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Signaling Pathways Regulating the Pathophysiological Responses of Astrocytes: A Focus on the IKK/NF- κ B System

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Abstract

Astrocytes are highly responsive to changes in their microenvironment, and undergo prominent functional alterations in pathological conditions, a process called astrogliosis. In such conditions, astrocytes can gain immune cell-like functions, form glial scars and promote brain repair and regeneration. However, astrogliosis can also contribute to disease pathogenesis by exacerbating inflammation and perturbing the normal physiological functions of astrocytes. The IKK/NF- κ B signaling system is a master regulator of inflammation, cell survival and differentiation, which also controls astrocyte functions, in particular their responses to pathological conditions. Activation of IKK/NF- κ B signaling in astrocytes is a key driver of neuroinflammation and astrogliosis, which can interfere with normal brain development and homeostasis and can aggravate various central nervous system (CNS) pathologies. Besides IKK/NF- κ B signaling, several other signaling pathways regulate pathophysiological responses of astrocytes, in particular hypertrophy, proliferation and the reactivation of neural stem cell-like properties of astrocytes. Further dissection of the role of these signaling pathways in the control of physiological functions and pathophysiological plasticity of astrocytes will reveal new insights into the pathogenesis of neurological diseases and might indicate new neuroprotective and regenerative therapeutic approaches.

Keywords: NF-kappa B, astrocytes, neuroinflammation, astrogliosis, neurodegeneration, brain development, brain homeostasis, signal transduction

1. Introduction

Astroglial cells, which comprise one of the major cell populations in the central nervous system (CNS), show a remarkable morphological and functional diversity and they are

highly important for brain development and homeostasis. For example, prototypical parenchymal astrocytes regulate the local cerebral blood flow and the transport of metabolites through the blood-brain-barrier (BBB) according to local demand [1]. These metabolites are then converted by astrocytes to metabolites required by neurons and other cells in the brain parenchyma [1]. Astrocytes also directly contact synapses with their cell processes and they are actively and specifically involved in synaptic signaling. They take up potassium ions and neurotransmitters like glutamate released by neurons and release gliotransmitters to modulate synaptic transmission [1]. These active functions in synaptic signaling led to the concept of the tripartite synapse, that is, the view that astrocytes processes are a third integral component of synapses beside the pre- and postsynaptic neuronal compartments [1]. Astrocytes also have important functions in development, as structural scaffold and in neuronal maturation [1]. Furthermore, neural stem cells (NSCs) in development (radial glia) and the adult brain show extraordinarily high similarity to astrocytes, and recent studies indicate that classical parenchymal astrocytes can regain NSC-like properties [2]. Therefore, NSCs might even be considered to be a part of a broad continuous spectrum of astrocyte-like cells [2].

For many of their diverse functions in normal brain development and homeostasis, astrocytes need to closely monitor and respond to changes in their environment. Therefore, it is not surprising that astrocytes also strongly respond to pathological conditions. This can result in the gain of novel functions, like immune cell-like functions, but also in the disruption of their normal homeostatic functions, adding an additional layer of complexity to astrocyte biology. Due to the important functions of astrocytes and their prominent alterations in pathologies, astrocytes are known or suspected to be involved in the pathogenesis of a large number of neurological conditions, from acute injury and inflammatory diseases to neurodegenerative and even psychiatric disorders [3, 4].

Astrocytes express a large set of receptors allowing them to detect a wide spectrum of changes in their environment, which activate various signaling pathways. Many of these receptors detect molecules occurring in pathological conditions, for example, pathogen-derived molecules, molecules derived from damaged cells (pathogen-associated molecular patterns/Danger associated molecular patterns (PAMPs/DAMPs)), and cytokines [5, 6]. Signaling of most of these receptors converges on one major signaling pathway, the IKK/NF- κ B signaling pathway. This pathway is a master regulator of inflammation, and one of the main pathways controlling the pathophysiological responses of astrocytes, as will be discussed in detail in this chapter.

2. Astrogliosis: responses of astrocytes to pathological conditions

Most CNS pathologies, ranging from acute damage in traumatic brain injury (TBI) or CNS infections to inflammatory disorders like multiple sclerosis (MS), epilepsy and classical chronic neurodegenerative diseases like Alzheimer's disease (AD) are associated with similar

characteristic histopathological alterations of astrocytes, which are generally referred to as astrogliosis [1]. Astrogliosis is usually associated with local inflammatory processes elicited by these pathological conditions. Similarly, microglia, the resident macrophages of the CNS, show characteristic alterations in these conditions, called microgliosis, which usually occur together with astrogliosis. [3, 7, 8].

