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IL-1 AND NEUROINFLAMMATION

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ABSTRACT

Inflammation is involved in many neurological diseases, which are mediated by IL-1 and other inflammatory cytokines. Microglia are brain macrophages responsible for innate immunity of the central nervous system (CNS) and can generate IL-1 when activated. In addition, microglia can phagocytize microorganisms and activate inflammasomes, and cellular sensors sensitive to pathogens such as infectious agents, excesses of neurotransmitters, and abnormal host proteins. For example, the NLRP3 inflammasome activates pro-caspase-1 and subsequently caspase-1, causing IL-1 to mature. IL-1 can be blocked by IL-1Ra, leading to therapeutic effects for limiting inflammation, including neuroinflammation. Here, we report evidence for the first time that dumping IL-1 by IL-1Ra can have therapeutic effects.

KEYWORDS: *neuroinflammation, brain damage, cytokines, IL-1, microglia*

INTRODUCTION

There is considerable scientific evidence indicating that inflammation contributes significantly to many neurological diseases (1-5). Inflammatory cytokines are responsible for many brain pathologies, altering the synthesis of proteins and the physiology of brain functioning. Brain pathologies such as stroke, Alzheimer's Disease, Parkinson's, trauma, haemorrhages, and others, present an inflammatory response that plays an important role in the pathological state of the disease.

Inflammation in degenerative states of the brain is largely mediated by IL-1 (6,7). Infections and brain tissue lesions can activate microglia, causing the generation of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF). The release of these cytokines occurs in defense against external insults, but they can cause inflammation and damage brain tissue, including neurons and cells.

After brain damage, microglia, a defensive cellular system in the brain, secrete IL-1, which feeds the inflammatory network. Neuroinflammation activates inflammasomes, which are cellular sensors sensitive to pathogens such as infectious agents, excesses of neurotransmitters, and abnormal host proteins. This process activates innate immunity by producing inflammatory proteins, including cytokines and chemokines released by microglia, the main innate immune cells of the brain.

Therefore, inflammasomes are mainly activated by brain microglia, but other types of central nervous system (CNS) cells, such as astrocytes and neurons, can also activate inflammasomes and generate IL-1. In addition, inflammasomes participate in degenerative brain diseases by activating the inflammatory network.

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IL-1 induces brain inflammation

The cytokine IL-1 is a key protein in in situ and systemic inflammation (8). The innate or adaptive immune response in the CNS can lead to neuroinflammation, which can be acute or chronic. IL-1 mediates a large number of inflammatory diseases and, when administered in vivo, is highly toxic, causing fever, arthralgia, myalgia, anorexia, gastrointestinal disturbances, and other serious pathologies (9).

IL-1 acts through the binding with its receptor IL-1R1, which exists on all cells and is increasingly expressed in inflammatory pathologies. The blockade of this receptor with IL-1Ra, an IL-1 receptor antagonist, exhibits therapeutic effects (10). It has been seen that IL-1Ra deficient mice show severe arthritic inflammation that can even lead the rodent to death (11). In experimental mouse models presenting a pathology similar to multiple sclerosis, a significant improvement in the disease was noted by inhibiting IL-1 with IL-1Ra, partly because IL-1Ra induces IFN-β, a therapeutic cytokine for multiple sclerosis (12). In addition, IL-1 is elevated in amyotrophic lateral sclerosis (ALS), a disease caused by the destruction of neurons due to a mutation of superoxide dismutase-1 (SOD1). There is strong evidence of inflammation in this disease, as seen by the lack of IL-1Ra (13).

Therefore, biological brain insults or traumatic injuries can lead to cerebral and systemic inflammation. Systemic inflammation can spread to brain tissue resulting in destruction, and this is an IL-1-mediated effect that can be targeted for therapeutic action. IL-1 can cause permeabilization of the blood-brain barrier (BBB) and can cross the BBB and reach the brain resulting in stimulation of adrenocorticotropic hormone (ACTH) with increased blood pressure (14) and worsening of the inflammatory process. The addition of IL-1 to cultured microglia activates the TLR, an important receptor that mediates the induction of the inflammatory response (15). IL-1 activates MAPK by upregulating other pro-inflammatory cytokines, such as TNF and IL-6, while also stimulating cyclooxygenase-2 (COX-2) with the formation of prostaglandin E2 (PGE2) synthesis (16).

The NLRP3 cellular protein complex can activate caspase-1 with the release of IL-1β and IL-18, cytokines that mediate the innate response in many inflammatory diseases, an effect that can potentially lead to patient death. The NLRP3 inflammasome activates pro-caspase-1 and subsequently caspase-1, causing IL-1 to mature. Inflammasome activation is crucial for host defense against pathogens, but it is correlated with cell death and inflammation when it increases dramatically. Therefore, the activation of caspase-1 leads to the formation of pro-IL-1, and subsequent mature IL-1, a phenomenon that occurs in the cytosol dependent on activating the P2X7 receptor (17).

Microglia are yolk sac-derived tissue-resident immune cells of the brain that are similar to macrophages and are responsible for the innate immunity of the CNS, where they control changes and antigen presentation. Microglia respond to antigens with or without phagocytosis by generating pro-inflammatory molecules, such as cytokines, that promote neuroinflammation.

Inflammation without infection, such as cancer, stroke, atherosclerosis, diabetes, myocardial infarction, etc., is termed "sterile inflammation", but, as in infectious inflammation, sterile inflammation is mediated by cytokines of the IL-1 family (18). Generally, the most important mediator in sterile inflammation is IL-1α (or IL-1F1), which is implicated in brain injury (19). Sterile inflammation initiates associated molecular damage models (DAMPs) produced by dead or transformed cells following a disease. These molecules are recognized by pattern recognition receptors (PRRs) located on immune cells that mediate inflammation and cytokine release, including those of the IL-1 family (19). Therefore, the mechanisms involved in inhibiting IL-1α and IL-1β lead to a great therapeutic relevance for neuroinflammation.

Conflict of interest

The author declares that they have no conflict of interest.

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