Tumor necrosis factor-alpha increases the steady-state reduction of cytochrome b of the mitochondrial respiratory chain in metabolically inhibited L929 cells. J Biol Chem 275(18):13353–13361
52. Clark I, Atwood C, Bowen R, Paz-Filho G, Vissel B (2012) Tumor necrosis factor-induced cerebral insulin resistance in Alzheimer’s disease links numerous treatment rationales. Pharmacol Rev 64(4):1004–1026. doi:10.1124/pr.112.008580
53. Oppenheim JJ, Lew W, Akahoshi T, Matsushima K, Neta R (1988) Aspects of cytokine induced modulation of immunity and inflammation with emphasis on interleukin 1. Arzneimittel - Forschung/Drug Research 38(3A):461–465
54. Clark IA (2007) How TNF was recognized to be a key mechanism of disease. Cytokine Growth FR 18:335–343
55. Clark IA, Richmond JE, Wills EJ, Allison AC (1977) Intraerythrocytic death of the parasite in mice recovering from infection with Babesia microti. Parasitology 75(2):189–196
56. Clark IA, Wills EJ, Richmond JE, Allison AC (1977) Suppression of babesiosis in BCG-infected mice and its correlation with tumor inhibition. Infect Immun 17(2):430–438
57. Clark IA (1978) Does endotoxin cause both the disease and parasite death in acute malaria and babesiosis? Lancet ii 8080:75–77
58. Clark IA, Virelizier J-L, Carswell EA, Wood PR (1981) Possible importance of macrophage-derived mediators in acute malaria. Infect Immun 32(3):1058–1066
59. Aggarwal BB, Kohr WJ, Hass PE, Moffat B, Spencer SA, Henzel WJ, Bringman TS, Nedwin GE, Goeddel DV, Harkins RN (1985) Human tumor necrosis factor: production, purification, and characterization. J Biol Chem 260(4):2345–2354
60. Spriggs DR, Sherman ML, Kufe DW, Frei E (1987) Tumour necrosis factor: clinical trials and future directions. In: Tumour Necrosis Factor and Related Cytokines, Ciba Foundation Symposium, John Wiley and Sons, Chichester, pp 206–227
61. Spriggs DR, Sherman ML, Michie H, Arthur KA, Imamura K, Wilmore D, Frei E, Kufe DW (1988) Recombinant human tumor necrosis factor administered as a 24-hour intravenous infusion. A phase 1 and pharmacologic study. J Natl Cancer Inst 80:1039–1044
62. Spriggs DR, Sherman ML, Arthur KA, Imamura K, Frei EP, Kufe DW (1988) Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: phase 1 toxicity and effects on lipid metabolism. J Clin Oncol 6:344–350
63. Demetri GD, Spriggs DR, Sherman ML, Arthur KA, Imamura K, Kufe DW (1989) A phase I trial of recombinant human tumor necrosis factor and interferon-gamma: effects of combination cytokine administration in vivo. J Clin Oncol 7(10):1545–1553
64. Clark IA (1982) Suggested importance of monokines in pathophysiology of endotoxin shock and malaria. Klin Wochenschr 60(14):756–758
65. Tracey KJ, Beutler B, Lowry SF, Merryweather J, Wolse S, Milscale IW, Hariri R, Fahey TJ, Zentella A, Albert JD, Shires GT, Cerami A (1986) Shock and tissue injury induced by recombinant human cachectin. Science 234(4775):470–474
66. Clark IA, Cowden WB, Butcher GA, Hunt NH (1987) Possible roles of tumor necrosis factor in the pathology of malaria. Am J Pathol 129(1):192–199
67. Hart BL (1988) Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 12(2):123–137
68. Clark IA, Budd AC, Alleva LM (2008) Sickness behavior pushed too far—the basis of the syndrome seen in severe protozoal, bacterial and viral diseases and post-trauma. Malar J 7:208
69. Bermudez LE, Young LS (1988) TNF, alone or in combination with IL-2, but not IFN-gamma, is associated with macrophage killing of Mycobacterium avium Complex. J Immunol 140(9):3006–3013
70. Rook GAW (1987) Progress in the immunology of the mycobacterioses. Clin Exp Immunol 69:1–9
71. Zhan YF, Liu ZQ, Cheers C (1996) Tumor necrosis factor alpha kills of Brucella abortus by different mechanisms. Infect Immun 64(7):2782–2786
72. Ahmed K, Al Matrouk KA, Martinez G, Oishi K, Rotimi VO, Nagatake T (1999) Increased serum levels of interferon-gamma and interleukin-12 during human brucellosis. AmJ Trop Med Hyg 61(3):425–427

