

Chapter 2

Biochemical Aspects of Neuroinflammation

2.1 Introduction

Neuroinflammation is a complex host defense mechanism that isolates the damaged brain tissue from uninjured area, destroys injured cells, and repairs the extracellular matrix (Minghetti et al. 2005). Neuroinflammation is orchestrated by microglia and astrocytes to re-establish homeostasis in the brain after injury-mediated disequilibrium of normal physiology. Microglial cells dynamically express distinct arrays of functions during the course of neuroinflammation and depending on neurological condition, such as neurotraumatic diseases (stroke, spinal cord injury (SCI), and traumatic head injury (TBI)), neurodegenerative diseases (Alzheimer disease (AD), Parkinson disease (PD), and *amyotrophic lateral sclerosis* (ALS), and neuropsychiatric diseases (depression, Schizophrenia, and bipolar disorders) (Colton 2009; Farooqui and Horrocks 2007; Farooqui 2010). Age is a major risk factor for stroke, AD, and PD. Although, normal aging is accompanied with increase in neuroinflammation in the hippocampus (Lynch 1998; Gemma and Bickford 2007), but the intensity of neuroinflammation is markedly increased in stroke, AD, and PD. There are two types of neuroinflammation (a) acute inflammation and (b) chronic inflammation. Stroke involves acute neuroinflammation and oxidative stress whereas AD and PD are associated with chronic neuroinflammation and oxidative stress (see below) (Farooqui et al. 2007; Farooqui 2010). Recently the role of inflammation in brain health has become a major focal point of studies related with aging and age-related neurological disorders (Farooqui 2010). Activation of inflammatory pathways in the brain has been increasingly emphasized as a major risk factor for the initiation, development, and progression of pathogenesis of stroke, AD, and PD (Farooqui 2010). Epidemiological studies on humans have indicated that long-term use of anti-inflammatory drugs not only protects brain from inflammation, but also delays the onset of cognitive decline (Launer et al. 1998; Arvanitakis et al. 2008). These studies are supported by animal studies, which provide additional support to the hypothesis that inflammation may contribute to the pathogenesis of stroke, AD, and PD (Lim et al. 2000; Heneka and O'Banion 2007). However, clinical studies on the treatment of stroke, AD, and PD with antiinflammatory drugs once the disease is clinically apparent have been largely unsuccessful (Aisen 2008; Meinert et al.

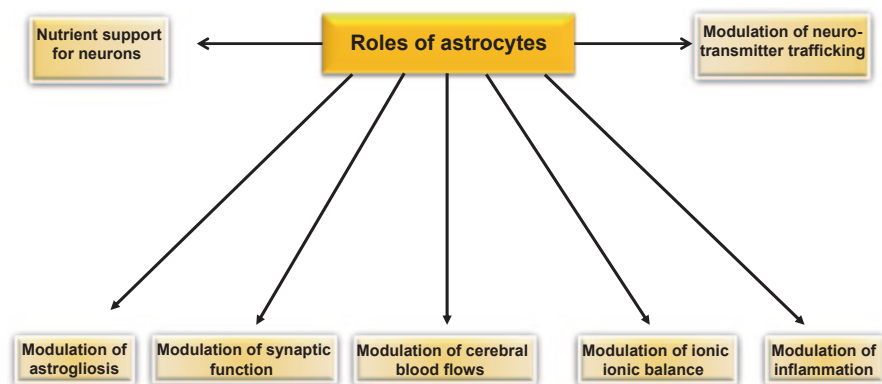


Fig. 2.1 Roles of astrocytes in the brain

2009; Breitner et al. 2009). Based on these observations it is suggested that the timing of anti-inflammatory treatment for neurological disorders is crucial, and that attenuation of inflammation is particularly important prior to clinical manifestation of stroke, AD, and PD.

