CHAPTER

34

Neuroinflammation

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OUTLINE

NEUROINFLAMMATION: INTRODUCTION

While the blood–brain barrier (BBB) generally protects the central nervous system (CNS) from peripheral immune and inflammatory responses, the CNS is also able to activate the protective innate immune system in response to several forms of injury, including trauma, infection, stroke and neurotoxins. This type of *acute* inflammatory response is short-lived and generally beneficial in neutralizing potential threats to the CNS by minimizing cellular damage (Skaper 2007). However, a long-standing *chronic* neuroinflammatory response can be detrimental and lead to neuronal damage and neurodegeneration via sustained accumulation of neurotoxic pro-inflammatory mediators.

The CNS's innate immune response involves intricate signaling circuitry and cellular networks. What was once considered an immune-privileged site is now recognized as having the capacity to synthesize and release a variety of reactive molecules and pro-inflammatory mediators, as well as an ability to respond to injury with anti-inflammatory, pro-homeostatic mechanisms (Wyss-Corray & Mucke 2002; Biron, 2010). Understanding CNS immunity requires attention to the temporal relationship between the inflammatory response and injury. Acute inflammation is defined as the immediate response that occurs at the initiation of injury. When the BBB is compromised, peripheral blood components such as lymphocytes suddenly have access to the CNS (Taupin, 2008). Alternatively, an injury that leaves the BBB intact results in activation of the processes described later in this chapter.

When acute inflammation does not produce resolution and repair and then cease within a relatively short time period, inflammation becomes chronic and often pathological (Streit et al., 2004). The once protective, reparative inflammatory response enters a destructive cycle that perpetuates the damage instigated by the original trigger. The term *neuroinflammation* generally refers to chronic inflammation of the CNS.

The role of microglia in neuroinflammation

The primary cells involved in neuroinflammation are the microglia (Fig. 34-1), which actively survey the brain microenvironment and, upon activation, serve as the resident macrophages in the CNS (del Rio Hortega, 1932). Microglia are derived from the bone marrow, take up residence in the brain during development, and ultimately comprise approximately 12% of the cells of the CNS. Microglia function as a major immune mediator in the CNS and perform the functions necessary for recruitment of the immune system. In the mature CNS, microglia are apparently dormant (resting microglia) but are actively monitoring the environment, contributing to the maintenance of neurovascular integrity to prevent access of potentially damaging immune system elements, and mitigating inflammation.

When presented with a noxious stimulus, resting microglia become activated and respond by recruiting the immune