73. Degm E, Buholm G (1990) Effect of tumor necrosis factor-alpha on infection with Salmonella typhimurium in a mouse model. J Biol Regul Homeost Agents 4(4):157–161

74. Bhutta ZA, Mansoorali N, Hussain R (1997) Plasma cytokines in paediatric typhoidal salmonellosis: correlation with clinical course and outcome. J Inf Secur 35(3):253–256

75. Rothe J, Lesslauer W, Lotscher H, Lang Y, Koebel P, Kontgen F, Althage A, Zinkernagel R, Steinmetz N, Blumenth H (1993) Mice lacking the tumour necrosis factor receptor-1 are resistant to TNF-mediated toxicity but highly susceptible to infection by Listeria monocytogenes. Nature 364(6446):798–802

76. Nakane M, Klinghofer V, Krak LA, Budzik GP, Pollock JS, Bashu F, Carter GW (1995) Novel potent and selective inhibitors of inducible nitric oxide synthase. Molec Pharmacol 47(4):831–834

77. Titus RG, Sherry B, Cerami A (1989) Tumor necrosis factor plays a protective role in experimental murine cutaneous leishmaniasis. J Exp Med 170:2097–2104

78. Raziuddin S, Abdalla RE, el Awad EH, al Janadi M (1994) Immunoregulatory and proinflammatory cytokine production in visceral and cutaneous leishmaniasis. J Infect Dis 170(4):1037–1040

79. Chang HR, Grau GE, Perchere JC (1990) Role of TNF and IL-1 in infections with Toxoplasma gondii. Immunol 69:33–37

80. Arsenijevic D, Girardier L, Seydoux J, Chang HR, Dulloo AG (1997) Altered energy balance and cytokine gene expression in a murine model of chronic infection with Toxoplasma gondii. Am J Physiol 272(5):E908–E917

81. Sladkova T, Kostolansky F (2006) The role of cytokines in the immune response to influenza a virus infection. Acta Virol 50(3):151–162

82. Hussell T, Pennycook A, Openshaw PJ (2001) Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunity of malaria. Parasitol Today 3(10):300–303

83. Perlmutter DH, Dinarello CA, Punsal PI, Colten HR (1986) Tumor necrosis factor-alpha potentiates intraneuronal CA2+ signaling via regulation of the inositol 1,4,5-trisphosphate receptor. J Neuroimmunol 162(1):89–96. doi: 10.1016/j.jneuroim.2005.01.015

84. Liu T, Clark RK, Mcdonnell PC, Young PR, Barone FC, Feuerstein GZ (1994) Tumor necrosis factor-alpha expression in ischemic neurons. Stroke 25(7):1481–1488

85. Patel A, Siegel A, Zalcman SS (2010) Lack of aggression and anxious-like behavior in TNF receptor (TNF-R1 and TNF-R2) deficient mice. Brain Behav Immun 24(8):1276–1280

86. Cunningham R, Machulich AM (2013) At the extreme end of the psychoneuroimmunological spectrum: delirium as a maladaptive sickness behaviour response. Brain Behav Immun 28:1–13. doi: 10.1016/j.bbi.2012.07.012

87. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK (2015) The interface between delirium and dementia in elderly adults. Lancet Neurol 14(8):823–832. doi: 10.1016/s1474-4422(15)00101-5

88. Zhan S, Cai GQ, Zheng A, Wang Y, Jia J, Fang H, Yang Y, Hu M, Ding Q (2011) Tumor necrosis factor-alpha regulates the hypocretin system via mRNA degradation and ubiquitination. Biochim Biophys Acta 1812(4):565–571. doi: 10.1016/j.bbadis.2010.11.003

89. Clark IA, Vissel B (2014) Inflammation-sleep interface in brain disease: TNF, insulin, orexin. J Neuroinflammation 11:51. doi: 10.1186/1742-2094-11-51

90. Marin I, Kipnis J (2013) Learning and memory and the immune system. Learn Mem 20(10):601–607. doi: 10.1101/lm.028357.112

91. Steinshamn S, Waage A (2000) Lack of endotoxin tolerance with respect to TNF alpha production in the subarachnoid space. APMS 108(2):107–112

92. Pappata S, Levasseur M, Gunn RN, Myers R, Crouzel C, Syrota A, Jones T, Kreutzberg GW, Banati RB (2000) Thalamic microglial activation in ischemic stroke detected in vivo by PET and [11C]PK1195. Neurology 55(7):1052–1054

93. Ramlachhansingh AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM, Gentleman S, Heckemann RA, Gunanayagam K, Gelosa G, Sharp DJ (2011) Inflammation after trauma: microglial activation and traumatic brain injury. Ann Neurol 70(3):374–383. doi: 10.1002/ana.22455

94. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W (2013) Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain 136(Pt 1):28–42. doi: 10.1093/brain/aws322

95. Kuno R, Wang J, KawanoKuchi J, Takeuchi H, Mizuno T, Suzumura A (2005) Autocrine activation of microglia by tumor necrosis factor-alpha. J Neuroimmunol 162(1–2):89–96. doi: 10.1016/j.jneuroim.2005.01.015

96. Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W (2013) Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain 136(Pt 1):28–42. doi: 10.1093/brain/aws322

97. Patel A, Siegel A, Zalcman SS (2010) Lack of aggression and anxious-like behavior in TNF receptor (TNF-R1 and TNF-R2) deficient mice. Brain Behav Immun 24(8):1276–1280

98. Cunningham R, Machulich AM (2013) At the extreme end of the psychoneuroimmunological spectrum: delirium as a maladaptive sickness behaviour response. Brain Behav Immun 28:1–13. doi: 10.1016/j.bbi.2012.07.012

99. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK (2015) The interface between delirium and dementia in elderly adults. Lancet Neurol 14(8):823–832. doi: 10.1016/s1474-4422(15)00101-5

100. Zhan S, Cai GQ, Zheng A, Wang Y, Jia J, Fang H, Yang Y, Hu M, Ding Q (2011) Tumor necrosis factor-alpha regulates the hypocretin system via mRNA degradation and ubiquitination. Biochim Biophys Acta 1812(4):565–571. doi: 10.1016/j.bbadis.2010.11.003

101. Clark IA, Vissel B (2014) Inflammation-sleep interface in brain disease: TNF, insulin, orexin. J Neuroinflammation 11:51. doi: 10.1186/1742-2094-11-51

102. Marin I, Kipnis J (2013) Learning and memory and the immune system. Learn Mem 20(10):601–607. doi: 10.1101/lm.028357.112

103. Pickering M, Cumiskey D, O'Connor JJ (2005) Actions of TNF-alpha on glutamate synaptic transmission in the central nervous system. Exp Physiol 90(5):663–670

104. Ferguson AR, Christensen RN, Gensel JC, Miller BA, Sun F, Beattie EC, Bresnahan JC, Beattie MS (2008) Cell death after spinal cord injury is exacerbated by rapid TNFalpha-induced trafficking of GluR2-lacking AMPARs to the plasma membrane. J Neurosci 28(44):11391–11400