Astrocytes are complex, highly differentiated cells of the brain. They play several important roles, such as regulating the external environment of neurons, participating in the physical structuring of the brain, providing metabolites to neurons, and maintaining the blood brain barrier (BBB) integrity. The cell body and the major processes of astrocytes are enriched with glial fibrillary acidic protein (GFAP) that forms intermediate filaments, whose recognition by Golgi staining is the reason for the classically star-shaped appearance of astrocytes (Bushong et al. 2002). Astrocytes outnumber neurons by over fivefold and play important role in the brain. It is well known that microvascular beds consist of endothelial cells, basal lamina, and astrocyte (Zoppo and Hallenbeck 2000). Astrocytes enwrap the vessel wall with a large number of end feet and support the formation of BBB, a neurovascular unit composed of endothelial cells, pericytes, astrocytes, and neurons (Hawkins and Davis 2005). An anatomical particularity of the BBB is that brain microvessel endothelial cells are connected by strong tight junctions that direct plasma substances into transcellular routes and reduce the paracellular diffusion of solutes and macromolecules (Benarroch 2011). However, the exact role of astrocytes in the BBB formation is poorly understood (Zoppo and Hallenbeck 2000). The tight organization of astrocytes around the vasculature is thought to be due to the necessity of glucose to reach neurons. In fact, it is hypothesized that astrocytes take up glucose since they express a large number of glucose transporters, convert it to lactate, and then deliver lactate to neurons (Takano et al. 2006). Astrocytes not only maintain BBB, regulate cerebral blood flow, and modulate synaptic function and plasticity, but also maintain the extracellular balance of ions, modulate neurotransmitter (glutamate) trafficking and recycling, and provide nutrient support for neurons (Fig. 2.1) (Nedergaard et al. 2003; Seifert et al. 2006). Another transmitter released

from astrocytes is ATP, which modulates the functions of gap junction channels. It is proposed that the release of ATP propagates a signal wave via activation of purinoceptors (Fam et al. 2000). The purinoceptor activation can stimulate trophic signaling pathways, through the activation of protein kinase (Neary et al. 1999) or changes in gene expression (Priller et al. 1998). Astrocytes also express numerous receptors including G protein-coupled receptors and ionotropic receptors, receptors for growth factors, chemokines and cytokines. Astrocytes display heterogeneity in their pattern of receptor expression and adjust the pattern according to their microenvironment (Wang and Bordey 2008). Astrocytes become highly reactive in response to any insult to the brain. Thus, astrocytes also respond to all forms of injuries including infection, SCI, TBI, ischemic injury and neurodegenerative disease by a process commonly known as reactive astrogliosis (Pekny and Nilsson 2005; Correa-Cerro and Mandell 2007). Although, astrocytes are multifunctional housekeeping cells, but their activation is associated with neuronal survival in many different ways. Depending on the type of the stimuli and/or pathological conditions reactive astrogliosis may lead to either neuroprotective or neurotoxic inflammatory responses.

Both astrocytes and microglia play a major role in regulation of neuroinflammation. Microglia invade the brain early in development and take on a resting 'protective' role as sentinels, scattered uniformly throughout the CNS and forming a network of potential effector cells. Astrocytes, which outnumber microglia within the CNS parenchyma, are the major components of the CNS innate immune system. Astrocytes have been reported to suppress T helper 1 (Th1) and T helper 2 (Th2) cell activation, the proliferation and effector functions of activated T cells, and possess a wide variety of molecular mechanisms to induce apoptosis in activated T cells (Amor et al. 2010). Activated astrocytes express an array of inflammatory cytokines and chemokines (Dong and Benveniste 2001). In addition to production of pro-inflammatory mediators, the stimulation of cultured astrocytes or cell lines results in expression of major histocompatibility complex (MHC) class II molecules and co-stimulatory molecules such as B7-1 and B7-2 (Soos et al. 1999). Although, earlier studies indicate that neurons play a passive role in inflammation, but recent studies indicate that neurons contribute to inflammation by providing many of their products (i.e. neuropeptides and transmitters), as well as the neuronal membrane proteins CD22, CD47, CD200, CX3CL1 (fractalkine), intercellular adhesion molecule (ICAM)-5, neural cell adhesion molecule (NCAM), semaphorins and C-type lectins. All these neuronal factors regulate neuroinflammation (Tian et al. 2009). In addition, neurons express low levels of major histocompatibility complex (MHC) molecules and actively promote T-cell apoptosis via the Fas-Fas ligand pathway (CD95-CD95 L). Accumulating evidence suggests that neurons use a variety of signals to modulate microglial cells and astrocytes. These signals can be categorized into excitatory and inhibitory signals. Inhibitory signals from neurons constitutively maintain microglial cells and astrocytes in their quiescent state and antagonize proinflammatory activity, whereas excitatory signals are inducible and incite activation of microglial cells and astrocytes under pathological conditions towards a beneficial or detrimental phenotype. Thus, various neuronal signaling molecules