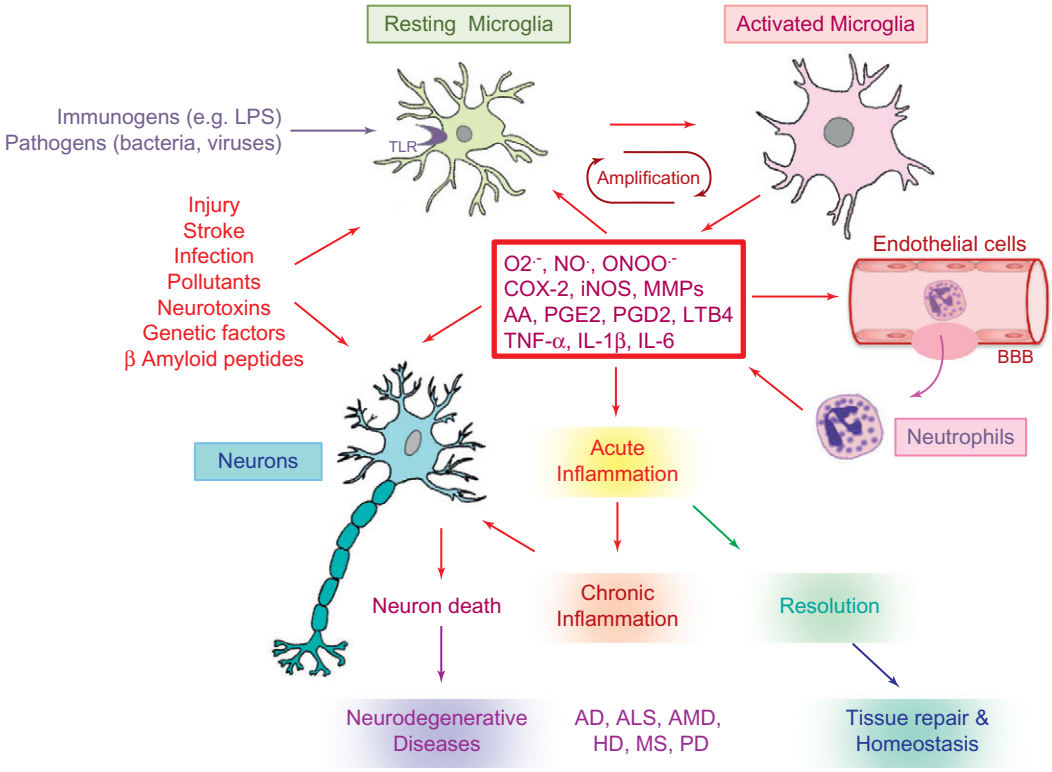

FIGURE 34-1 **Microglia activation in neuroinflammation and neurodegeneration.** Resting microglia are activated upon exposure to a variety of CNS stimuli, including traumatic injury, stroke, infection, air pollutants such as ozone and airborne particulate matter, various neurotoxin agents, dysregulated cellular functions of genetic origin or the accumulation of β-amyloid peptides. Despite the protective nature of the blood–brain barrier (BBB), any BBB disruption can expose microglia to a variety of circulating pro-inflammatory agents that can lead to activation upon recognition by microglia surface receptors. These include pro-inflammatory cytokines (e.g., IL-1, IL-6, TNFα), nitric oxide (NO) and other reactive oxygen species (ROS), as well as immunogenic molecules (e.g., LPS, bacterial DNA) that activate microglial toll-like receptors (TLRs). Upon activation, microglia trigger the release of pro-inflammatory mediators, including: reactive oxygen species (ROS) (e.g., superoxide (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide ($NO^·$) and peroxynitrite ($ONOO^-$), as well as cytokines and chemokines (e.g., IL-1β, IL-6, TNFα). Activation of the lipid mediator cascades triggers the release of arachidonic acid (AA), which is readily oxygenated with cyclooxygenases (COX-1, COX-2) and lipoxygenases (5-LO, 15-LO) to form a series of eicosanoids (e.g., prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) or lipoxins (LX)). Similarly, release of docosahexaenoic acid (DHA) and subsequent enzymatic oxygenation leads to resolvins (e.g., RvD1) and neuroprotectins (e.g., NPD1). As a result of the release of pro-inflammatory mediators, this process is rapidly amplified via the further activation of microglia, resulting in an acute inflammatory response that can be beneficial to the CNS, provided that is short lived. The normal progression of acute inflammation towards resolution, tissue repair, phagocytic clearance, and homeostasis is presumably mediated by anti-inflammatory cytokines (e.g., IL-10), and the release of anti-inflammatory and pro-resolving lipid mediators, such as lipoxins, resolvins and neuroprotectins. Prolonged and unresolved inflammatory response leads to destructive chronic inflammation (neuroinflammation) that results in neuronal death and ultimately to the onset of neurodegenerative diseases, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), age-related macular degeneration (AMD), Huntington's disease (HD), multiple sclerosis (MS) and Parkinson's disease (PD).

system and initiating tissue repair. Activation of microglia (Block et al., 2007) takes place upon exposure to a variety of CNS stimuli, including trauma to brain or spinal cord, ischemic or hypoxic infarction, infection, air pollutants (Block & Calderón-Garcidueñas, 2009) such as ozone and airborne particulate matter, various neurotoxic agents, dysregulated cellular functions of genetic origin or the accumulation of β-amyloid peptides. Despite the protective nature of the BBB, any BBB disruption can expose microglia to a variety of circulating pro-inflammatory agents as well as immunogenic molecules (e.g., lipopolysaccharide (LPS), bacterial DNA) that also activate microglia upon their recognition by microglial surface toll-like receptors (TLR).

Upon activation, microglia trigger the release of pro-inflammatory mediators, including reactive oxygen species (ROS) (e.g., superoxide (O_2^-), nitric oxide (NO), and peroxynitrite ($ONOO^-$)) and pro-inflammatory enzymes (e.g., COX-2, iNOS), as well as a number of cytokines and chemokines (e.g., IL-1β, IL-6, TNF-α and others). Activation of the lipid mediator cascades triggers the release of arachidonic acid (AA). Arachidonic acid (AA) is readily oxygenated by catalytic actions of cyclooxygenases (COX-1, COX-2) and lipoxygenases (5-LO, 15-LO) to form a series of pro-inflammatory eicosanoids (e.g., prostaglandins (PG), leukotrienes (LT), and others). Activation of matrix metalloproteinases (MMPs) leads to increased BBB permeability, which permits local infiltration of neutrophils and other leukocytes, which release additional pro-inflammatory mediators that further activate microglia and exacerbate the inflammatory response. These are all steps in the process of *acute inflammation*.

Under normal physiological conditions, the acute inflammatory response is a relatively short-lived process effective in eliminating many potential CNS damaging agents. Once the trigger has been eliminated, the process is followed by resolution of the inflammation and a return to homeostasis. However, the dysregulation or overactivation of microglia and the resulting prolonged and unresolved *chronic inflammation* have neurotoxic consequences that can lead to decomposition and death of neurons and glia. The accumulation of activated microglia, known as *microgliosis* (Block et al., 2007), results from either direct overactivation due to neurotoxic stimuli or as a reaction to neuronal damage. Ultimately, neuroinflammation becomes a secondary pathogenic process accompanying neurodegenerative CNS diseases initiated by various genetic and/or environmental molecular pathogenic stimuli (Frank-Cannon et al., 2009). These diseases are discussed in Part VI.

The astrocyte is another resident cell of the CNS that plays an integral role in maintaining homeostasis. Of all the glial cell types, astrocytes are the most abundant (Araque & Naverrete, 2010), and these cells modulate the neuronal networks by modifying the synaptic environment. Similar to microglia, astrocytes have processes that are highly dynamic and that extend, move and retract (Carson et al., 2006). They also express ion channels and neurotransmitter transporters. Moreover, although they do not communicate electrically, evidence suggests that astrocytes play a part in calcium signaling. Thus, astrocytes have the ability to regulate how, when and what neurons are able to communicate with each other. In summary, targeting the neuroprotective abilities of the supportive cells in the CNS provides a window of opportunity for the treatment of neurodegenerative diseases.

THE HIGHLY REGULATED ACTIVATION OF MICROGLIA AND PHAGOCYTOSIS

Microglial activation

There are two phases of microglial activation. The first phase involves immunophenotypical, morphological and functional changes. Immunophenotypical events include the expression of molecules found exclusively on cells of the immune system, namely, major histocompatibility complexes (MHC). MHC antigen expression allows microglia to function as antigen-presenting cells. Morphological changes involve transformation of the ramified microglia to a more ameboid shape. Functional changes include release of cytokines and other cytotoxic mediators such as ROS. In addition, there is increased proliferation and recruitment of microglia to the site of tissue injury. In the second phase of microglial activation, these cells become phagocytic.

