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REVIEW

The interleukin-1 signalling pathway in astrocytes: a key contributor to inflammation in the brain

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Abstract

A dysregulated inflammatory response in the central nervous system (CNS) lies at the heart of many neuropathological conditions such as multiple sclerosis and Alzheimer's disease. A key component of these inflammatory conditions is the accumulation of leukocytes in the CNS. The infiltration of leukocytes into the brain is dependent on the induction of leukocyte adhesion molecules and chemoattractant chemokines. Recent studies have suggested the astrocyte to be a key cell in mediating the inflammatory process in the brain and in expressing adhesion molecules and chemokines. Here I overview work in my laboratory and others that demonstrates interleukin-1 (IL-1) to be a key inducer of the expression of these molecules in astrocytes. The temporal expression is sustained in nature and this is due to prolonged activation of the transcription factor NFκB. The molecular basis to the sustained activation of NFκB is also discussed. The IL-1 signalling pathway thus emerges as a valuable therapeutic target in the treatment of presently incurable neuropathological conditions.

Key words adhesion molecules; astrocytes; interleukin-1; neuroinflammation; NF-κB.

Introduction

Neurological disorders represent some of the most debilitating diseases known. Many of these diseases are underpinned by a dysregulated inflammatory response in the central nervous system (CNS). Inflammation is normally a defence system in the body that protects against invasion by foreign agents and repairs tissue damage. However, it is imperative that this process is tightly controlled. The inappropriate or chronic deployment of the inflammatory system can lead to a loss of its protective and reparative function and its emergence as a destructive force in pathogenic processes such as multiple sclerosis and Alzheimer's disease. In an effort to develop urgently needed therapeutic agents for these currently incurable diseases, it is necessary to probe the cellular and molecular components of the inflammatory network that facilitates and drives the inflammatory process in the brain. This article will explore the cytokine interleukin-1 (IL-1) as a key player in neuroinflammation and will especially focus on its pro-inflammatory effects on astrocytes.

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Inflammation in the brain

Inflammation forms an integral part of the innate immune system. It is triggered in response to infection, damage and ischaemia. The cardinal signs of inflammation are redness, swelling, pain and heat, all of which result from the vascular response in which vasodilation and increased vascular permeability allow for the movement of soluble mediators and leukocytes from the blood vessel lumen to the site of inflammation. The arrival of leukocytes at the site of infection and/or damage is followed by their release of degradative enzymes and reactive oxygen species, ultimately leading to the destruction of the invading agent and damaged tissue and allowing for tissue repair. However, it is crucially important that the recruitment of leukocytes into tissue is strictly regulated because the effector systems used by these cells in eliminating the foreign body are also potentially toxic to normal tissue. Thus the chronic recruitment and retention of leukocytes in tissues will lead to tissue destruction and disease. This is evident

in multiple sclerosis, in which pathology is accompanied by a strong infiltration of the CNS by pro-inflammatory leukocytes (Traugott et al. 1983; Hafler & Weiner, 1987). Much effort has been invested to understand the mechanistic basis to the leukocyte recruitment process.

The pro-inflammatory cytokines, IL-1 and tumour necrosis factor (TNF), are crucially important in mediating the infiltration of tissue by leukocytes, via the initial induction of leukocyte adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1) and E-selectin on endothelial cells (Bevilacqua, 1993; Ramilo et al. 1990). IL-1 and TNF are primarily produced by monocytes and macrophages but can also be generated by a variety of resident cells in tissues (Rothwell & Luheshi, 2000). The induction of adhesion molecules by these cytokines allows for the adhesion of leukocytes to endothelial cells. The endothelium retracts, allowing for the migration of the transiently adhered leukocytes into the inflamed tissue in response to chemoattractant cytokines that are also induced by IL-1 and TNF. It is clear that the induction of adhesion molecules and chemokines by these pro-inflammatory cytokines orchestrates the recruitment process and many studies suggest that such induction is at the centre of promoting chronic infiltration of leukocytes in the CNS, leading to neuropathogenesis. Thus the brain levels of IL-1 and TNF increase dramatically in neuropathological states (Hofman et al. 1986; Dinarello, 1991) and increased levels of these cytokines are associated with breakdown of the blood–brain barrier and recruitment of neutrophils into the CNS (Ferrari et al. 2004). Neutralizing antibodies to the two cytokines reduce the CNS accumulation of leukocytes in neuropathology (Ramilo et al. 1990). Furthermore, the adhesion molecules VCAM-1 and ICAM-1 are elevated in multiple sclerosis lesions and make a major contribution to the extravasation of leukocytes across the blood–brain barrier (Brosnan et al. 1995; Cannella & Raine, 1995). The importance of adhesion molecules in neuropathology is clearly evident by a study describing that an antibody that blocks the interaction of leukocytes with VCAM-1 also reduces the severity of experimental multiple sclerosis (Yednock et al. 1992).