actively modulate microglial functions and contribute to the inflammatory milieu in neurodegenerative diseases (Biber et al. 2007; Farooqui 2010). Neurons also favor the differentiation of T-regulatory cells, by providing a local microenvironment dominated by transforming growth factor- β 1 (TGF- β 1) (Amor et al. 2010). Collective evidence suggest that communication among neurons, microglia, and astrocytes is essential in maintaining homeostasis in the brain as well as responding appropriately to a variety of neuroimmune challenges. Physiological, morphological, and functional alterations in neurons and microglia during aging, stress, and inflammation disrupt the normal cross-talk among these cells in resulting in a dysregulated neuroimmune environment with potential deleterious consequences on brain function and behavior. Although, increase in microglia activation and neuronal injury can be the result of an exaggerated neuroimmune responses, but it remains unknown if microglial overactivation precedes and causes neuronal damage, or if activation occurs in response to loss of normal neuronal integrity. Injured neurons trigger glial activation, resulting in the production of inflammatory molecules and phagocytosis of injured neurons by glial cells. On the other hand, these neurons can also suppress glial activation through the induction of anti-inflammatory cytokines and chemokines. It is proposed that astrocytes and microglia interact with neurons at the synapse to modulate synaptic function and plasticity (Eroglu and Barres 2010), and are also vital for host defense mechanisms and response to stress (Ransohoff and Perry 2009).

2.2 Contribution of Microglial Cells in Neuroinflammation

Microglial cells are resident macrophages of the brain. They account for 10–12% of the total glial cell population in the brain. They are predominately found in the grey matter, with especially high concentrations in the hippocampus, hypothalamus, basal ganglia and substantia nigra (Block et al. 2007; Mittelbronn et al. 2001). They originate from yolk sac and invade the brain tissue during early embryonic development and proliferate locally in the brain (Ginhoux et al. 2010; Schulz et al. 2012). In contrast to other yolk sac-derived macrophages, they are not replaced during the postnatal period and later life by liver- or bone marrow-derived macrophages (Hoeffel et al. 2012). The total number and density of microglia have been shown to increase significantly with age in various regions of the brain, including the hippocampus (Mouton et al. 2002), visual and auditory cortices (Tremblay et al. 2010, 2012), and the retina (Damani et al. 2011). Under normal physiological conditions microglial cells have a small, somewhat elongated cell body with long, fine processes. The ramified microglial cells are rather evenly spaced throughout the brain, with their processes pervading the entire brain. It is generally accepted that ramified microglia constantly survey the CNS and synapses for intruders/stressors which may disrupt structure and function of neuronal circuits (Wake et al. 2009). Microglia function is crucial for the homeostasis of the brain in health and disease,