A common feature of astrogliosis is astrocyte hypertrophy, along with an upregulation of proinflammatory mediators and intermediate filaments like the classical astrocyte and astrogliosis marker GFAP [1, 5, 6, 9]. Depending on the severity and type of insult, this hypertrophic response can also be accompanied by astrocyte proliferation and can result in the formation of dense glial scars [10].

The production of inflammatory mediators like cytokines (e.g. TNF, IL-1 β) and chemokines (e.g. MCP1 (CCL2), RANTES (CCL5) and IP-10 (CXCL10)) by reactive astrocytes is crucial for the recruitment of peripheral immune cells into the CNS and their subsequent activation [3, 5]. This astrocyte-mediated immune cell recruitment is essential to fight infections and repair tissue damage, but exacerbated or chronic immune cell infiltration also drives autoimmune pathologies like MS, and can aggravate other pathologies associated with neuroinflammation, like neurodegenerative disorders [3, 11].

In response to pathological conditions, beside recruiting professional immune cells, astrocytes themselves contribute to inflammation and immune responses by producing a variety of acute phase response factors, like complement proteins (e.g. C1q, C3) or Lcn2 [12, 13]. While these factors can have important protective functions, for example, by inhibiting bacterial growth in case of an infection, they can also promote synapse elimination and neuronal cell death [12, 13]. Interestingly, reactive astrocytes also upregulate MHC class II genes and have phagocytic capabilities [14, 15]. Therefore reactive astrocytes might act as professional antigen-presenting cells, similar to macrophages and dendritic cells [14, 15].

Overall, these inflammation-related and immune cell-like properties gained by reactive astrocytes suggest that astrocytes, beside microglia, are a second major component of the innate immune system of the brain.

The inflammatory functions of astrocytes are important for a fast and strong early response of the CNS to pathological conditions, which can be crucial to limit damage, for example, in infections or acute injury. This local response is particularly important in the CNS, because as an immune-privileged organ it has limited surveillance by peripheral immune cells. But inflammation increases cellular stress by various mechanisms, therefore chronic or exaggerated inflammatory astrocyte activation can have severe adverse effects resulting in neurotoxicity [16]. These early inflammatory responses of astrocytes are similar to the early responses of microglia and macrophages to pathological conditions, often described as proinflammatory M1 polarization [17]. Therefore, this type of astrocyte responses was recently described as A1 activation [16].

In addition to increased inflammatory stress, this type of astrocyte activation can also disrupt their normal homeostatic functions, like BBB maintenance, or the clearance of extracellular

neurotransmitters (e.g. glutamate) and potassium ions released during synaptic activity [1, 18, 19]. Disruption of these astrocyte functions can cause edema formation and alters neuronal excitation and network activity, which can result in behavioral changes, epileptic seizures and excitotoxic neurodegeneration [3, 18, 19].

Beside the described prominent proinflammatory phenotype, which in some conditions can have adverse consequences, reactive astrocytes also seem to occur in more “benign” states, which has been described as A2 activation, in analogy to a similar anti-inflammatory, pro-regenerative state of microglia and macrophages (M2 polarization) [16, 17].

In chronic neurodegenerative or neuroinflammatory pathologies, A1 astrocyte activation seems to dominate, whereas after acute injury or ischemia, this A2 activation seems to determine the overall functional consequences of astrogliosis [16]. In these acute insults, reactive A2 astrocytes upregulate neurotrophic factors and can gain overall neuroprotective functions [16].

After acute brain injury, for example, in models of cortical stab wound injury or spinal cord injury (SCI), but not in chronic neurodegenerative or neuroinflammatory pathologies, astrocytes also respond by proliferation and the formation of dense astroglial scars [10, 20, 21]. It is often assumed that this glial scar is required to restrict the spreading of tissue damage in the acute stage of the injury, but interferes with CNS regeneration on the long term, for example, by preventing axonal regrowth through the scar tissue. However, several studies indicate that also on the long term, the astrocytes of the glial scar rather promote repair and regeneration [10, 20]. Specifically, ablation of proliferating astrocytes has been shown to interfere with the repair of the BBB in cortical stab wound injury and SCI models, and prevented axonal regrowth after SCI stimulated by a conditioning lesion and neurotrophin application [20, 22, 23]. In addition, recent studies suggest that astrocytes not only protect the surviving of neurons in the damaged tissue, but might also reactivate a NSC-like potential, and might thereby contribute to the (very limited) generation of new neurons after injury [21, 24–26].