Microglial phagocytosis

The phagocytic role of microglia is actively displayed during early embryonic brain development, in which the microglia ingest cellular debris of excess neurons that have undergone programmed cell death. Furthermore, microglia assist in clearing synapses that have been tagged for elimination. Microglial phagocytosis is also of importance in regeneration and remodeling of neuronal connections after injury. Within hours after injury in the CNS, microglia are recruited to the injury site and participate in removal of damaged dendrites. Phagocytosis of cellular debris and of apoptotic cellular remnants by microglia is essential to sustaining CNS homeostasis (see Apoptosis in Ch. 37).

Receptors in microglia

Toll-like receptors are pattern recognition receptors, the ligands of which are the pathogen-associated molecular pattern (PAMP) molecules that are common to a number of pathogens, but different from host cells. TLRs are present on the cell surface of microglia and are integral to microglial response to certain stimuli, especially microbes. TLRs1–13 have been identified in humans; however, only TLRs1–9 are present on microglia. TLR2 and TLR3 are associated with microglial response to viruses. Upon activation, TLR2, TLR4 and TLR9 result in increased NO production by microglia. TLR4 is the receptor through which lipopolysaccharide carries out its effect. However, TLR4 can also have neuroprotective effects, thus increasing repair and improving myelination and protection of brain tissue. TLR9 recognizes bacterial DNA, and binding of this receptor results in increased production of NO and tumor necrosis factor α (TNFα) by microglia.

Scavenger receptors recognize oxidized low-density lipoproteins. In microglia, scavenger receptor types A and B clear cellular debris and function in the adhesion of microglia to amyloid-β proteins (Khoury et al., 1996; Khoury et al., 1998). Other receptors are also involved in the function of microglia, including those that recognize phosphatidylserine, those that assist in the clearance of apoptotic cellular

debris by the microglia, and those that trigger production of anti-inflammatory cytokines. In addition to TLRs and scavenger receptors, Fc-receptors and complement receptors are also responsible for the pro-inflammatory processes of activated microglia. Trigger receptor expressed on myeloid cell-2 (TREM-2) is another type of receptor expressed by microglia. TREM-2 receptors bypass inflammatory pathways to clear cellular debris; thus patients lacking TREM-2 receptors are predisposed to developing neurodegeneration due to inflammation.

Microglia in neurodegenerative diseases

Microglia are involved in multiple sclerosis, Alzheimer's disease, Parkinson's disease, HIV dementia, retinal degenerative diseases and many other conditions. In multiple sclerosis, phagocytic microglia are located in the lesion sites. In animal models, phagocytic microglia have been identified with lysosomes containing myelin degradation products. The overactivation and recruitment of microglia in Alzheimer's disease is due to accumulation of amyloid-β proteins, which further activate microglia through neuronal damage. Activated microglia migrate to the site of plaque formation and penetrate the plaques, which leads to production of pro-inflammatory, cytotoxic molecules such as NO and TNFα. The dying dopaminergic neurons in Parkinson's disease result in overactivation of microglia through their release of matrix metalloproteinase-2, α-synuclein and neuromelanin—signals that subsequently trigger pro-inflammatory events in the activated microglia. In HIV dementia, microglia function as storage cells for the virus in the brain. The interaction of the HIV viral proteins with microglia results in their activation. Chronic activation of microglia in the retina leads to overactivation and results in retinal cell damage as an early event in retinal degenerative diseases.

MICROGLIAL DYSFUNCTION DURING AGING

Microglia in the brain contribute to maintaining homeostasis, and alterations of microglial function and morphology that accompany aging reflect neurodegeneration. This dysregulation seems to be a consequence of the accumulation of insults to which microglia have been exposed. Two parallel processes are involved in the dysregulation of microglial activity. First, there is decreased mitotic ability of microglia with aging, which limits their self-renewing ability (Streit et al., 2004; Streit, 2006). Second, aged microglia display enhanced inflammatory responsiveness, namely, enhanced ability to act as antigen-presenting cells and to increase production of inflammatory cytokines with a shift to favor pro-inflammatory molecules (Henry et al., 2009). There are increases in interleukin (IL)-1β, TNFα, and IL-6, accompanied by a decrease in production of the anti-inflammatory cytokine IL-10 (Streit et al., 2004; Ye & Johnson, 1999; Godbout & Johnson, 2004). These changes are accompanied by altered morphology, which differentiates aged microglia from normal adult microglia.

As mentioned above, aged microglia also have higher surface expression of MHC II (Henry et al., 2009), as well as scavenger receptors, TLRs and astrocytic markers, all of which allows them to act more like antigen-presenting cells and which enhances their ability to function as immune cells (Leteimbre et al., 2007; Wong et al., 2005). In aged microglial cultures, there is an inability to respond as robustly to TGF-β1, a cytokine that works to limit proliferation and regulate microglial activation (Rozovsky et al., 1998). Furthermore, it takes longer for aged mice to recover from neurotoxic stimuli. Recovery begins at 4 hours in adult mice and is complete by 24 hours. In aged mice, however, recovery begins at 8 hours and is still not complete by 24 hours (Johnson & Godbout, 2006; Godbout et al., 2005; Godbout et al., 2008). Microglia that are primed for long periods of time activate more quickly and demonstrate a more robust activation, which suggests that as microglia age they are more likely to become overactive (Godbout et al., 2005; Dilger & Johnson, 2008; Sparkman & Johnson, 2008); however, they are not as efficient at dealing with the insult.

Morphologically, microglia become dystrophic with age, characterized by a decrease in ramifications, and the processes that are present become atrophic and beaded (Streit et al., 2004; Streit, 2006; Ye & Johnson, 1999). There is also an alteration in the cytoplasm with increased lectin staining, especially around the nucleus. Aged microglia also display cytoplasmic fragmentation and nuclear condensation, in addition to increases in lipofuscin granules (Streit et al., 2004). Overall, resting microglia from aged animals demonstrate a morphology that is consistent with activated microglia (Conde & Streit, 2006).