as they represent the first line of defense against pathogens and injuries, contributing to immune responses, but are also involved in tissue repair and remodeling (Lindsey et al. 1979). Toll-like receptors (TLRs) are first-line molecules for initiating innate immune responses (Akira and Takeda 2004). When activated through TLR signaling, microglial cells respond to injury and damaged neuronal cells by secreting chemokines and cytokines and express co-stimulatory molecules needed for protective immune responses to pathogens and efficient clearance of damaged tissues (Takeuchi and Akira 2010). Recent studies have indicated that distinct functional microglial phenotypes, ranging from the so-called M1-like proinflammatory to the M2-like antiinflammatory, can affect differently the health of mature, pre-existing neurons and the fate of neural stem progenitor cells (Ekdahl et al. 2009). The balance between pro- and antiinflammatory functions of microglia has been reported to affect the outcome of neuroinflammatory and regenerative and reparative mechanisms (Minghetti et al. 2005; Ekdahl et al. 2009). Microglial cell activation is characterized by conspicuous changes in their ramified morphology to an intermediate and amoeboid forms resulting in round morphological profile of full phagocytes (Morioka et al. 1993; Thored et al. 2009). The morphological changes are accompanied not only by the upregulation of nuclear factor- κ B (NF- κ B) in cytoplasm and increase in expression of MHC classes I and II, complement C3, Fc, thrombin, scavenger receptors (i.e., CD36, SR-A, CD204, SR-BI), cytokine, chemokine in the nucleus. In addition, CD4 and CD8 receptors, toll-like receptors, P2X7 purinergic receptor, and several oxidative enzymes, such as NADPH oxidase (Streit et al. 1999; Husemann et al. 2002; Block et al. 2007; Ransohoff and Perry 2009; Helmut et al. 2011) are also increased. Activation of P2X7 purinergic receptor and NADPH oxidase induces the production of the superoxide, in primary rat microglia (Fig. 2.2).

The occurrence of activated microglial cells and enhancement of superoxides production have been reported in various brain regions (hippocampus, substantia nigra and spinal cord) of stroke, AD, PD, and ALS patients. The involvement of microglial cells in the pathogenesis of stroke, AD, PD, and ALS is supported by studies in animal and cell culture models of neurodegenerative diseases. It is shown that (a) microglial cell activation precedes the neurodegenerative changes; (b) activated microglial cells surround the region that undergo neurodegeneration and phagocytose the degenerating cells; (c) activated microglia not only release neurotoxic molecules such as interleukin (IL)-1 β , IL-6, TNF- α , glutamate, aspartate, and quinolinic acid, nitric oxide, and reactive oxygen species (ROS) (Fig. 2.2), but also facilitate the assembly and activation of so called “inflammasomes” a cytoplasmic caspase-1 activating and self-oligomerizing signaling complex with molecular mass of greater than 700 kDa (Chakraborty et al. 2010); (d) inhibition of microglial activation results in the amelioration of neurodegeneration, and (e) microglia derived from aged animal exert more toxicity to neurons in an age-dependent fashion, in the same way neurodegenerative disorders occur. The release of interleukin (IL)-1 β , IL-6, TNF- α leads to marked enhancement in activities of PLA₂, COX-2, and 5-LOX and generation of proinflammatory eicosanoids and platelet activating factor (Phillis et al. 2006) (Fig. 2.3). These pro-inflammatory mediators along with proteinases, and complement proteins