105. Stellwagen D, Malenka RC (2006) Synaptic scaling mediated by regulation of the GluR2-lacking AMPARs to the plasma membrane. J Neurosci 28(44):11391–11400

106. Cumiskey D, Butler MP, Moynagh PN, O'Connor JJ (2005) Evidence for a role in the mammalian glutamate receptor in the inhibitory effect of tumor necrosis factor-alpha on long-term potentiation. Brain Res 1136(1):13–19

107. Bernardino L, Agasse F, Silva B, Ferreira R, Grade S, Malva JO (2008) Tumor necrosis factor-alpha modulates survival, proliferation, and neuronal differentiation in neonatal subventricular zone cell cultures. Stem Cells 26(9):2361–2371

108. Park KM, Yule DJ, Bowers WJ (2008) Tumor necrosis factor-alpha potentiates intraneuronal CA2+ signaling via regulation of the inositol 1,4,5-trisphosphate receptor. J Biol Chem 283:33069–33079
109. Chirila AM, Brown TE, Bishop RA, Bellono NW, Pucci FG, Kauer JA (2014) Long-term potentiation of glycineergic synapses triggered by interleukin 1beta. Proc Natl Acad Sci U S A 111(22):8263–8268. doi:10.1073/pnas.140103111

110. Clark IA, Vissel B (2016) Excess cerebral TNF causing glutamate excitotoxicity rationalizes treatment of neurodegenerative diseases and neurogenic pain by anti-TNF agents. J Neuroinflammation 13(1):236. doi:10.1186/s12974-016-0708-2

111. Allan SM, Lawrence CB, Rothwell NJ (1998) Interleukin-1 beta and interleukin-1 receptor antagonist do not affect glutamate release or calcium entry in rat striatal synaptosomes. Mol Psychiatry 3(2):178–182

112. Sommer C, Lindenlaub T, Teuteberg P, Schafers M, Hartung T, Toyka KV (2001) Anti-TNF-neutralizing antibodies reduce pain-related behavior in two different mouse models of painful mononeuropathy. Brain Res 913(1):86–89

113. Liu Y, Liu F, Grundke Iqbal I, Iqbal K, Gong CX (2011) Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. J Pathol 225(1):54–62

114. Clark IA, Alleva LM, Vissel B (2010) The roles of TNF in brain dysfunction and disease. Pharmacol Ther 128:519–548

115. Clark IA, Alleva LM (2009) Is human malarial coma caused, or partially the same story in Alzheimer's disease. J Alzheimers Dis 14(3):236–249. doi:10.3233/JAD-2009-12539

116. Gordon GR, Baimoukhametova DV, Hewitt SA, Rajapkasha WR, Fisher TE, Bains JS (2005) Norepinephrine triggers release of gial ATP to increase postsynaptic efficacy. Nat Neurosci 8(8):1078–1086

117. Thiel A, Cechetto DF, Heiss WD, Hachinski V, Whitehead SN, Clark IA, Vissel B (2013) Neuroinflammation and interleukin-1 receptor antagonist do not affect glutamate release or calcium entry in rat striatal synaptosomes. Mol Psychiatry 35(9):929–933. doi:10.1038/mp.2013.174

118. Acosta SA, Tajiri N, Sanberg PR, Kaneko Y, Borlongan CV (2016) Increased amyloid precursor protein and tau expression manifests as key secondary cell death in chronic traumatic brain injury. J Cell Physiol. doi:10.1002/jcp.25629

119. Tancredi V, D'Arcangelo G, Grassi F, Tarroni P, Palmieri G, Santoni A, Eusebi F (1992) Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. Neurosci Lett 146(2):176–178

120. Rowan MJ, Klyubin I, Wang Q, Hu NW, Anwyl R (2007) Synaptic memory mechanisms: Alzheimer's disease amyloid beta-peptide-induced dysfunction. Biochem Soc Trans 35(Pt 5):S2