PROTEIN AGGREGATION

Protein aggregation is a pathological feature of a number of neurodegenerative diseases. The aggregation of mutated or improperly folded proteins underlies the pathogenesis of Alzheimer's disease, Parkinson's disease, Huntington's disease, prion diseases and amyotrophic lateral sclerosis, to name a few of many that are discussed in Part VI (Rodolfo et al., 2010). The protein accumulation results in a number of molecular effects that lead to neuronal cell death. Intracellular accumulations of these proteins can affect the neurons directly, wreaking havoc on the internal cellular machinery, including the mitochondria and the endoplasmic reticulum, and can result in cell death. Extracellular protein accumulations also cause neuronal degeneration, which may be mediated, at least partially, through microglia activation in the surrounding tissue.

There are varying types of misfolded protein aggregates present in pathological brain tissue depending on the disease type and, even more specifically, on the mutation responsible for the disease. Huntington's disease, which is characterized by polyglutamate repeats at the N-terminus of the huntingtin protein, results in intracellular aggregates of the huntingtin protein (Ross & Poirier, 2004). The pathology of Alzheimer's disease involves two types of protein aggregates: intracellular occlusions, termed neurofibrillary tangles, composed of hyperphosphorylated tau protein or neuritic plaques which are extracellular aggregates of Aβ peptide, a product of amyloid

precursor protein (Ross & Poirier, 2004). Parkinson's disease involves the intracytoplasmic presence of Lewy bodies, aggregates of the α-synuclein protein. In amyoptrophic lateral sclerosis, superoxide dismutase 1 (SOD1) accumulation occurs in the cytoplasm of the affected neurons. Discussions of the neurodegenerations and dysregulations of protein folding are found in Part VI.

The effects of protein aggregation on microglial function

Amyloid plaques, a pathological feature of Alzheimer's disease, contain accumulations of amyloid-β protein together with glial and neuritic debris. It has been shown that microglia associate with these plaques (Haga et al., 1989). The amyloid protein, either in the protomeric or oligomeric stages (see in Ch. 46), may be the primary factor predisposing microglia to activation and causing an abnormally robust neuroinflammatory response (Garden & Moller, 2006). The gliosis and neuroinflammation resulting from accumulation of the amyloid-β protein is itself neurotoxic. This concept is further supported by other observations. It has been shown that amyloid-β proteins result in degeneration and metabolic dysfunction of microglia in culture (Korotzer et al., 1993). The fact that microglia are a significant component of the plaques suggests that microglia participate in mediating the toxic effects of this protein accumulation (Irizarry et al., 1997). The areas of amyloid plaques in the brains of Alzheimer's patients are surrounded by activated microglia, which suggests that the cytokines and cytotoxic molecules released from microglia may play a role in the disease (McRae et al., 1997). There are also increases in the number of microglia in the CNS of Alzheimer's patients, with clusters of microglia present in grey matter. Furthermore, microglial cell processes are found surrounding the core of the plaques. Stimulation of microglia with amyloid-β results in the production of TNFα through nuclear factor kappa B (NF-κB) activity. The increase of TNFα results in the production of nitric oxide by microglia, leading to neuronal cell death (Combs et al., 2001). IL-6 is detected even before the formation of amyloid plaques and remains present upon the formation of these plaques (Bauer et al., 1991; Huell et al., 1995).

CYTOKINES/CHEMOKINES

Cytokines are responsible for microglia activation

Cytokines comprise a diverse group of proteins secreted from both glial and immune cells responsible for intercellular signaling. In the CNS, cytokines are responsible for the activation of microglia; in addition, they are produced by the activated microglia. Interferon-γ, IL-1 and IL-6 are the cytokines that result in microglia activation as well as the increased production of immunomolecules and cytotoxic mediators from microglia (Gehrmann et al., 1995). IL-3, granulocyte-macrophage colony stimulating factor (GM-CSF), and macrophage colony stimulating factor (M-CSF) are also involved in the proliferation and activation of microglia in the CNS; they are produced by astrocytes as well as by the microglia themselves. Cytokines with the ability to effect the movement of target cells are called chemokines. The chemokine CX3CL1 is involved in the interaction between neurons and microglia (Biber et al., 2007).

Cytokines are produced by activated microglia

Activated microglia release the cytokines IL-1β, TNFα, and IL-6. Of these, IL-1 and TNFα have been associated with Alzheimer's disease, as they have been found to be produced by activated microglia in regions surrounding amyloid plaques. Upon release from activated microglia, IL-1 results in the proliferation of astrocytes and neovascularization in damaged brain tissue. TNFα is cytotoxic and results in the demyelination of oligodendrocytes (Gehrmann et al., 1995).

IL-6 overexpression in transgenic mice causes an increase in neurological disease that is correlated with the level of this cytokine (Campbell et al., 1993). The presence of IL-6 in neuronal culture also predisposes the neurons to glutamate toxicity mediated through N-methyl-D-aspartate (NDMA) receptors (Qiu et al., 1998). Pretreatment of microglia with IL-4 results in neurotrophic action upon lipopolysaccharide treatment. These neurotrophic effects include the decreased production of TNFα and the upregulation of insulin-like growth factor (IGF)-1.

Anti-inflammatory interleukin-10 and TGF-β1

Interleukin-10 and TGF-β1 are cytokines that downregulate microglial activation and therefore possess anti-inflammatory activity. TGF-β1 is produced by T-cells. Pretreatment with IL-10 decreases the production of IL-6 in microglia treated with LPS by decreasing the nuclear translocation of the p50 and p65 subunits of NF-κB, thereby decreasing the production of IL-6 mRNA and the protein (Heyen et al., 2000). In addition to its ability to decrease IL-6 production, IL-10 also negatively affects the production of TNFα. Furthermore, IL-10 decreases the expression of the cytokine receptors IL-2 and IL-6 on the microglial surface (Sawada et al., 2001). Because of the anti-inflammatory and regulatory actions of IL-10 and TGF-β1, these cytokines offer potential for therapeutic intervention.

