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Review Article

Stress and aging act through common mechanisms to elicit neuroinflammatory priming

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A B S T R A C T

Over the course of an animal's lifespan, there is a protracted breakdown in basic homeostatic functions. Stressors (both psychological and physiological) can accelerate this process and compromise multiple homeostatic mechanisms. For example, both stress and aging can modulate neuroinflammatory function and cause a primed phenotype resulting in a heightened neuroinflammatory profile upon immune activation. Microglia, the brain's resident myeloid cell, produce "silent" immune machinery in response to stress and aging that does not cause immediate immune activation; rather, these changes prime the cell for a subsequent immune insult. Primed microglia exhibit a hyperinflammatory response upon immune activation that can exacerbate pathology. In this review, we will explore parallels between stress- and aging-induced neuroinflammatory priming. First, we will provide a background on the basic principles of neuroimmunology. Next, we will discuss evidence that neuroinflammatory responses become primed in the context of both stress and aging. We will also describe cell-specific contributions to neuroinflammatory priming with a focus on microglia. Finally, common mechanisms underlying priming in the context of stress and aging will be discussed: these mechanisms include glucocorticoid signaling; accumulation of danger signals; dis-inhibition of microglia; and breakdown of circadian rhythms. Overall, there are multifarious parallels between stress- and aging-elicited neuroinflammatory priming, suggesting that stress may promote a form of premature aging. Further unravelling mechanisms underlying priming could lead to improved treatments for buffering against stress- and aging-elicited behavioral pathologies.

1. Background

The concept that stress and aging are interrelated has pervaded the gerontology literature in two main forms (Sapolsky et al., 1986). First, aging activates stress response pathways in a maladaptive, chronic manner, leading to reduced adaptivity to stress in senescence. Consequently, physiological systems in aged animals inadequately respond to stressors (Haigis and Yankner, 2010). For example, aged and young animals typically show comparable thermoregulation at baseline, but aged animals exhibit thermoregulatory impairments when heat- or cold-challenged (Degroot and Kenney, 2007; Tournissac et al., 2017). Second, chronic stress accelerates the aging process. Selye (Selye and Tuchweber, 1976) and later Sapolsky (Sapolsky et al., 1986) postulated that prolonged stress prematurely depletes an organisms energy reserves, accelerating the onset of senescence. Experimental evidence supports this theory. For example, hypocortisolism, which can develop from chronic stress exposure, is associated with shortened telomere length, a hallmark of aging (Wikgren et al., 2012).

The aging process is characterized by a protracted breakdown in basic homeostatic functions over the course of the lifespan. Stress can accelerate this process and compromise multiple homeostatic mechanisms. Of special interest here, aging and stress both have profound effects on neuroimmune regulation. For example, young animals maintain an adaptive balance between pro- and anti-inflammatory mechanisms in the brain: the healthy adult immune system is not activated at baseline but is poised for an effective immune response to infection or damage. In contrast, with aging, this balance shifts towards a potentially pathological sensitized neuroimmune state at baseline (Fonken et al., 2016b). Similarly, exposure to acute and chronic stressors can release inhibitory mechanisms that regulate immune cell activity in the central nervous system (CNS), leading to heightened neuroinflammatory responses to immune challenge (Frank et al., 2018a,b).

This shift towards a baseline sensitized inflammatory phenotype has been termed neuroinflammatory "priming". Priming is defined as a process whereby an antecedent condition or prior exposure to a stimulus potentiates the immune response to a subsequent condition or stimulus. In particular, priming of the neuroinflammatory response is attributed to microglia, the major CNS immune cell. Primed microglia exhibit a much stronger response to an inflammatory stimulus than that observed in stimulus-naïve microglia. Indeed, aging and stressors (both physiological and psychological) cause microglia to develop a primed phenotype, resulting in a protracted neuroinflammatory profile upon immune activation.

Here, we will explore the common mechanisms that mediate stress and aging induced neuroinflammatory priming. First, we will provide a brief background on some basic principles of neuroimmunology. Next,

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we will discuss cell specific contributions to neuroinflammatory priming with a focus on microglia. We will then explore evidence that neuroinflammatory responses become primed in the context of stress and aging with a focus on the common mechanisms that underlie priming in these two conditions. Finally, we will conclude by discussing the translational relevance of neuroinflammatory priming.

2. Key principles of neuroimmunology

Del Rio-Hortega provided a comprehensive characterization of the brain's non-neuronal cellular components about 100 years ago. In particular, del Rio-Hortega was the first to identify and accurately assess the origin and role of microglia; he proposed that these cells were of mesodermal origin and helped clear debris during CNS pathology (Somjen, 1988). A number of diverse functional roles have since been attributed to microglia. We now know that glial cells are present in healthy unstimulated brain and regulate basic homeostatic functions including synaptic development and pruning (Stogsdill and Eroglu, 2017; Wu et al., 2015), neuronal migration (Deverman and Patterson, 2009), and progenitor cell differentiation (Gonzalez-Perez et al., 2010). Microglia form and function are tightly regulated in the CNS to help regain homeostasis following activation. However, prolonged or exaggerated immune activation can cause maladaptive neuroinflammatory changes, or as del Rio-Hortega described, cause microglia to take on the phenotype of "voracious monsters". This introductory section will review the basic constituents of the brain's immune system and describe how immune activity is communicated to the CNS.