3. The IKK/NF- κ B signaling pathway: a central signaling hub in inflammation, cell survival, proliferation and differentiation

The IKK/NF- κ B pathway is a master regulator of inflammation, which is also implicated in a wide range of other biological processes, including cell death/survival, proliferation and differentiation [27–29]. This signaling pathway integrates signals from a large number of different receptors, converging in the activation of the I κ B kinase (IKK) complex, the key activator of the NF- κ B family of transcription factors in canonical NF- κ B signaling [28]. In mammals, the NF- κ B family includes the five members—RelA, RelB, c-Rel, p105/p50 and p100/p52, which form homo- and heterodimers [28]. In the basal state, these dimers are kept inactive in the cytoplasm by binding to proteins of the inhibitor of NF- κ B (I κ B) family [28].

The IKK complex, consisting of the kinase subunits IKK1 and IKK2 (also called IKK α and IKK β) and the regulatory subunit NEMO (IKK γ), can activate NF- κ B dimers by phosphorylating I κ B proteins through IKK2 as active kinase subunit [28]. This induces the poly-ubiquitination and subsequent proteasomal degradation of the I κ B proteins, resulting in the release of the NF- κ B dimers [28]. These dimers then can translocate to the nucleus, where they can activate or repress a large number of target genes [28].

Various inflammation-mediating receptors activate NF- κ B through this canonical signaling pathway, including the TNF receptor TNFR1 and the IL-1 β receptor as prototypical examples [28]. Upon activation, these receptors recruit K63-ubiquitin ligases like the cIAP proteins, and the linear ubiquitin assembly complex (LUBAC) [30, 31]. These ubiquitin ligases build K63- and linear (M1-) poly-ubiquitin chains on receptor-associated scaffolding proteins, which form the backbone for the assembly of large signaling complexes [30, 31]. The TAK1/TAB2/3 and IKK kinase complexes then bind to these poly-ubiquitin chains, allowing the phosphorylation of IKK2 at two conserved serine residues by TAK1 and IKK2 itself [30, 31]. This dual phosphorylation of IKK2 is the key step in the activation of the IKK complex, which is then capable of phosphorylating I κ B proteins [30, 31].

Beside TNFR1 and the IL-1 β receptor, among the receptors activating this canonical NF- κ B signaling pathway there are also many pattern recognition receptors (PRRs), like Toll-like receptors (TLRs) and NOD-like receptors (NLRs) [6, 28, 32]. These receptors are sensors of molecular danger signals, like conserved pathogen-derived molecules (pathogen-associated molecular patterns, PAMPs) and molecules released by damaged cells (danger-associated molecular patterns, DAMPs), which are driving the initiation of inflammatory responses [6, 28, 32].

Some other extracellular signals, like CD40L, LT β , BAFF or RANKL, can activate an alternative NF- κ B signaling pathway, by activation of IKK1 via the NF- κ B inducing kinase (NIK). This induces the proteasomal processing of the NF- κ B precursor subunit p100, resulting in the degradation of an inhibitory I κ B domain of p100 [27]. This processing leaves the active subunit p52, which can translocate to the nucleus as a p52/p52 or RelB/p52 dimer [27].

In addition, several other stimuli, including neurotrophins and general cellular stress, like DNA damage and high levels of reactive oxygen species, can activate NF- κ B signaling. In these cases, NF- κ B activity is often regulated via atypical NF- κ B signaling pathways, which involve various posttranslational modifications of IKK and NF- κ B subunits [28, 33–35].

As diverse as the range of NF- κ B activating stimuli are the target genes of the NF- κ B transcription factors. NF- κ B signaling controls the expression of a large number of inflammatory cytokines, chemokines, cell adhesion molecules, immunoreceptors and acute phase response genes [36]. As NF- κ B signaling is activated by a wide range of inflammatory stimuli, and induces a large number of proinflammatory target genes, it can both initiate inflammatory responses and enhance them by positive feedback loops via NF- κ B activating cytokines. These properties make the NF- κ B signaling system a critical master regulator of inflammatory processes. In fact, IKK/NF- κ B activation alone is sufficient to initiate and maintain inflammatory responses

in many tissues, which often phenotypically closely resemble classical autoimmune/inflammatory diseases. This has been shown by us and others by conditional genetic activation of IKK/NF- κ B in pancreatic acinar or β -cells, hepatocytes, cardiomyocytes and airway or intestinal epithelial cells [37–43]. Vice versa, genetic inactivation of IKK/NF- κ B signaling strongly suppresses inflammation in many mouse models of pathological conditions. This often ameliorates pathology, for example, in a model of cerebral ischemia with inactivated neuronal IKK/NF- κ B signaling [44], or in an MS model with inactivated IKK/NF- κ B signaling in all neuroectodermal cells [45].