LIPID MEDIATOR PATHWAYS IN NEUROINFLAMMATION

Initiation of inflammation: prostaglandin and leukotriene pathways

Several oxygenation pathways of arachidonic acid (AA) and docosahexaenoic acid (DHA) have emerged as key players in CNS inflammation and resolution (Fig. 34-2). Regardless of the nature of the pro-inflammatory stimulus, among the earlier events in the inflammatory response is the release of AA and the activation of oxygenating enzymes (COX-1, COX-2, 5-LO, 12/15-LO, P-450) that rapidly convert AA to a variety of eicosanoids.

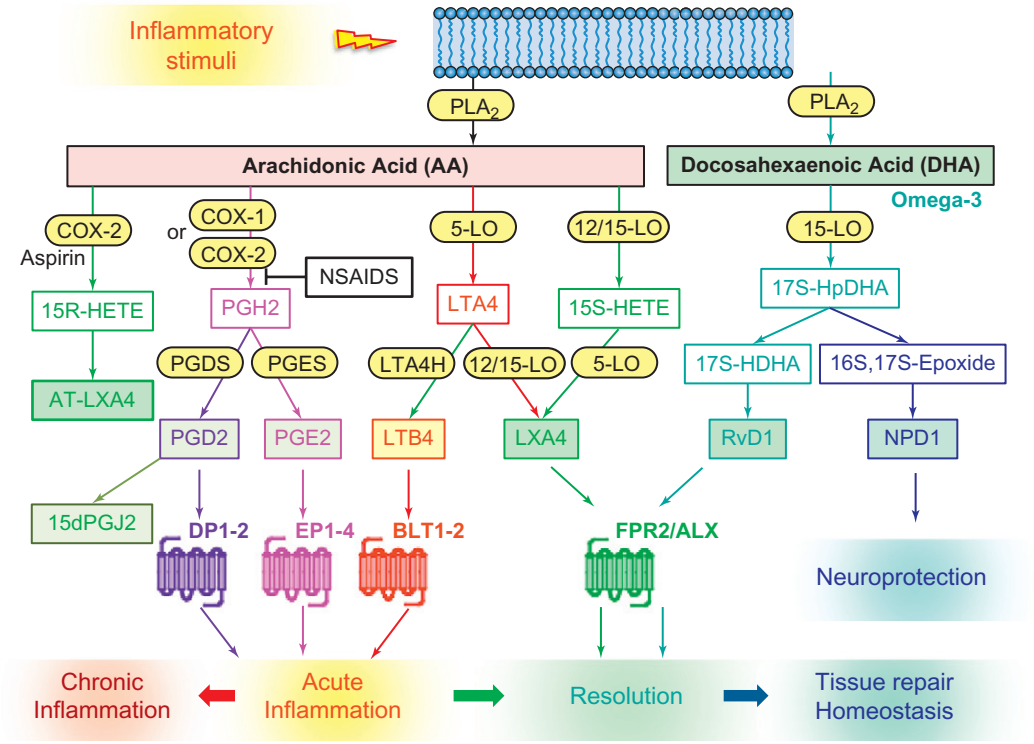

FIGURE 34-2 Oxygenation pathways of arachidonic acid (AA) and docosahexaenoic acid (DHA) in CNS inflammation and resolution. In response to various inflammatory stimuli (see Fig. 34-1) activated microglia and infiltrating neutrophils release arachidonic acid (AA), which is rapidly converted to prostaglandins (PGE2, PGD2) catalyzed by COX-1 or COX-2, or to leukotrienes (LTA4, LTB4, LTC4) that act on their respective receptors (DP1-2, EP1-4, BLT1-2.). As a result of the release of pro-inflammatory mediators, this process is rapidly amplified, resulting in an acute inflammatory response that can be beneficial to the CNS, provided that it is short lived. The progression of acute inflammation towards resolution, tissue repair, phagocytic clearance and homeostasis is mediated by anti-inflammatory cytokines (e.g., IL-10), and the release of anti-inflammatory and pro-resolving lipid mediators, such as lipoxins, resolvins and neuroprotectins. Lipoxin A4 (LXA4) is formed either from LTA4 via 12/15-LO or from AA via the sequential action of 12/15-LO and 5-LO. Similarly, release of docosahexaenoic acid (DHA) and subsequent enzymatic oxygenation leads to resolvins (e.g., RvD1) and neuroprotectins (e.g., NPD1). Binding of LXA4 or RvD1 to the FPR2/ALX receptor leads to suppression of inflammation and initiation of resolution, while NPD1 promotes neuroprotection via several mechanisms. The COX-2 pathway also forms pro-resolving mediators from AA, including 15dPGJ2, a metabolite of PGD2. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS) act on COX-1/COX-2 and block the conversion of AA to PGH2, preventing the biosynthesis of PGs and LTs. However, in the presence of aspirin, COX-2 is able to convert AA to 15R-HETE, which is transformed to the 15-epimeric or aspirin-triggered lipoxin A4 (AT-LXA4), having similar pro-resolving properties with LXA4. In the absence of these pro-resolution pathways, the inflammatory response persists over extended time (chronic inflammation) and leads to neuron damage and neurodegenerative diseases (see Fig. 34-1).

