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Presidential Address

Feeding the beast: Can microglia in the senescent brain be regulated by diet?

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ABSTRACT

Microglial cells, resident macrophages in the central nervous system (CNS), are relatively quiescent but can respond to signals from the peripheral immune system and induce neuroinflammation. In aging, microglia tend to transition to the M1 pro-inflammatory state and become hypersensitive to messages emerging from immune-to-brain signaling pathways. Thus, whereas in younger individuals where microglia respond to signals from the peripheral immune system and induce a well-controlled neuroinflammatory response that is adaptive (e.g., when well controlled, fever and sickness behavior facilitate recovery from infection), in older individuals with an infection, microglia overreact and produce excessive levels of inflammatory cytokines causing behavioral pathology including cognitive dysfunction. Importantly, recent studies indicate a number of naturally occurring bioactive compounds present in certain foods have anti-inflammatory properties and are capable of mitigating brain microglial cells. These include, e.g., flavonoid and non-flavonoid compounds in fruits and vegetables, and *n*-3 polyunsaturated fatty acids (PUFA) in oily fish. Thus, dietary bioactives have potential to restore the population of microglial cells in the senescent brain to a more quiescent state. The pragmatic concept to constrain microglia through dietary intervention is significant because neuroinflammation and cognitive deficits are co-morbid factors in many chronic inflammatory diseases. Controlling microglial cell reactivity has important consequences for preserving adult neurogenesis, neuronal structure and function, and cognition.

1. Channels of communication between the immune system and brain

Neurobehavioral changes due to influenza infection have been well documented (Hart, 1988). One explanation is that influenza virus enters the brain where it is detected by neurons that control behavior. This is possible since neurons express toll-like receptors (TLR) that are up regulated and rendered more sensitive to TLR ligands upon exposure to the anti-viral cytokine interferon-γ (Tang et al., 2007). However, most influenza strains, including those responsible for pandemics, are non-neurotropic (Kobasa et al., 2007; Schlesinger et al., 1998; Wang et al., 2010), suggesting that neurobehavioral symptoms associated with influenza infection are not due to virus entering the CNS. Instead, peripheral sentinel immune cells such as monocytes and macrophages play a critical role. These cells are also equipped with TLRs that recognize unique molecules associated with groups of pathogens (i.e., pathogen associated molecular patterns; see (Moresco et al., 2011)). Stimulation of TLRs that recognize viruses (TLR3 and TLR7) and bacteria (TLR4) on immune sentinel cells can have profound neurobehavioral effects, indicating the immune system conveys a message to the brain after detecting an infectious agent. This message is cytokine based, as macrophages and monocytes produce inflammatory cytokines [e.g., interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNFα)] that facilitate communication between the periphery and brain. Several cytokine-dependent pathways that enable the peripheral immune system to transcend the blood-brain barrier have been dissected (Banks, 2012; Quan, 2008).

First, there is evidence that inflammatory cytokines present in blood can be actively transported by the endothelial cells of the blood-brain barrier into the brain parenchyma (Banks and Kastin, 1991; Banks et al., 1994a,b, 1995; Gutierrez et al., 1993). A fundamental point, however, is that inflammatory cytokines produced in the periphery need not enter the brain to elicit neurobehavioral changes. This is because inflammatory cytokines in the periphery can induce microglia—macrophage-like cells present in the brain—to produce a similar repertoire of inflammatory cytokines, thus recapitulating the message from the peripheral immune system (Ban et al., 1992; Laye et al., 1994). This often involves peripheral inflammatory cytokines acting on peripheral tissues to

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release chemical mediators of inflammation such as the prostaglandins (Saper et al., 2012). Hence, in a second pathway inflammatory cytokines in the periphery bind receptors on blood-brain barrier endothelial cells (Ching et al., 2007; Li et al., 2011) and either directly or indirectly with prostaglandin intermediates induce perivascular microglia or macrophages to express cytokines that are released into the brain parenchyma (van Dam et al., 1992, 1995). Furthermore, in a third pathway inflammatory cytokines in the periphery convey a message to the brain via sensory nerves. After immune challenge, dendritic cells and macrophages that are closely associated with the abdominal vagus have been shown to express IL-1β protein (Goehler et al., 1999); IL-1 binding sites have been identified in several regions of the vagus as well (Goehler et al., 1997). When activated by immune stimuli, the vagus can activate specific neural pathways that are involved in perception of pain (Watkins et al., 1994), fever (Romanovsky et al., 1997), food intake (Bret-Dibat et al., 1995), and sickness behavior (Bluthe et al., 1996). However, activation of the vagus by peripheral immune stimuli also leads to the expression of inflammatory cytokines in the brain (Laye et al., 1995), presumably by microglia. Vagal afferents project to the nucleus of the solitary tract which in turn projects to other CNS locations including the locus coeruleus, the primary site of norepinephrine production (Berridge and Waterhouse, 2003). This is noteworthy because microglia express adrenergic receptors. Resting microglia primarily express β_2 receptors but switch to α_{2A} receptors under pro-inflammatory conditions (Gyoneva and Traynelis, 2013). Norepinephrine was shown to enhance motility of resting and activated microglia via the β_2 and α_{2A} receptors, respectively (Gyoneva and Traynelis, 2013). Furthermore, intracerebroventricular injection of isoproterenol, a β_1 and β_2 receptor agonist, enhanced the sensitivity of microglia to an inflammatory stimulus (Johnson et al., 2013). Finally, a fourth pathway provides a slower immune-to-brain signaling mechanism based on volume transmission (Dantzer et al., 2000; Konsman et al., 1999). In this method of immune-to-brain communication, production of IL-1β by the brain first occurs in the choroid plexus and circumventricular organs—brain areas devoid of an intact blood-brain barrier. The cytokines then slowly diffuse throughout the brain by volume transmission, along the way activating microglia, neurons and neural pathways that induce sickness behavior and inhibit cognition. Fig. 1 summarizes the channels of communication, lists several neurobehavioral effects of infection, and highlights the neurobehavioral effects with a picture of Michael Ancher's 1882 oil painting entitled "The Sick Girl".