Among the large spectrum of NF- κ B targets are also many genes controlling cell proliferation, differentiation and survival, like growth factors, cyclins and apoptosis regulators of the Bcl-2 and IAP families [29, 36]. Therefore NF- κ B signaling represents a crucial link between inflammation and cancer [29, 36]. In addition, in the CNS, NF- κ B signaling regulates neuronal differentiation and function, for example, dendrite formation and synaptogenesis, via various target genes like neurotrophins or IGF2 [34, 46–48].

In conclusion, the NF- κ B signaling pathway is a central signaling hub integrating a large spectrum of signals to regulate a similar broad range of biological processes. One important function is the transduction of pathophysiological alarm signals, which is crucial for the cellular responses to these signals, in particular for inflammatory responses. Due to its diverse other biological functions, the NF- κ B signaling pathway is a critical molecular link between inflammation and various physiological processes known to be dysregulated in inflammatory conditions.

4. Activation of the IKK/NF- κ B pathway in astrocytes

Considering the responsiveness of astrocytes to pathological conditions and the central role of NF- κ B in the transduction of such responses, it is not surprising that NF- κ B signaling in astrocytes is activated in many pathological conditions and regulates many of these pathophysiological responses.

Astrocytes express a large number of cytokine receptors including TNFR1 and IL-1RI; PRRs including TLRs (TLR2,3,5,9); NLRs including NOD2 and NLRP3 and RIG-1 like receptors (RLRs), which can activate NF- κ B signaling in pathological conditions [5, 49, 50].

Accordingly, astrocytes activate NF- κ B signaling *in vitro* after stimulation with ligands of these receptors, and *in vivo* in various neuropathological conditions associated with neuroinflammation.

For example, *in vitro*, stimulation of primary mouse astrocytes with TNF α or IL-1 β induces nuclear accumulation of RelA indicating NF- κ B activation (e.g. [45]). *In vivo*, astroglial NF- κ B activation was described, for example, in MS [51], traumatic brain injury (TBI) [52], in chronic neurodegenerative pathologies such as ALS [53] and Huntington's disease (HD) [54], but remarkably also in a post-mortem study in autism spectrum disorders [55].

5. Functions of astroglial IKK/NF- κ B signaling: a central regulator of the pathophysiological responses of astrocytes

To investigate the specific functions of NF- κ B signaling in astrocytes *in vivo*, we and other groups have developed conditional transgenic mouse models allowing the genetic activation or inactivation of NF- κ B signaling specifically in astrocytes and closely related cell types.

One much-studied mouse model was developed by the group of John R. Bethea, the GFAP-I κ B α -dn transgenic mouse line [56]. In this mouse model, astroglial NF- κ B signaling is strongly inhibited by overexpression of a dominant-negative, non-degradable mutant of the NF- κ B inhibitor I κ B α [56]. The transgene expression is driven by the GFAP promoter, which restricts its expression to astrocytes and closely related cell types [56].

Vice versa, to genetically activate IKK/NF- κ B signaling, we generated a mouse model allowing the inducible overexpression of a constitutively active mutant of IKK2 specifically in astrocytes (GFAP.tTA/tetO.IKK2-CA) [57]. Using a so-called Tet-off conditional expression system, the expression of this transgene is driven by the GFAP promoter and can be reversibly repressed by the administration of doxycycline, allowing both constitutive and time-controlled transient activation of astroglial IKK/NF- κ B signaling [57, 58].

Other strategies to manipulate astroglial IKK/NF- κ B signaling include the Cre-mediated deletion of components of the IKK complex to block NF- κ B activation [45], or deletion of I κ B α to enhance astroglial NF- κ B signaling [59].

A number of studies using these or similar approaches have revealed important functions of astroglial NF- κ B signaling in normal CNS development and homeostasis, as well as critical roles in the regulation of astroglial responses to pathological conditions.

5.1. Astroglial IKK/NF- κ B signaling is a central regulator of neuroinflammation

In line with the key role of IKK/NF- κ B signaling in the regulation of inflammation in other cell types, and the important role of astrocytes in neuroinflammation, a number of studies have established that astroglial IKK/NF- κ B activation is a critical step in the initiation and propagation of neuroinflammatory processes.