In response to various inflammatory stimuli (see Fig. 34-1), activated microglia and infiltrating neutrophils release AA, which is rapidly converted to *prostaglandins* (PGE2, PGD2) catalyzed by cyclooxygenases (COX-1, COX-2). Oxygenation of AA mediated by 5-LO generates *leukotrienes* (LTB4, LTC4), which are potent pro-inflammatory and chemotactic agents, helping to recruit neutrophils to the site of inflammation. The release of PGs and LTs followed by activation of their respective receptors (see Fig. 34-2; DP1-2, EP1-4, BLT1-2) is associated with the initial events in inflammation (e.g., pain, fever, edema, vasodilation). Typically, the inducible isoform COX-2 has been associated with the acute inflammatory response because its gene expression is induced by several regulatory elements associated with inflammation (NF-κB, Sp1, TATACREB) while COX-1 is the constitutive isoform. However, in the brain, both COX-1 and COX-2 are constitutively expressed, but at different sites (Choi et al., 2009; Aïd & Bosetti, 2011). While both isoforms occur in vascular cells, COX-1 is mainly expressed in the microglia, while COX-2 exists in neuronal dendrites and excitatory terminals. Given its presence in microglia, COX-1 has recently emerged as a dominant enzyme in neuroinflammation and neurodegeneration, while COX-2 plays a different role in the CNS including involvement in long-term potentiation, and in the direct inflammatory challenge of neurons (Choi et al., 2009; Aïd & Bosetti, 2011).

As mentioned in the introduction, as a result of the release of pro-inflammatory lipid mediators, this process is rapidly amplified, producing an environment of acute inflammation. If it is short-lived and able to remove the pro-inflammatory trigger, this process is beneficial to the CNS. However, if it persists and remains unresolved, this initial response can be followed by neutrophil infiltration and further amplification of inflammation (see Fig. 34-1), leading to a variety of CNS diseases. For example, the potent neutrophil chemoattractant LTB4 has been linked to the pathogenesis of traumatic spinal cord injury (Saiwai et al., 2010).

Resolution of inflammation: lipoxin, resolvin, and neuroprotectin pathways

The progression of acute inflammation towards resolution, tissue repair, phagocytic clearance and homeostasis is mediated by anti-inflammatory cytokines (e.g., IL-10), and by the release of anti-inflammatory and pro-resolving lipid mediators (Ariel & Serhan, 2007; Serhan et al., 2008a; Serhan et al., 2008b; Bannenberg & Serhan, 2010; Serhan, 2010) such as *lipoxins*, *resolvins* and *neuroprotectins* (Fig. 34-2). Lipoxin A4 (LXA4) is generated from AA either through LTA4 via 12/15-LO, or from the sequential oxygenation of AA via the action of 12/15-LO and 5-LO. LXA4 is a very potent lipid mediator that counters the effects of PGs and LTs, and upon binding to its FPR2/ALX receptor it suppresses inflammation, initiates resolution and promotes clearance and tissue repair.

The COX-2 pathway also forms pro-resolving mediators from AA, including 15dPGJ2, a metabolite of PGD2. Aspirin and other nonsteroidal anti-inflammatory drugs act on COX-1/COX-2 and block the conversion of AA to PGH2, preventing the biosynthesis of PGs and LTs, and suppressing inflammation. However, in the presence of aspirin, COX-2 is able to convert AA to 15R-HETE, which is transformed to the 15-epimeric or aspirin-triggered lipoxin A4 (AT-LXA4), having similar pro-resolution properties with LXA4 (Petasis et al., 2005; Serhan, 2005).

Release of docosahexaenoic acid (DHA), a polyunsaturated fatty acid (PUFA) found predominately in CNS tissues, is also triggered during the inflammatory response. As detailed in Chapter 35, enzymatic oxygenation of DHA initiated by lipoxygenases (e.g., 15-LO) leads to the formation of resolvins (e.g., RvD1) that have potent pro-resolving properties, and neuroprotectins (e.g., NPD1) that promote neuroprotection via several mechanisms (Serhan et al., 2008a; Serhan et al., 2008b; Bazan, 2006; Bazan, 2009). In the absence or dysregulation of these pro-resolution pathways, the inflammatory response remains unresolved and persists over extended time (chronic inflammation), leading to neuronal damage and neurodegenerative diseases (see Figs. 34-1, 34-2).

The discovery of these pro-resolution pathways originating from DHA has provided the first molecular-level support for the multiple beneficial effects of DHA in normal brain function and in its ability to provide protection against neurodegenerative diseases.

ISCHEMIA-REPERFUSION DAMAGE

Ischemia in cerebral tissue results in the generation of oxygen free radicals and triggers inflammatory cascades in the brain, upregulating chemokines and cytokines (see also in Ch. 35). This inflammation can continue to cause damage in the brain even after the initial insult has been resolved, and can lead to an increase in the lesion size (Montaner et al., 2003). The cytokines released during an ischemic episode result in recruitment and activation of microglia to the site of ischemia. Microglial activation results in the production of TNFα, IL-6, and IL-1β, all of which are pro-inflammatory cytokines. Furthermore, activated microglia have phagocytic capabilities. The combination of all of the inflammatory and immune responses that occur during stroke ultimately result in loss of integrity of the blood–brain barrier (Danton & Dietrich, 2003; Simard et al., 2007). This allows for the infiltration of peripheral immune cells to the site of ischemia, further enhancing the inflammatory response.

The initial trigger in ischemic injury is hypoxia, which causes neuronal cell death and microglial activation. Microglial activation in hypoxia may be the result of direct activation or secondary activation caused by the neuronal cell death associated with this condition. Upon activation, microglia respond with pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, and NO, all of which have been shown to be upregulated in ischemic models. In addition, MMPs are present during ischemia and result in the demise of the blood–brain barrier. MMP9 is especially important with respect to neuroinflammation.