121. Beutler B, Poltonak A (2001) Sepsis and evolution of the innate immune response. Crit Care Med 29(7 Suppl S):S2–S6

122. Garwood CJ, Pooler AM, Atherton J, Hanger DP, Noble W (2011) Astrocytes are important mediators of Abeta-induced neurotoxicity and tau phosphorylation in primary culture. Cell Death Dis 2(6):e167

123. Chou RC, Kane M, Ghimire S, Gautam S, Gui J (2016) Treatment for rheumatoid arthritis and risk of Alzheimer's disease: a nested case-control analysis. CNS Drugs. doi:10.1007/s40263-016-0374-z

124. Clark IA, Alleva LM, Vissel B (2011) TNF and leptin tell essentially the same story in Alzheimer's disease. J Alzheimer's Dis 22(2):201–205

125. Clark IA, Vissel B (2013) Treatment implications of the altered cytokine-insulin axis in neurodegenerative disease. Biochem Pharmacol 86:862–871. doi:10.1016/j.bcp.2013.07.030

126. Wright AL, Zinn R, Hohensinn B, Konen LM, Beynon SB, Tan RP, Clark IA, Abdipranoto A, Vissel B (2013) Neuroinflammation and neuronal loss preceed Abeta plaque deposition in the hAPP-J20 mouse model of Alzheimer's disease. PLoS One 8(4):e59586. doi:10.1371/journal.pone.0059586

127. Morris GP, Clark IA, Vissel B (2014) Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathol Commun 2:135. doi:10.1186/s40478-014-0135-5

128. Clark IA, Vissel B (2015) A neurologist's guide to TNF biology and to the principles behind the therapeutic removal of excess TNF in disease. Neural Plast 2015:358263. doi:10.1155/2015/358263

129. Hefendehl JK, LeDue J, Ko RW, Mahler J, Murphy TH, MacVicar BA (2016) Mapping synaptic glutamate transporter dysfunction in vivo to regions surrounding Abeta plaques by iGluSnFR two-photon imaging. Nat Commun 7:13441. doi:10.1038/ncomms13441

130. Wang QW, Wu QJ, Rowan MJ, Anwyl R (2005) Beta-amyloid inhibition of long-term potentiation is mediated via tumor necrosis factor. Eur J Neurosci 22(11):2827–2832

131. Beutler B, Milsark IW, Cerami AC (1995) Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effects of endotoxin. Science 229(4716):869–871

132. Tracey KJ, Fong Y, Hesse DG, Manogue KR, Lee AT, Kuo GC, Lowry SF, Cerami A (1987) Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal shock bacteraemia. Nature 330(6149):662–664

133. Fekade D, Knox K, Hussein K, Melka A, Laloo DG, Coxon RE, Warrell DA (1996) Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against tumor necrosis factor alpha. N Engl J Med 335(5):311–315

134. Abraham E, Anzueto A, Gutierrez G, Tessler S, Sanpedro G, Wunderink R, Dalsogare A, Nasarway S, Berman S, Cooney R, Levy H, Baughman R, Rumbak M, Light RB, Poole L, Allred R, Constant J, Pennington J, Porter S (1998) Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. Lancet 351(9107):929–933

135. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwiererman WD, Siegel JN, Braun MM (2001) Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 345(15):1098–1104. doi:10.1056/NEJMoa011110

136. Nathan C, Ding A (2010) Nonresolving inflammation. Cell 140(6):871–882. doi:10.1016/j.cell.2010.02.029

137. Tobinick EL, Gross H, Weinberger A, Cohen H (2006) TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study. MedGenMed NeuroL Neurosurg 8(2):25

138. Tobinick E, Kim NM, Reyzin G, Rodriguez-Romanacce H, DePuy V (2012) Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. CNS Drugs 26(12):1051–1070. doi:10.1007/s40263-012-0013-2