In the initial description of the GFAP-I κ B α -dn model, it was shown that IKK/NF- κ B inhibition in astrocytes in SCI reduced the expression of the proinflammatory chemokines CCL2 (MCP-1) and CXCL10 (IP-10), which are important regulators of immune cell recruitment [56]. This study also showed that the upregulation of the astrogliosis-promoting cytokine TGF β 2 after SCI is mediated by astroglial NF- κ B signaling [56].

A subsequent study on the role of NF- κ B signaling in experimental autoimmune encephalitis (EAE), a model of MS, showed that inhibition of NF- κ B signaling in all neuroectodermal cells (Nes-Cre/NEMO fl/fl and Nes-Cre/IKK2 fl/fl) prominently reduced the expression

of a large spectrum of inflammatory mediators in this pathology [45]. This study indicated that inhibition of astroglial NF- κ B signaling was predominantly responsible for this amelioration of neuroinflammation, which was confirmed later by astrocyte-specific NF- κ B inhibition using the GFAP-I κ B α -dn model [60]. GFAP-I κ B α -dn transgenic mice in this study showed a similar reduction of the expression of inflammatory mediators after EAE [60]. These mediators included various chemokines and cell adhesion molecules involved in the recruitment of peripheral immune cells, and the major proinflammatory cytokines TNF, IL-1 β and IFN- γ , as well as inflammatory effector genes like complement factors [45, 60].

These findings suggest that astroglial IKK/NF- κ B signaling is important for the recruitment and activation of immune cells in neuroinflammatory conditions. Indeed, in both mentioned models, a reduced infiltration of immune cells after EAE induction was found in mice with inhibited astroglial IKK/NF- κ B signaling [45, 61], although originally also an increase of (regulatory) T cell infiltration was described for the GFAP-I κ B α -dn model [60].

Similar to the situation in EAE and SCI, inhibition of astroglial NF- κ B signaling by GFAP-I κ B α -dn also resulted in a reduced induction of multiple proinflammatory factors in models of retinal ischemia-reperfusion injury [62] and optic neuritis [63]. While this reduced microgliosis and astrogliosis in ischemic injury [62], infiltration of peripheral immune cells in optic neuritis was not obviously altered, although this was not quantified in this study [63].

Overall, these studies demonstrate that astroglial NF- κ B signaling mediates the coordinated induction of various inflammatory mediators in various neuropathologies. However, the consequences of this proinflammatory signaling for local glial reactivity and the infiltration of peripheral immune cells depend on the specific pathological context. Whether these context-dependent effects in different pathologies are due to different levels of NF- κ B activation, or whether additional signaling pathways are required for astrocytes to modulate neuroinflammation, was not investigated by these studies. Also, they could not address the question, whether astroglial NF- κ B activation can only modulate neuroinflammation induced by other processes in these specific pathologies, or whether it is actually a driving force of neuroinflammation, which is sufficient to initiate neuroinflammation.

To address these questions, we generated the GFAP:tTA/tetO.IKK2-CA model, which allows astroglial NF- κ B activation in normal physiological conditions, that is, in the absence of an external pathogenic trigger that could induce neuroinflammation [57]. Remarkably, both in the developing, early postnatal brain and in the adult brain, the selective activation of astroglial NF- κ B in this model was sufficient to initiate and maintain a prominent global neuroinflammatory response [57, 58, 64]. This inflammatory response was characterized by strong astrogliosis and microgliosis, as well as a prominent infiltration of innate immune cells, and, in adult animals, also T cells [57, 58, 64]. On a molecular level, in particular the chemokines CCL2(MCP-1), CCL5(Rantes) and CXCL10(IP-10), the cell adhesion molecule Madcam1, the MHC class II protein CD74 and some acute phase effector genes (Lcn2, C3) were highly upregulated by astroglial IKK/NF- κ B activation [57, 58]. These inflammatory mediators and

effectors were upregulated both in brain tissue and in primary astrocytes, suggesting that they are direct targets of IKK/NF- κ B signaling in astrocytes [57, 58]. In contrast, TNF and IL-1 β were induced in adult cerebellar tissue of these animals [58], but not in primary astrocytes [57]. This indicates that these major proinflammatory cytokines are not direct NF- κ B targets in astrocytes, but that they are produced by other cell types as an indirect consequence of astroglial IKK/NF- κ B activation.

In conclusion, these studies show that astroglial IKK/NF- κ B signaling is a key regulator of inflammatory responses in the CNS, whose activation is required and can be sufficient to initiate and maintain neuroinflammation. Specifically, astroglial IKK/NF- κ B activation alone is sufficient to induce the infiltration of peripheral immune cells into the brain, probably via the strong induction of chemokines. However, in specific disease contexts this can also occur independently of astroglial IKK/NF- κ B signaling, and other cell types or signaling pathways are likely required for the production of major cytokines to activate these immune cells. Furthermore, astroglial IKK/NF- κ B activation can trigger astrogliosis and induce a number of acute phase response factors, which might be important for the rapid response of the CNS to acute pathological insults, to limit potential further damage, for example, in an infection or injury.