THE INTERFACE BETWEEN INFLAMMATION AND THE IMMUNE SYSTEM IN THE CNS

Aβ Immunotherapy

The last decade has seen a surge of *in vivo* studies, in both transgenic animal models and humans, testing the efficacy of amyloid beta (Aβ) immunotherapy. The underlying concept is centered on the hypothesis that soluble, amyloid oligomers and insoluble, extracellular aggregates are at the core of Alzheimer's disease (AD) pathogenicity. Numerous studies have established Aβ's injurious effects on synaptic function and neuronal survival. The hope has been that anti-Aβ antibodies might neutralize or clear amyloid aggregates and plaques before they trigger their neurodegenerative effects (Lemere & Masliah, 2010). Both active and passive forms of immunization have been developed and have demonstrated potential as beneficial therapies for AD. Worldwide, over a dozen clinical trials are aimed at assessing the value of Aβ immunotherapy and the progression of disease. Preliminary results have shown a wide range of outcomes. Studies have seen a reduction in plaques and a halt in volumetric reductions of AD-vulnerable structures, such as the hippocampus. Nevertheless, Aβ immunotherapies have caused a range of side effects in patients, including aseptic meningoencephalitis, microhemorrhages, leukoencephalopathy and vasogenic edema (Boche et al., 2010). Important issues that remain to be understood with regard to anti-Aβ antibody treatment include the age at which treatment should begin, genetic susceptibility to disease (i.e., APOε-4 carriers), and dosing.

The inflammasome

The innate immune system has developed an array of pattern recognition receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) (Martinon et al., 2009; Kawai & Akira, 2010). The interaction among PRRs, PAMPs and DAMPs are the body's first defense against infectious and non-infectious triggers of the inflammatory response

(Lamkanfi et al., 2007; Takeuchi & Akira, 2010). The variety of PRRs ensures the ability to respond to numerous intra- and extracellular pathogens and endogenous signals of danger. The nucleotide-binding domain leucine-rich repeat-containing or NOD-like receptors (NLRs) are cytoplasmic PRRs that have the capacity to recognize both PAMPs and DAMPs (Becker & O'Neill, 2007). NLRs have three defining characteristics: the C-terminal leucine-rich repeats (LRRs), N-terminal caspase recruitment or pyrin domains (CARD or PYD), and the NOD or NACHT domain (Drenth & van der Meer, 2006). The leucine-rich domain binds or senses ligands; the CARD domain allows protein–protein interactions; and NACHT mediates oligomerization via an ATP-dependent mechanism.

The NLR family has three subfamilies: NOD, NLRP and IPAF. Members of the NLR subfamily of proteins are the integral, self-oligomerizing components of the inflammasome. The inflammasome is a cytoplasmic multiprotein complex that regulates the activation of pro-inflammatory caspases (Chakraborty et al., 2010). Caspases are cysteine proteases that play vital roles in the mediation of programmed cell death and inflammatory signaling. Caspase 1 cleaves the inactive, pro-form of IL-1β and IL-18 into their active forms. IL-1β is considered one of the key cytokines mediating the inflammatory response (Kanneganti, 2010; Dixit & Lamkanfi, 2009). It is also a pyrogen that activates lymphocytes, induces cyclooxygenase (COX)-2 activity, and activates the NFκB signaling cascade (Dinarello, 2010). IL-18 is not a pyrogen and participates in the induction of the adaptive immune response. It is critical to the activation of macrophages and triggers the release of interferon-γ (IFN-γ).

Several inflammasomes have been identified in recent years, such as NLRP1, NLRP3 and IPAF. AIM2 is the first inflammasome whose oligomerizing components are not formed by members of the NLR family (Schroder & Tschopp, 2010). Upon activation, inflammasomes are triggered to self-assemble and undergo an elaborate sequence of events to form the high-molecular-weight complex. Each type of inflammasome is activated under different conditions, and a number of theories exist with regard to the mechanism that propagates activation of the inflammasome once triggered. For example, NLRP3 activation can be initiated by an incredibly diverse group of pathogens, including fungi, bacteria and viruses, in addition to endogenous signals emerging from injured cells. Recently it was discovered that the NLRP3 inflammasome is also activated by Aβ, suggesting a role in Alzheimer's disease (Schroder & Tschopp, 2010). Much remains to be unearthed regarding inflammasome structure, function and contribution to the inflammatory response.

MITOCHONDRIA: A CONNECTION BETWEEN INFLAMMATION AND NEURODEGENERATION

The inflammatory response is tightly correlated with the progression of neurodegenerative diseases. Mitochondria are the primary generators of cellular energy and actively participate in important cellular functions such as calcium signaling and modulation of apoptosis. Furthermore, they are particularly unique in that they have their own maternally inherited, double-stranded DNA (mtDNA) (see Mitochondria in Ch. 43) (DiMauro & Schon, 2003). Impairments in mitochondrial structure and function are known to have specific implications in neurodegenerative diseases such as Parkinson's, Huntington's and Alzheimer's diseases (Di Filippo et al., 2010; Mahad et al., 2008).

Adenosine triphosphate (ATP) is the currency of cellular energy generated from oxidative phosphorylation in the electron transport chain of the inner mitochondrial membrane (Ch. 43). The reduction of molecular oxygen in the electron transport chain can result in the release of ROS. Normally, cells are endowed with several mechanisms that offset ROS accretion. However, excessive ROS accumulation induces oxidative stress that sets inflammatory signaling pathways in motion (Patten et al., 2010). When triggered, activated microglia release TNFα and other pro-inflammatory mediators along with ROS and reactive nitrogen species (RNS) (Ferger et al., 2010). Nitrosative stress exerts actions in parallel with ROS and contributes to mitochondrial dysfunction, inflammatory events and neurodegenerative pathology. The release of pro-inflammatory mediators results in morphological and functional changes in mitochondria. Consequently, mitochondria release ROS that further propagate inflammation in an already activated innate immune system (see Chs. 36, 46–49 for information on Parkinson's, Alzheimer's, Huntington's disease, and multiple sclerosis).