The astrocyte and its role in leukocyte migration into brain

Although leukocyte–endothelial interactions are crucial to the leukocyte migration process, various lines of evidence strongly suggest that the astrocyte is a key cell type that facilitates leukocyte recruitment to the CNS. Firstly, the prominent expression of leukocyte adhesion molecules in astrocytes is restricted to conditions such as multiple sclerosis (Cannella & Raine, 1995) and Alzheimer's disease (McGeer & McGeer, 2003), in which leukocyte infiltration in the CNS is high. Secondly, strategies that interfere with the adhesive function of adhesion molecules inhibit leukocyte–astrocyte interactions (Hery et al. 1995) and reduce the severity of experimental multiple sclerosis (Yednock et al. 1992). Thirdly, whereas astrocyte expression of chemokines is negligible in the normal CNS, a wide variety of chemokines are expressed by astrocytes in a number of CNS diseases, including multiple sclerosis, Alzheimer's disease and Parkinson's disease (Dong & Benveniste, 2001). Thus the induction of chemokines and adhesion molecules in astrocytes is likely to make a major contribution to the recruitment and retention of leukocytes in the CNS, the prologue to neuropathology. I and others have shown that the pro-inflammatory cytokine IL-1 is a key stimulus in the induction of adhesion molecules and chemokines in astrocytes (Moynagh et al. 1994; Shrikant et al. 1994; Rosenman et al. 1995; Bourke & Moynagh, 1999). Interestingly, my studies have shown that IL-1 induces sustained expression of the chemoattractant cytokine IL-8 and the adhesion molecules VCAM-1 and ICAM-1 in astrocytes (Moynagh et al. 1994; Bourke & Moynagh, 1999). Such sustained expression may underlie the chronic nature that is typical of the CNS inflammatory response in the neuropathological conditions mentioned above. I have thus attempted to address the molecular basis to the prolonged induction of these pro-inflammatory proteins in astrocytes.

IL-1 causes sustained activation of NFκB in astrocytes

The transcription factor NFκB is a crucial mediator in the IL-1 signalling pathway and acts as a major driving force behind the induction of adhesion molecules and chemokines (Moynagh et al. 1994; Bourke & Moynagh, 1999). The study of the temporal activation of NFκB by IL-1 in astrocytes has shed important light on the likely mechanism dictating prolonged expression of adhesion molecules and chemokines in response to IL-1 in these cells (Fig. 1).

NFκB exists in the cytosol of resting cells as a homo- or heterodimer of proteins of the Rel family of

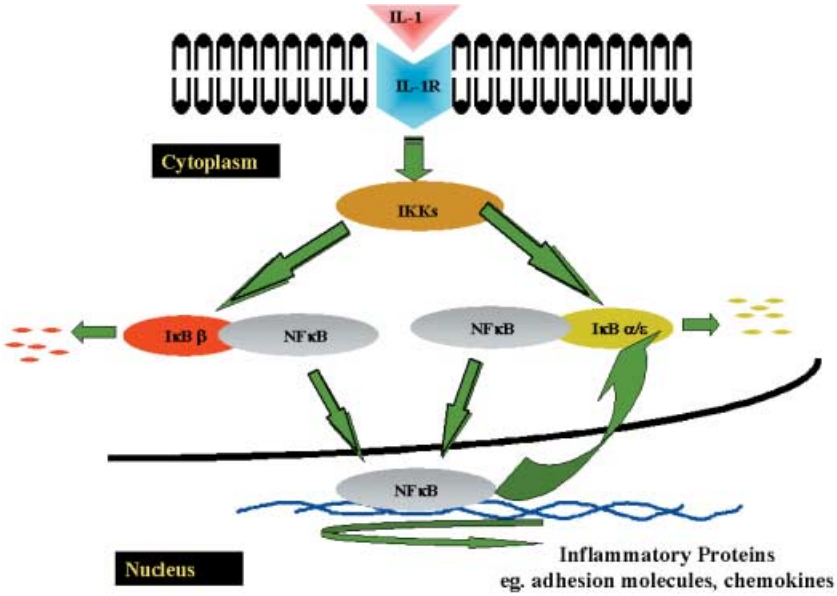

Fig. 1 Model for sustained activation of NFκB by IL-1 in astrocytes. Engagement of the IL-1 receptor (IL-1R) leads to activation of IκB-kinases and subsequent phosphorylation and degradation of the various IκB isoforms. NFκB translocates to the nucleus and induces the expression of leukocyte adhesion molecules, chemokines, IκB-α, IκB-ε but not IκB-β. The form of NFκB that is susceptible to inhibition by IκB-β thus remains bound to DNA for sustained periods of time.