139. Ignatowski TA, Spengler RN, Dhandapani KM, Folkersma H, Butterworth RF, Tobinick E (2014) Perispinal etanercept for post-stroke neurological and cognitive dysfunction: scientific rationale and current evidence. CNS Drugs 28:679–697. doi:10.1007/s40263-014-0174-2

140. Sumbria RK, Boado RJ, Partridge WM (2012) Brain protection from stroke with intravenous TNFalpha decoy receptor-Trojan horse fusion protein. J Cereb Blood Flow Metab 32(10):1933–1938. doi:10.1038/jcbfm.2012.97

141. Clark IA (2016) Letter by Clark regarding article, “clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in stroke: a phase 1/2a study”. Stroke 47(12):e268. doi:10.1161/strokeaha.116.014920

142. Steinberg GK, Kondziolka D, Wechsler LR, Lunson JD, Coburn ML, Billigen JB, Kim AS, Johnson JN, Bates D, King B, Case C, McGrogan M, Yankee EW, Schwartz NE (2016) Clinical outcomes of transplanted modified bone marrow-derived mesenchymal stem cells in...
mesenchymal stem cells in stroke: a phase 1/2a study. Stroke 47(7):1817–1824. doi:10.1161/strokeaha.116.012995

143. Dinarello CA, Cannon JG, Wolff SM, Bernheim HA, Beutler B, Cerami A, Figari IS, Palladino MA, O’Connor JV (1986) Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin-1. J Exp Med 163:1433–1450

144. Elliott MJ, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, Leeb B, Breedveld FC, Macfarlane JD, Bijl H et al (1994) Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 344(8930):1105–1110

145. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M (1989) Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet 2(8657):244–247

146. Butler DM, Maini RN, Feldmann M, Brennan FM (1995) Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti-TNF-alpha antibody with the interleukin-1 receptor antagonist. Eur Cytokine Netw 6(4):225–230

147. Lorenz HM, Antoni C, Valerius T, Repp R, Grunke M, Schwerdtner N, Nusslein H, Woody J, Kalden JR, Manger B (1996) In vivo blockade of TNF-alpha by intravenous infusion of a chimeric monoclonal TNF-alpha antibody in patients with rheumatoid arthritis. Short term cellular and molecular effects. J Immunol 156(4):1646–1653

148. Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Eberl G, deWoody K, Feldmann M, Maini RN (1999) Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol 163(3):1521–1528

149. Nathan C (1987) Secretory products of macrophages. J Clin Invest 79:319–326

150. Le JM, Weinstein D, Gubler U, Vilecek J (1987) Induction of membrane-associated interleukin 1 by tumor necrosis factor in human fibroblasts. J Immunol 138(7):2137–2142

151. Nawroth PP, Bank I, Handley D, Cassimeris J, Chess L, Stern D (1986) Tumor necrosis factor/cachectin interacts with endothelial cell receptors to induce release of interleukin 1. J Exp Med 163(6):1363–1375

152. Philip R, Epstein LB (1986) Tumour necrosis factor as immunomodulator and mediator of monocyte cytotoxicity induced by itself, gamma-interferon and interleukin-1. Nature 323(6083):86–89. doi:10.1038/323086a0

153. Stashenko P, Dewhirst FE, Peros WI, Kent RL, Ago JM (1987) Synergistic interactions between interleukin 1, tumor necrosis factor, and lymphotoxin in bone resorption. J Immunol 138(5):1464–1468

154. Elias JA, Gustilo K, Freundlich B (1988) Human alveolar macrophage and blood monocyte inhibition of fibroblast proliferation. Evidence for synergy between interleukin-1 and tumor necrosis factor. Am Rev Respir Dis 138(6):1595–1603. doi:10.1164/ajrccm.138.6.1595