2.1. Immune to brain signaling

Neuroimmune activation can be induced by signals originating both inside and outside the CNS. Peripheral immune stimulation dramatically alters neural activity and induction of cytokines in the CNS (Dantzer et al., 2008). Exposure to pathogens or injury activates pattern recognition receptors (PRRs), that function as 'danger' sensors on peripheral innate immune cells, to initiate inflammatory cascades. PRRs bind both pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved molecular motifs from microbial organisms, as well as danger-associated molecular patterns (DAMPs), which are endogenous cellular products that are released following injury or stress. DAMPS include proteins, purine metabolites, DNA, and RNAs that are either typically found inside the cell (so once extracellular they signal damage) or are mediators that are secreted actively to drive inflammation (reviewed in Schaefer, 2014). In response to PRR activation, innate immune cells including macrophages, monocytes, and neutrophils secrete inflammatory mediators such as pro-inflammatory cytokines [(e.g. interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon γ (IFNγ)]. The blood-brain barrier (BBB) generally prevents peripheral pathogens from entering the brain and directly activating CNS immune cells (Banks, 2015); however, inflammatory signals can be communicated from the periphery to the CNS through various pathways, including neural (e.g. vagus) and blood-borne (e.g. circulating PAMPs reach the circumventricular organs) routes (reviewed in (Dantzer et al., 2008).

2.2. Immune response in the CNS

In response to peripheral cytokines, a variety of changes occur in brain including *de novo* production of cytokines, chemokines, reactive oxygen species and secondary messengers that propagate CNS inflammation (Hansen et al., 1998; van Dam et al., 1992). These mediators are produced by resident CNS glia (microglia and astrocytes), endothelial cells, and peripherally-derived immune cells. The detection and propagation of an immune signal throughout the CNS causes a suite of behavioral and physiological modifications, collectively known as the sickness response (Dantzer et al., 2008). Behavioral changes associated with increased inflammatory molecules within the CNS include reduced food and water intake, decreased exploration and social behavior, hyperalgesia (pain hypersensitivity) and global changes in mood and cognition. Overall, the sickness response represents a shift in the motivational state of an organism and is considered highly adaptive and critical for host defense (Hart, 1988). This response, however, can become pathological when immune cell activation in the CNS is exaggerated or persists long-term, such as in neurodegenerative diseases.

In addition to immune activation originating peripherally, CNS-localized injury and disease states can also lead to pathological persistent neuroinflammation. For example, spinal cord injury causes a robust CNS immune response with activation of CNS glia and recruitment of peripheral inflammatory cells to the lesion site (Popovich et al., 1997). Unfortunately, after CNS injury, the persistent inflammatory response can become increasingly pro-inflammatory over time, rather than repairing and resolving the injury, as in the periphery (Gaudet et al., 2017; Kigerl et al., 2009). Indeed, multiple CNS pathologies can be caused or exacerbated by neuroinflammation, including multiple sclerosis, ischemic stroke, Parkinson's disease, and Alzheimer's disease (Dendrou et al., 2015; Perry and Holmes, 2014; Ritzel et al., 2016).

2.3. Dynamic changes in microglia phenotype

Microglia are phagocytic myeloid cells that are distributed throughout the brain parenchyma and are the major source of cytokines and other inflammatory molecules in the CNS (Ransohoff and Perry, 2009). Microglia functions mirror those of tissue-resident macrophages but differ in a few key ways. Other types of myeloid cells in the brain, including meningeal, choroid plexus, and perivascular macrophages (Butovsky et al., 2014; Gautier et al., 2012), typically reside outside the parenchyma and have distinct developmental origins. Microglia are derived from progenitors in the yolk sac that colonize the brain around embryonic day 8 in mice (Alliot et al., 1999). Unlike monocytes, which continuously renew from bone marrow hematopoietic stem cells, microglia persist throughout adulthood by a self-renewal process (Ajami et al., 2007; Askew et al., 2017; Tay et al., 2017). Microglia numbers are tightly maintained in the adult brain by spatial and temporal coupling of proliferation and apoptosis (Askew et al., 2017). Undefined local signals cause microglia to develop region-specific phenotypes (variations in anatomical features, lysosome content, membrane properties, and transcriptomic profile) during the second postnatal week (De Biase et al., 2017). These region-specific phenotypes can cause microglia from different brain regions to demonstrate functional differences. For example, Grabert et al found that microglia isolated from the cerebellum, as compared to the cortex, have enhanced phagocytic activity *ex vivo* (Grabert et al., 2016). Microglia continuously assess their surrounding microenvironment via extension, withdrawal, and reformation of long cellular processes (Nimmerjahn et al., 2005). This active surveying of the microenvironment likely serves a housekeeping function, enabling microglia to effectively monitor and clear accumulated metabolic products and tissue debris.

Various homeostatic perturbations in the CNS can trigger microglia activation. Microglia that detect a homeostatic disturbance or "danger" signal can undergo rapid morphological and functional changes in order to: (1) phagocytose microbes and cellular debris; (2) migrate or proliferate to increase density in specific regions (Tay et al., 2017); and (3) produce and secrete inflammatory molecules (Yirmiya et al., 2015). Phenotypic shifts in microglia activity occur across a broad spectrum in the sense that microglia can synthesize a number of both pro- and anti-inflammatory cytokines and release other molecular mediators (e.g. DAMPs).

Microglial activation in the adult CNS is tightly controlled by endogenous signaling. Notably, unstimulated microglia express much lower levels of cytoplasmic and cell surface molecules than do other types of tissue-resident macrophages, gating their transition to a pro-inflammatory state (Gautier et al., 2012). Exposure to neuronal cell-