The brain is an organ heavily reliant on oxidative metabolism and is particularly susceptible to the generation of reactive, and potentially damaging, oxygen species. For example, mitochondrial complex I (NADH dehydrogenase) impairment yields the idiopathic Parkinson's disease phenotype; similarly, injury of complex II (succinate dehydrogenase) yields the Huntington's disease phenotype. mtDNA mutations that are either inherited or caused by oxidative damage have been shown to contribute to Alzheimer's disease pathology. Indeed, amyloid-β also accumulates in mitochondria and targets complex IV of the electron transport chain. Specific complex I blockers such as MPTP, 6-OHDA and rotenone mimic symptoms of Parkinson's disease, whereas complex II inhibitors like 3-NP mimic Huntington's disease (Nicholls, 2008; Frank-Cannon et al., 2009). Reactive oxygen species are envisioned as both a cause and consequence of mitochondrial dysfunction. Of equal importance are the effects that impaired mitochondria have on calcium homeostasis and apoptotic signaling. Mitochondrial function provides a link between neuroinflammatory changes and neurodegenerative disease.

NEUROPROTECTIVE SIGNALING CIRCUITS

Although our discussion has centered mostly on the damage and injury aspects of inflammatory signaling under physiological conditions, these mechanisms were evolutionarily developed to be protective. Resting glia are constantly surveying the environment, probing for changes in the cellular milieu that may disrupt homeostasis. When a threat presents itself—such as a misfolded protein, an infectious agent or excitotoxic levels of glutamate—microglia are activated and aggressively defend the surrounding environment by releasing pro-inflammatory mediators and phagocytosing debris

MICROGLIAL CELLS ARE MAJOR SENSORS FOR CNS HOMEOSTASIS DISRUPTION: SIGNIFICANCE FOR THE STROKE PENUMBRA AND NEURODEGENERATIVE DISEASES

Nicolas Bazan, Aram Asatryan, Ludmila Belayev

Microglia (about 10–15% of CNS glial cells) are immunocompetent cells, with a small soma and extensive branches (see Ch. 1) that actively monitor the cellular environment with a high degree of sensitivity to disruptions of homeostasis. Microglia responses are complex and include protection/repair as well as contributions to CNS function and to pathology. Microglial signaling is involved in protection, repair, neurotrophic bioactivity, synaptic circuitry plasticity and neurogenesis. In addition, these cells sense alterations in their surroundings and rapidly respond to trauma, stroke, and the onset and progression of neurodegenerative diseases, including Parkinson's, Alzheimer's and amyotrophic lateral sclerosis (Belayev et al., 2011; Lue et al., 2010; Perry et al., 2010). Often, microglia—after becoming amoeboid, macrophage-like cells (often referred to as "resident" macrophages)—remove cellular debris or leukocytes. Another microglial phenotype furthers injury and neuroinflammation, thereby contributing to cell damage (Perry et al., 2010; Prinz & Mildner, 2011). Microglia may display the features of activated macrophage M1 as well as M2 phenotypes.

Activated M1 microglia release cytokines that induce inflammation, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β), as well as reactive oxygen species and nitric oxide (NO). Overexpression of TNF-α or IL-1β exacerbates ischemic damage, whereas their inhibition decreases infarct size. The microglial production of TNF-α receptors TNFR1 and TNFR2 is upregulated after ischemia. However, both *in vitro* and *in vivo* evidence suggests that IL-1β and TNF-α, have neurotrophic functions, in addition to harmful effects (Polazzi & Monti, 2010; Ransohoff & Perry, 2009). The differential TNF-α responses are likely mediated by its receptors, where TNF-R1 is responsible primarily for the neurotoxic effects, and TNF-R2 for the protective responses. NO can combine with superoxide anion-radical (O^{2-}) to form peroxynitrite ($ONOO^{-}$). The resultant reactive nitrogen species (RNS) induces oxidative stress, and lipid peroxidation and produces alterations in proteins and DNA. This is a pathogenic factor for neurodegenerative diseases and especially stroke, based on the abundance of reactive oxygen species (ROS) during and after the infarct.

M2 microglia display enhanced neurotrophin synthesis, release insulin-like growth factor 1 (IGF-1) and transforming growth factor beta 1 (TGFβ1), attenuate pro-inflammatory cytokines, and likely play a role in inflammation resolution. The precise mechanism/s that governs the appearance and proliferation of these different microglial phenotypes are incompletely understood. Microglia and macrophages are major contributors to the development of the stroke penumbra. Radioligands to image microglia activation in experimental models as well for clinical studies have been developed. One of the ligands takes advantage of the increased abundance in TSPO (translocator protein 18-kDa) in injury-activated microglia as well as in arriving macrophages. The TSPO is a hetero-oligomeric complex of the voltage-dependent anion channel and an adenine nucleotide carrier of the permeability transition pore of the outer mitochondrial membrane. Its function in microglia is not clear, but it seems to be involved in steroid synthesis and cholesterol translocation. TSPO used to be referred to as the peripheral benzodiazepine receptor. TSPO expression in brain under resting conditions is low. TSPO ligands are being used for *in vivo* imaging in animals and humans using positron emission tomography and single-photon emission CT as a sensitive marker to detect early neuroinflammation (Ransohoff & Perry, 2009; Thiel & Heiss, 2011). This is very important because of the potential to use these markers to assess the evolution of the penumbra during stroke. Timing the progression of infarct and penumbra evolution is critical to establishing the window for intervention methods (see references listed below).

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(Gonzalez-Scarano & Baltuch, 1999; Rock et al., 2004). Hence, the acute microglial response is protective, whereas chronic microglial activation is neurodegenerative (Schwartz et al., 2006). Of the myriad of functions that microglia perform, the ability to phagocytose and clear cellular debris is of paramount importance in their ability to protect the CNS from injury (Napoli & Neumann, 2010) (Box 34).

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