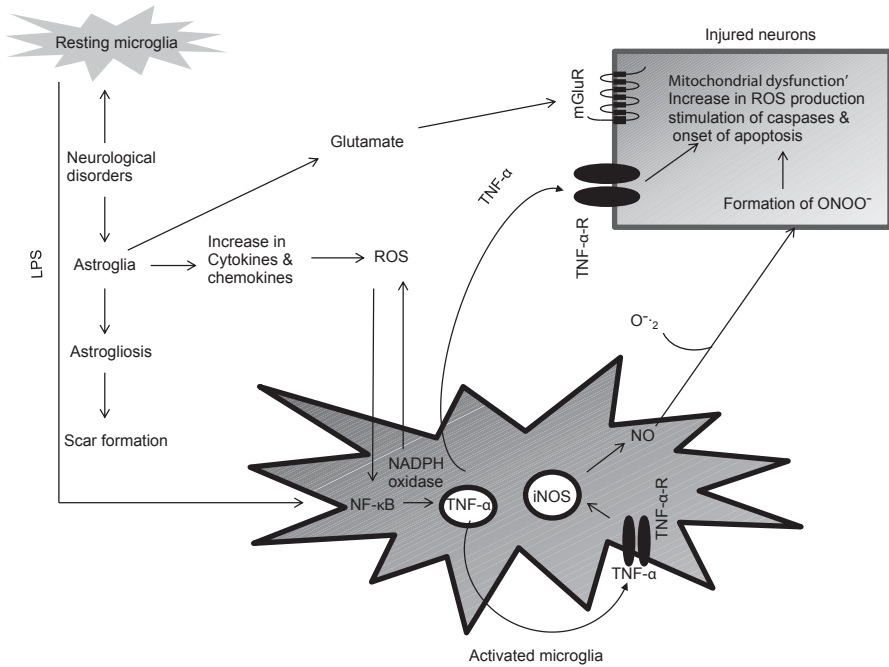


Fig. 2.2 Neurochemical changes associated with the activation of microglial cells and interactions among activated microglia, astroglia, and neurons. Lipopolysaccharide (*LPS*), Reactive oxygen species (*ROS*), nuclear factor kappa-B (*NF-κB*), tumor necrosis factor-α (*TNF-α*), tumor necrosis factor-α receptor (*TNF-α-R*), inducible nitric oxide synthase (*iNOS*), nitric oxide (*NO*), superoxide (*O₂⁻*), and peroxynitrite (*ONOO⁻*). The free radical *NO* reacts with *O₂⁻* to produce peroxynitrite (*ONOO⁻*), a powerful oxidant, which decomposes to form hydroxyl radical (*HO•*)

intensify neuroinflammation. At this time it is difficult to establish the correct sequence of these events, so it is not clear whether activation of microglia and the associated inflammatory changes play a part in triggering neurodegenerative processes or whether cell activation is a response to the early changes associated with neurotraumatic and neurodegenerative diseases. In brain activated microglial cells not only express receptors for neurotransmitters such as ATP, adenosine, glutamate, GABA, acetylcholine, dopamine and adrenaline (Lee 2013), but also secrete a variety of immune system modulators including complement proteins, adhesion molecules, colony-stimulating factor-1, tumor and growth factors (TGF-α and β), monocyte chemoattractant protein (MCP-1), and macrophage inflammatory peptide-1α (MIP-1α) (Minghetti et al. 2005; Galimberti et al. 2006; Janelins et al. 2005). MCP-1 is a major chemokine that in cardiovascular and cerebrovascular systems attracts more monocytes to the plaque to enhance the inflammation. MCP-1 is abundantly expressed in atherosclerotic arterial lesions. The chemotactic response of the mononuclear cells is dependent on the presence of the chemokine receptor-2 (CCR-2) on its surface (Charo and Peters 2003).

Inflammatory response also involves the recruitment of polymorphonuclear leukocytes (PMN) from the blood stream into brain tissue. The PMN migration involves