5.2. Astroglial IKK/NF- κ B activation can interfere with postnatal brain development

Astrocytes and related cell types, like radial glia, have important functions in CNS development [1], and neuroinflammatory conditions like brain infections, which are associated with NF- κ B activation in astrocytes, are known to be major risk factors for neurodevelopmental disorders [65, 66]. This suggests that NF- κ B-mediated astroglial responses during CNS development might contribute to the pathogenesis of such inflammation-associated neurodevelopmental disorders.

Indeed, in line with this hypothesis, we found that constitutive activation of astroglial IKK/NF- κ B signaling during early postnatal brain development in the GFAP.tTA/tetO.IKK2-CA model resulted in lethality due to neuroinflammation-associated hydrocephalus formation [57]. Hydrocephalus is a known complication of neuroinflammatory insults, in particular during brain development [57]. In the GFAP.tTA/tetO.IKK2-CA model, hydrocephalus formation was caused by impaired differentiation of the ependymal cells lining the cerebral ventricles, which failed to develop motile cilia [57]. These cilia are required to facilitate the flow of the cerebrospinal fluid through the cerebroventricular system, and defects of these cilia can cause hydrocephalus also in other mouse models [57]. Ependymal cells are closely related to astrocytes and develop postnatally from radial glia, which are common progenitors of both astrocytes and ependymal cells [2]. Thus, at least some ependymal cells expressed the IKK2-CA transgene [57]. Therefore, it is not clear whether this defect is cell-intrinsic, or whether non-cell-autonomous effects of astrocyte-mediated neuroinflammation contribute to this defect [57]. Beyond hydrocephalus formation, astroglial IKK/NF- κ B activation in the GFAP.tTA/tetO.IKK2-CA model resulted in additional defects in late developing brain regions, specifically in a disorganization of the hippocampus, most prominently

in the dentate gyrus, and a delayed maturation of the cerebellum [57]. These defects might be caused by an impaired migration of neural progenitors, as this migration is guided by chemokine gradients, which are likely disturbed by the massive NF- κ B-mediated upregulation of chemokines by astrocytes, and the overall inflammatory environment [57].

These findings demonstrate that astroglial IKK/NF- κ B activation can interfere with normal brain development, providing a potential molecular link between neuroinflammation and neurodevelopmental disorders. On the other hand, inhibition of IKK/NF- κ B signaling in astrocytes does not cause obvious defects of brain development and homeostasis [45, 56]. Therefore, it will be interesting to study to what extent inhibition of astroglial IKK/NF- κ B signaling can ameliorate inflammation-associated neurodevelopmental defects.

5.3. Roles of astroglial IKK/NF- κ B signaling in normal adult brain homeostasis and function

Mice with IKK/NF- κ B inhibition in astrocytes do not show obvious phenotypes in normal physiological conditions [45, 56], demonstrating that astroglial NF- κ B signaling is not broadly required for normal brain development, homeostasis and function. However, two studies reported subtle behavioral phenotypes of mice with reduced basal astroglial IKK/NF- κ B signaling, specifically a sex-specific impairment in learning and memory in female GFAP-I κ B α -dn mice [67], and reduced food intake in mice with Cre-mediated astroglial IKK2 inactivation (GFAP-Cre/IKK2 fl/fl) [68].

On the other hand, as described in Section 5.1, activation of astroglial IKK/NF- κ B signaling in normal physiological conditions in the adult brain in the GFAP.tTA/tetO.IKK2-CA model induces prominent global neuroinflammation [58, 64]. This indicates that activation of IKK/NF- κ B signaling in astrocytes might have more severe consequences for brain homeostasis and function than its inhibition. Interestingly however, this prominent global neuroinflammatory phenotype had obvious consequences for brain homeostasis only in one specific brain region, the cerebellum [58]. In the cerebellum, with some delay massive neurodegeneration was observed, which predominantly affected Purkinje cells, the output neurons of the cerebellum and resulted in severe motor impairment [58]. This was found to be due to the dysfunction of the Bergmann glia, a specific population of astrocytes with radial glia-like morphology, which is essential for the function and survival of the Purkinje neurons [58]. IKK2 activation in Bergmann glia resulted in prominent astrogliosis-like alterations, including prominent upregulation of GFAP and morphological alterations disrupting their specialized morphology [58]. These alterations were shown to represent an irreversible “point of no return” resulting in inevitable Purkinje cell degeneration [58]. Of note, this phenotype resembles alterations found in inflammatory cerebellar neurodegenerative disorders, for example, in paraneoplastic cerebellar degeneration, which are also characterized by prominent selective Purkinje cell degeneration [58]. Therefore, these findings suggest a mechanism how cerebellar neuroinflammation caused by various insults might result in the common pathology of Purkinje cell degeneration: Inflammation-induced IKK/NF- κ B activation in Bergmann glia would cause irreversible Bergmann glia dysfunction, which consequentially would drive Purkinje cell degeneration [58].