transcription factors (Blank et al. 1992; Narayanan et al. 1993). The transcriptional activity of the Rel proteins is tightly regulated by their association with members of the inhibitory molecule family IκB (Baeuerle & Baltimore, 1988). The most extensively characterized isoforms are IκB-α, IκB-β and IκB-ε (Thanos & Maniatis, 1995). The IκB proteins sequester NFκB in the cytosol by masking its nuclear localization signal (NLS) and also prevent NFκB from binding to DNA by masking its DNA-binding domain. Exposure of cells to pro-inflammatory stimuli such as IL-1 causes phosphorylation of IκB on two specific N-terminal serines by the IκB-kinases (IKK), IKKα and IKKβ, which are activated by a complex signal transduction pathway (May & Ghosh, 1998). The phosphorylation of IκB proteins represents a signal for ubiquitin conjugation, followed by their degradation via the 26S proteosome (Traenckner et al. 1994, 1995). This allows for translocation of NFκB to the nucleus, where it activates the promoter regions of genes, especially those encoding pro-inflammatory proteins such as adhesion molecules and chemokines (Beg et al. 1993; Henkel et al. 1993).

Following stimulation, the duration of NFκB activation may be transient or persistent, depending on the cellular stimulus and cell type. The temporal profile is of considerable clinical relevance because sustained activation of NFκB has been demonstrated to be associated with chronic inflammatory diseases (Bureau et al. 2000). Interestingly, it has recently been shown that NFκB activation is sustained in astrocytes in response to stimulation with IL-1 (Bourke et al. 2000). Again, this is of clinical relevance because the sustained activation of NFκB in brain cells will lead to prolonged induction of leukocyte adhesion molecules and chemokines (Bourke & Moynagh, 1999) that will facilitate cerebral recruitment of leukocytes culminating in the generation of neuropathological states as described above. Thus the mechanisms controlling the temporal activation of NFκB by IL-1 in astrocytes have been probed. The study shows that the IκB isoforms (α, β and ε) play key roles in regulating the longevity of NFκB activity in astrocytes (Bourke et al. 2000). Thus stimulation of these cells with IL-1 causes rapid but transient degradation of IκB-α and IκB-ε. However, NFκB remains active even after these IκB isoforms have returned to control levels. By contrast, the IκB-β isoform fails to reappear following its initial degradation by IL-1, coincident with sustained activation of NFκB. In addition, *in vivo* overexpression of the various IκB isoforms revealed that IκB-β is the only isoform that has the ability to inhibit IL-1-induced NFκB-driven transcription. Hence the activation of NFκB by IL-1 in astrocytes is sustained due to the inability of the newly synthesized IκB-α and IκB-ε to inhibit NFκB coupled to the prolonged disappearance of IκB-β in response to IL-1 (Fig. 1). As sustained activation of NFκB is likely to lead to a chronic inflammatory state, the temporal regulation of NFκB in astrocytes may provide a means for controlling inappropriate deployment of the inflammatory response in diseases such as multiple sclerosis.

IL-1 as a therapeutic target in neurodegeneration

It is clear from above that the IL-1 signalling presents itself as a potential therapeutic target in the treatment of neurodegenerative disorders. Indeed, studies have reported that polymorphisms in genes encoding IL-1 are associated with an increased risk of early onset Alzheimer's disease (Grimaldi et al. 2000; Nicoll et al. 2000). It is interesting to note that anti-inflammatory glucocorticoids, which have value in the treatment of some neuropathological conditions (McGeer et al. 1996), can induce the expression of IκB proteins and thus inhibit IL-1 activation of NFκB (Auphan et al. 1995; Scheinman et al. 1995). This may at least partly contribute to the anti-inflammatory effects of steroids in the CNS. Perhaps more compelling findings in support of the IL-1 pathway as a valuable target in neuroprotection come from various *in vivo* studies in which the protective effects of various agents that specifically inhibit the IL-1 pathway were assessed in models of cerebral ischaemia or mechanical injury (Rothwell, 1999; Touzani et al. 1999). Such agents included the highly specific and endogenous IL-1 receptor antagonist (IL-1ra), neutralizing IL-1 antibodies and inhibitors of the processing of immature IL-1 into the mature and active IL-1 form. These agents achieved a considerable reduction in neuronal loss in the various rodent models. Interestingly, IL-1ra, the most specific and effective blocker of IL-1, improved neurological function after injury and this was associated with attenuation of neutrophil invasion (Rothwell, 1999). These studies strongly suggest that IL-1 plays a key role in promoting neurodegeneration, and interventative stratagies that regulate IL-1 signalling may emerge to be of great clinical value.

Conclusions

The dysregulated inflammatory response lies at the heart of many neuropathological conditions. Because cytokines such as IL-1 orchestrate the inflammatory response it is not surprising that accumulating evidence is making a compelling case for a key role for IL-1 in the generation of neurological disorders. A complete understanding of the molecular mechanisms by which IL-1 produces its effects in the CNS will aid greatly in the design of novel therapies for the treatment of currently incurable inflammatory diseases of the brain.

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