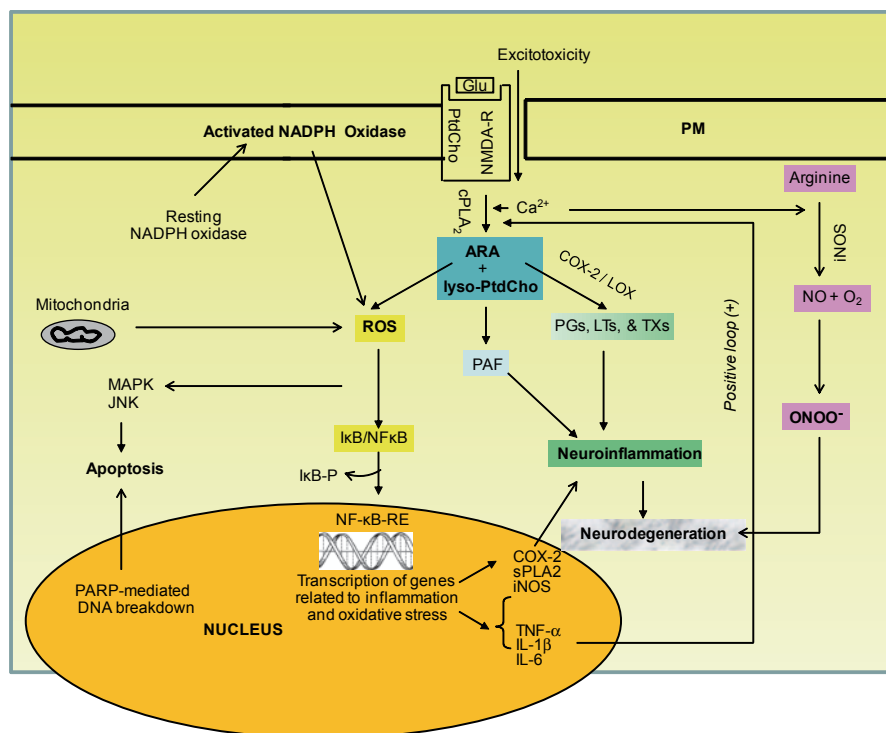


Fig. 2.3 Generation of reactive oxygen species (ROS), activation of NF-κB, and expression of cytokines. Cytokines stimulate PLA₂, COX-2, and iNOS and contribute to the generation of PGs, LTs, TXs, and PAF. Phosphatidylcholine (PtdCho), lyso-phosphatidylcholine (lyso-PtdCho), arachidonic acid (ARA), platelet-activating factor (PAF), cytosolic phospholipase A₂ (cPLA₂), cyclooxygenase-2 (COX-2), lipoxygenase (LOX), reactive oxygen species (ROS), prostaglandins (PGs), leukotrienes (LTs), thromboxanes (TXs), nuclear factor kappaB (NF-κB), nuclear factor κB-response element (NF-κB-RE), inhibitory subunit of NF-κB (IκB), phosphorylated IκB (IκB-P), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), nitric oxide (NO), superoxide (O₂⁻), mitogen activated protein kinase (MAPK), and c-Jun amino-terminal kinase (JNK)

chemotaxis, adhesion of PMN to endothelial cells in the area of inflammation, and diapedesis (Farooqui et al. 2007). PMN facilitate the elimination of invading antigens by phagocytosis and release free radicals and lytic enzymes into phagolysosomes. This is followed by a process called resolution, which is a turning off mechanism by neural cells to limit tissue injury. Lipoxin, another oxidized product of ARA metabolism by 5-LOX, is closely associated with resolution due to its anti-inflammatory effects. Neuro-inflammation involves several converging mechanisms responsible for sensing, transducing, amplifying, and turning off mechanisms that involve the participation of eicosanoids (Serhan et al 2007; Lawrence and Gilroy 2007). Some PGs and LTs produce proinflammatory effects while others induce antiinflammatory effects. In addition, eicosanoids also serve as autocrine

factors regulating platelet aggregation, vascular tone, and edema (Farooqui 2011). The sustained release of inflammatory mediators works to perpetuate the inflammatory cycle, activating additional microglia, promoting their proliferation, and resulting in further release of inflammatory factors. Owing to the chronic and sustained nature of the inflammation, there is often compromise of the BBB which increases infiltration of peripheral macrophages into the brain parenchyma to further perpetuate the inflammation. Collective evidence suggests that neuroinflammatory cascade is an attempt by the brain to eliminate the challenge imposed by the injury or infection, clear the system of the dead and damaged neurons, and rescue the normal functioning of this vital organ (Correale and Villa 2004). At the same time neuroinflammation promotes neurogenesis. Inflammatory factors released during mild acute neuroinflammation usually stimulate neurogenesis; whereas the factors released by uncontrolled inflammatory response block neurogenesis (Correale and Villa 2004; Helmut et al. 2011; Gomes-Leal 2012).