Interestingly, it was also found that astroglial IKK/NF- κ B activation in the GFAP.tTA/tetO.IKK2-CA model resulted in the downregulation of the glutamate transporters EAAT1 (GLAST) and EAAT2 (GLT-1) in the cerebellum and the medulla oblongata [58]. Downregulation of these transporters is found in many neurological disorders, including cerebellar neurodegenerative disorders, and is believed to contribute to the pathogenesis of these disorders [18, 69]. By impairing the uptake of the excitatory neurotransmitter glutamate by astrocytes, downregulation of these transporters can result in neuronal hyperexcitation and excitotoxic neurodegeneration [18, 69].

Another recent study found that astroglial IKK/NF- κ B activation also impairs the astroglial uptake of the neurotransmitter GABA, at least in the hypothalamus, which resulted in increased activity of specific neurons in hypothalamic nuclei [68]. In this model, a constitutively active IKK2 allele was activated by GFAP-Cre-mediated recombination (GFAP-Cre/Rosa26-LSL-IKK2CA) [68]. This resulted in more moderate astroglial IKK/NF- κ B activation, which was not sufficient to induce neuroinflammation in heterozygous mice [68]. In this model, astroglial IKK/NF- κ B activation led to mild astrogliosis-like changes, specifically increased astrocyte numbers and altered morphology (shortened processes) [68]. These alterations resulted in changes in the systemic metabolism, which is controlled by the hypothalamus, specifically in a metabolic syndrome-like phenotype with insulin resistance, increased blood pressure and increased fat deposition [68].

Given the important functions of astrocytes in neuronal metabolism and signaling, and their prominent alterations in pathological conditions, it is likely that astroglial IKK/NF- κ B activation also causes additional more subtle alterations in neuronal communication in the CNS. Indeed, we have found a moderate reduction of striatal dopamine levels in the GFAP.tTA/tetO.IKK2-CA model [64]. However, more research is needed to examine the functions of astroglial IKK/NF- κ B in the modulation of neurotransmitter signaling.

Another mechanism beside the uptake of neurotransmitters and release of gliotransmitters, by which astrocytes modulate neuronal communication, is the regulation of synapse formation, maturation and elimination. On a molecular level, complement proteins, including C3, which is highly induced by astrocytes upon NF- κ B activation, contribute to the elimination of synapses [70]. Indeed, it has recently been demonstrated, that astroglial NF- κ B activation by GFAP-Cre-mediated I κ B α deletion promotes synapse elimination and alters neuronal signaling via C3 induction [70].

5.4. Roles of astroglial IKK/NF- κ B signaling in models of specific pathological conditions

Astrogliosis and neuroinflammatory processes are occurring in most neurological disorders, most prominently in autoimmune/inflammatory disorders and acute injury. Often these processes contribute to the pathogenesis of these disorders, but depending on the conditions they can also have protective roles. Astroglial IKK/NF- κ B signaling is a key regulator of these pathophysiological responses, therefore a number of studies have addressed the role of astroglial IKK/NF- κ B signaling in specific CNS disease and injury models.

The first neuropathological condition, in which the role of astroglial NF- κ B signaling was studied using the GFAP-I κ B α -dn model, was SCI, a condition in which inflammatory processes are believed to prominently contribute to pathogenesis [56, 71]. In line with the idea that astroglial NF- κ B signaling promotes neuroinflammation and that this aggravates pathogenesis of SCI, functional recovery was improved in mice with inhibited astroglial NF- κ B signaling [56]. Histologically, microgliosis and astrogliosis were less pronounced in the absence of astroglial NF- κ B signaling after SCI [71]. This was associated with improved white matter preservation, probably due to reduced secondary inflammatory white matter damage [56], which also improved axonal integrity [71]. Also, a reduced intra-lesional deposition of chondroitin sulfate proteoglycans (CSPGs) was observed [56]. CSPGs are important components of the glial scar, which interfere with regenerative axonal outgrowth [56]. In this model of contusive SCI, even some degree of axonal sprouting across the lesion was observed upon inhibition of astroglial NF- κ B signaling, but not in wildtype animals [71]. This indicates that NF- κ B-mediated scar formation contributes to the inability of the CNS to regenerate lost axons. However, this regenerative response was not able to bridge the lesion in a complete spinal cord transection, showing that astroglial NF- κ B inhibition is not sufficient to allow axonal regeneration [71]. In conclusion, these studies show that astroglial NF- κ B signaling might contribute to the pathogenesis of SCI by aggravating inflammatory secondary tissue damage and by interfering with regenerative processes.