155. Ogawa H, Nielsen S, Kawakami M (1989) Cachectin/tumor necrosis factor and interleukin-1 show different modes of combined effect on lipoprotein lipase activity and intracellular lipolysis in 3T3-L1 cells. Biochim Biophys Acta 1003(2):131–135

156. Bluthe RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, Dantzer R (1994) Synergy between tumor necrosis factor alpha and interleukin-1 in the induction of sickness behavior in mice. Psychoneuroendocrinology 19(2):197–207

157. Rockett KA, Awbourn MM, Rockett EJ, Clark IA (1994) Tumor necrosis factor and interleukin-1 synergy in the context of malaria pathology. Am J Trop Med Hyg 50(6):735–742

158. Rondeau JM, Ramage P, Zurini M, Gram H (2015) The molecular mode of action and species specificity of canakinumab, a human monoclonal antibody neutralizing IL-1beta. MAbs 7(6):1151–1160. doi:10.1080/19420862.2015.1081323

159. Goh AX, Bertin-Maghit S, Ping Yeo S, Ho AW, Derks H, Mortellaro A, Wang CI (2014) A novel human anti-interleukin-1beta neutralizing monoclonal antibody showing in vivo efficacy. MAbs 6(3):765–773. doi:10.4161/mabs.28614

160. Seckinger P, Lowenthal JW, Williamson K, Dayer JM, MacDonald HR (1987) A urine inhibitor of interleukin 1 activity that blocks ligand binding. J Immunol 139(5):1546–1549

161. Arend WP (1993) Interleukin-1 receptor antagonist. Adv Immunol 54:167–227

162. Dinarello CA, van der Meer JW (2013) Treating inflammation by blocking interleukin-1 in humans. Semin Immunol 25(6):469–484. doi:10.1016/j.smim.2013.10.008

163. Loddis SA, Wong ML, Bongiorno PB, Gold PW, Licinio J, Rothwell NJ (1997) Endogenous interleukin-1 receptor antagonist is neuroprotective. Biochem Biophys Res Commun 234(1):211–215. doi:10.1016/bbrc.1997.6436

164. Greenhalgh AD, Galea J, Denes A, Tyrell PJ, Rothwell NJ (2010) Rapid brain penetration of interleukin-1 receptor antagonist in rat cerebral ischaemia: pharmacokinetics, distribution, protection. Br J Pharmacol 160(1):153–159. doi:10.1111/j.1476-5381.2010.00684.x

165. Galea J, Ogungbenro K, Hulme S, Greenhalgh A, Aarons L, Scarth S, Hutchinson P, Grainger S, King A, Hopkins SJ, Rothwell N, Tyrell P (2011) Intravenous anakinra can achieve experimentally effective concentrations in the central nervous system within a therapeutic time window: results of a dose-ranging study. J Cereb Blood Flow Metab 31(2):439–447. doi:10.1038/jcbfm.2010.103

166. Singh N, Hopkins SJ, Hulme S, Galea JP, Hoadley M, Vail A, Hutchinson PJ, Grainger S, Rothwell NJ, King AT, Tyrell PJ (2014) The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. J Neuroinflammation 11:1. doi:10.1186/1742-2044-11-1

167. Savman K, Blennoow M, Hagberg H, Tarkowski E, Toreten M, Mortellaro A, Wang CI (2014) The effect of intravenous interleukin-1 receptor antagonist in cerebrospinal fluid from preterm infants with posthaemorrhagic ventricular dilatation. Acta Paediatrica (Oslo, Norway : 1992) 91(12):1357–1363

168. Rajatileka S, Odd D, Robinson ML, Spittle AC, Dwomoh L, Williams M, Harding D, Wagstaff M, Owen M, Crosby C, Ching J, Molnar E, Luyt K, Varadi A (2017) Variants of the EAA12 glutamate transporter Gene promoter are associated with cerebral palsy in preterm infants. Mol Neurobiol. doi:10.1007/s12035-017-0462-1