Acute neuroinflammation occurs in neurotraumatic injuries, such as ischemic injury, SCI and TBI where as chronic neuroinflammation occurs in neurodegenerative diseases. Ischemic injury (stroke), a highly dynamic multifactorial metabolic insult caused by severe reduction or blockade in cerebral blood flow due to the formation of a clot. This blockade not only decreases oxygen and glucose delivery to brain tissue but also results in the breakdown of BBB and build-up of potentially toxic products in brain (Farooqui 2010). SCI and TBI are caused by mechanical trauma to spinal cord and brain. Ischemic injury, SCI and TBI trigger a complex series of biochemical and molecular mechanisms that impair the neurologic functions through the breakdown of cellular and subcellular integrity, alterations in ionic balance, increase in excitatory amino acids, elevation in intracellular calcium, activation of nitric oxide synthesis, and alterations in redox status, generation of free-radicals, induction of proinflammatory cytokine and development of neuroinflammation. Activated microglia can produce large amounts of nitric oxide, which in turn can react with superoxide to form peroxynitrite, leaving nitrotyrosine as an identifiable marker. The footprint of excess NO formation in SCI and TBI is confirmed by the increased amounts of nitrotyrosine-modified proteins (Farooqui 2010). These mechanisms occur over a range of time, with early events within minutes of energy loss, and then progress after hours and days following the metabolic or mechanical insult leading to cell injury and tissue death (Farooqui 2010). Many of these processes are mediated by the activation of NF- κ B, which is a master regulator of neuroinflammation. The activity of NF- κ B is tightly regulated. Under normal conditions in the cytoplasm NF- κ B occurs in bound form with its inhibitory protein, I κ -B α . NF- κ B is activated by cytokines or neural trauma leading to the dissociation of I κ -B α and freeing NF- κ B, which is translocated to the nucleus, where it activates the target genes containing a consensus κ B site in their promoters (Chen et al. 1995). I κ B α is degraded by the ubiquitin proteasome system. Mice deficient in I κ B α display deregulated and sustained NF- κ B activation and early postnatal lethality, highlighting a critical role of I κ -B α in NF- κ B regulation (Beg et al. 1995). Activation of NF- κ B is coupled with the stimulation of phospholipases A₂, C, and D (PLA₂, PLC and PLD), cyclooxygenases (COXs), lipoxygenases (LOXs), epoxygenases (EPOXs), calcium/calmodulin-

dependent kinases (CaMKs), mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK), nitric oxide synthases (NOS), calpains, calcineurin, and endonucleases. Activation of these enzymes results in breakdown of neural membrane phospholipids with release of arachidonic acid (ARA), which is metabolized by COX-2 and 5-LOX leading to production of proinflammatory prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs). The other product of PLA₂-catalyzed reaction (lyso-phospholipids) is used for the synthesis of pro-inflammatory platelet-activating factor (PAF) (Fig. 2.3). While an acute insult triggers oxidative and nitrosative stress, it is typically short-lived and unlikely to be detrimental to long-term neuronal survival. Therefore, it is believed that an acute neuroinflammatory response is generally beneficial to the CNS, since it tends to minimize further injury and contributes to repair of damaged tissue (Phillis et al. 2006; Farooqui 2010, 2011).

Although, little is known about molecular mechanisms and internal and external factors that control and modulate the dynamics of acute and chronic neuroinflammation, but it is becoming increasingly evident that neuroinflammation is not only modulated by interactions among microglia, astrocytes, neurons, PMN, and endothelial cells, but also by cross-talk among various lipid mediators that originate from enzymic and non-enzymic degradation of neural membrane glycerophospholipids and sphingolipids. In addition, receptors, like TLR and transcription factors such as peroxisome proliferator-activated receptor (PPAR) also contribute to the modulation of neuroinflammation (Farooqui 2009a).

2.3 Contribution of Astrocytes in Neuroinflammation

As stated above, astrocytes are complex, highly differentiated cells of the brain. They respond to neurotraumatic and neurodegenerative injuries by a process commonly known as reactive astrogliosis. This process involves activation of astrocytes leading to production of proinflammatory mediators, such as cytokines, chemokines, glutamate, aspartate, and quinolinic acid, reactive oxygen species (ROS) and prostanoids, (Pekny and Nilsson 2005; Correa-Cerro and Mandell 2007) (Fig. 2.3). During astrogliosis, astrocytes become hypertrophic with upregulated expression of intermediate filaments (e.g., glial fibrillary acidic protein, vimentin, nestin) and inflammatory/immune/oxidative stress markers, extracellular matrix (ECM) molecules, and growth factors and cytokines. Astrogliosis ultimately leads to the formation of glial scar as a physical barrier which inhibits axonal regeneration. Reactive astrogliosis is not merely a marker of neuropathology, but plays essential roles in orchestrating the injury response as well as in regulating the inflammation and repair in a manner that markedly impacts functional and clinical outcomes. Astrocytes contribute to neuroinflammation by interacting extensively with microglia, and can exert both pro- and anti-inflammatory effects (Farina et al. 2007).