2. What are microglia, what do they do, and what goes wrong during aging?

An important point is that the aforementioned communication pathways share a common need to activate microglial cells and induce neuroinflammation. Celsus' original definition of inflammation was based on four cardinal signs: dolor (pain), calor (heat), rubor (redness), and tumor (swelling); function laesa (loss of function) was added later by Virchow. While neuroinflammation can resemble its peripheral counterpart in circumstances such as viral and bacterial meningitis, head trauma, or autoimmune diseases of the CNS, the term neuroinflammation is increasingly used to identify a fundamentally different event that is exclusively driven by microglial cells and shows few if any of the cardinal signs originally described by Celsus (Aguzzi et al., 2013).

Microglia account for 12–15% of the cells in the brain. They originate from macrophages produced by primitive hematopoiesis in the yolk sac and migrate to the neural tube, where they give rise to microglia (Ginhoux et al., 2010). Bone marrow-derived monocytes do not contribute to the mature microglia pool in the healthy brain, suggesting microglia numbers are sustained by local progenitors. Microglia serve at least two vital functions during development. First, microglia were recently proven to be "gate keepers" regulating the number of neural precursor cells in the developing cerebral cortex. In an elegant sequence of experiments, Cunningham et al. (2013) demonstrated that microglia selectively colonize the cortical proliferative zones in the developing neocortex, have an activated morphology and express markers indicative of activation, and phagocytize neural precursor cells in the late stages of cortical neurogenesis. Maternal immune activation during pregnancy further activated fetal microglia and reduced the number of neural precursor cells; conversely, eliminating or

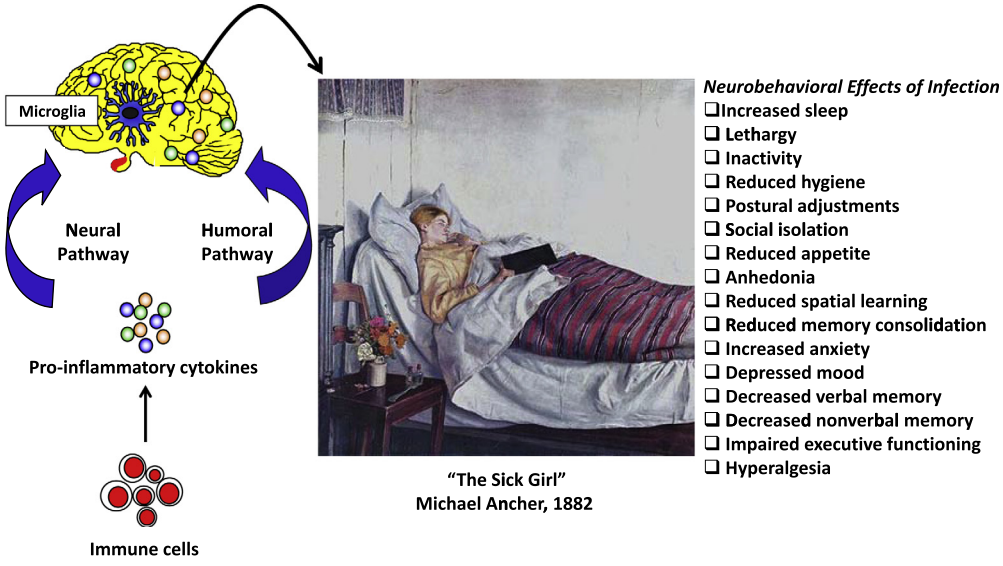

Fig. 1. The peripheral immune system conveys information to the brain via humoral and neural pathways. Brain microglia respond to signals from the peripheral immune system and produce pro-inflammatory cytokines that induce the neurobehavioral changes associated with infection. Some of the neurobehavioral effects are evident in Michael Ancher's 1882 oil painting entitled "The Sick Girl" (This work is in the United States public domain).