Astrocyte-release glutamate, which diffuses in the extrasynaptic space and may bind to glutamate receptors, including mGluRs and *N-methyl-D-aspartate* receptors

(NMDARs) on neighboring presynaptic terminals, activating PLC-mediated signaling and modulating the release of neurotransmitter (Jourdain et al. 2007; Bonansco et al. 2011). Formation of astrocytic scar not only acts as neuroprotective barriers to inflammatory cells and infectious agents, but is also promotes reorganization and induces structural changes that are long lasting and persist long after the triggering insult may have resolved (Sofroniew and Vinters 2010). The migration of astrocytes is a critical step in the formation of a densely-packed glial scar (Saadoun et al. 2005) and TGF- β 1 has been reported to play an important role in glial scar formation (Kohta et al. 2009). Glial scar formation is prevented by cysteinyl leukotrienes (CysLT) receptor antagonists or 5-LOX inhibitors supporting the view that cysteinyl leukotriene receptor 1 (CysLT₁R) are closely associated with astrocyte proliferation and glial scar formation after brain injury (Yu et al. 2005; Zhou et al. 2006). Astrocytes not only participate in the local innate immune responses through the involvement of TLRs, nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, scavenger receptors, mannose receptor and components of the complement system, but also play an important role in the neuroinflammation and tissue repair through the secretion of soluble mediators, such as CXCL10, CCL2, interleukin-6 and BAFF (Zhao et al. 2011). In brain TLRs are not only involved in peripheral innate immunity but may also play a role in the development and regulation of CNS inflammation, neurodegeneration and brain trauma. These receptors initiate downstream signaling to activate the key transcription factor, NF- κ B, producing inflammatory cytokines (Kawai and Akira 2010; Crack and Bray 2007). Recent studies have indicated that in primary cultures of human astroglial (HAG) cells miRNA-146a is an important regulator of the innate immune response and pro-inflammatory signaling (Aronica et al. 2010). It is shown that miRNA-146a modulates the interleukin-1 receptor-associated kinase-1 and 2 (IRAK-1 and IRAK-2) expression in IL-1 β +A β 42-treated HAG cells. IRAK-1 and IRAK-2 are essential components of Toll-like/IL-1 receptor signaling. Using miRNA-146a-, IRAK-1-, or IRAK-2 promoter-luciferase reporter constructs, it is shown that the decrease in IRAK-1 and increase in miRNA-146a and IRAK-2 expression in interleukin-1 β (IL-1 β) and amyloid- β -42 (A β 42) peptide-stressed HAG cells are closely associated with neuroinflammation. MyD88, a mammalian adapter protein serves as a bridge between TLR4 and IL-1 receptor associated kinase (IRAK1) that then recruits into the complex TNF receptor-associated factor 6 (TRAF6) (Aronica et al. 2010; Saugstad 2010). This chain of events triggers the activation of I- κ B kinase and JNK, which in turn, modulates the downstream NF- κ B, a transcription factor located in the cytoplasm. The dissociation of NF- κ B-I- κ B complex results in translocation of free NF- κ B to the nucleus, where it binds to target sequences in the genome and facilitates the expression of a number of proteins including many enzymes (sPLA₂, COX-2, NADPH oxidase, and inducible nitric oxide synthase (iNOS), NADPH oxidase and matrix metalloproteinases (MMPs)) and cytokines (TNF- α , IL-1 β , and IL-6), chemokines, and other proteins including, intracellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), E-selectin (Table 2.1). The production of above inflammatory mediators is regulated by the negative feedback provided by the hypothalamus-pituitary-adrenal (HPA) axis (Farooqui 2010).

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Disorders

Effect of Lifestyle, Genes, and Age

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