Another well studied neurological disorder with an obviously strong inflammatory pathogenic component is MS, the most common autoimmune disease of the CNS. A number of studies have therefore investigated whether astroglial NF- κ B signaling contributes to pathogenesis of demyelination in this disease [45, 60, 61, 63, 72, 73].

In an early study indicating that indeed astroglial NF- κ B signaling might contribute to MS pathogenesis, the core components of the IKK complex were inactivated in neuroectodermal cells (neurons, astrocytes and oligodendrocytes) in a mouse model using nestin-promoter driven Cre expression (Nes-Cre \times IKK1 fl/fl or IKK2 fl/fl or NEMO fl/fl) [45]. After induction of EAE, mice with conditional IKK2 and NEMO inactivation, but not with IKK1 inactivation, displayed prominently reduced neurological deficits [45]. This indicates that canonical, but not non-canonical NF- κ B signaling in astrocytes, oligodendrocytes and neurons, contributes to EAE pathogenesis [45]. These reduced neurological deficits were accompanied by reduced demyelination and immune cell infiltration, and a reduced expression of proinflammatory genes in primary astrocytes [45]. Because microglia and astrocytes are the main cell types in the CNS parenchyma that regulate inflammatory processes, and microglia are not targeted by the Nes-Cre-driven ablation approach, the authors concluded that reduced proinflammatory signaling by NF- κ B inhibition in astrocytes is likely responsible for the amelioration of the phenotype [45]. This hypothesis was confirmed by astrocyte-specific NF- κ B inhibition in EAE in the GFAP-I κ B α -dn model [60, 61]. Astrocyte-specific NF- κ B inhibition in this model also reduced neurological deficits after EAE induction, along with a reduced expression of inflammatory mediators, and led to improved remyelination and neuronal survival at chronic stages [60, 61]. Vice versa, GFAP-Cre-mediated inactivation

of A20, a negative feedback regulator of NF- κ B signaling, in astrocytes, increased expression of proinflammatory NF- κ B target genes and inflammatory infiltration after EAE, which resulted in aggravated neurological deficits and demyelination [72]. Interestingly, the observed myelin preservation after inhibition of astrocyte-specific NF- κ B signaling is not restricted to EAE, which is driven by an autoimmune attack, that is, a very strong inflammatory insult. Increased myelin preservation was also observed in a model of cuprizone-induced toxic demyelination, where inflammatory events are not the primary cause but rather a co-pathogenic consequence of the myelin damage [73]. This indicates that NF- κ B-mediated astroglial responses contribute to the pathogenesis of demyelination not only by inflammatory signaling, for example, by promoting the recruitment of peripheral immune cells, but that astrocytes gain additional pathogenic properties after NF- κ B activation. In line with this idea, demyelination in the optic nerve, one of the earliest symptoms of MS, is reduced in EAE in the GFAP-I κ B α -dn model even without any obvious differences in local immune cell infiltration [63]. It was proposed that astroglial NF- κ B signaling in the latter paradigm contributes to myelin damage by increasing oxidative stress, as it induces the NAD(P)H oxidase subunits Cybb/NOX2 and Ncf1 [63].

Overall, these studies provide clear evidence that activation of NF- κ B-mediated inflammatory responses of astrocytes aggravate demyelination and associated neurological defects in different animal models, indicating that these NF- κ B-mediated astrocytic responses likely contribute to the pathogenesis of MS and other demyelinating disorders.

For other neurological disorders, the functions of astroglial NF- κ B signaling are less well studied.

In a model of ischemic retinal injury, astroglial NF- κ B inhibition in GFAP-I κ B α -dn mice was shown to be neuroprotective, likely by suppressing the induction of Nos2 (iNos) and NADPH-oxidase genes after ischemia [62, 74]. This resulted in a reduction of oxidative stress, a crucial pathogenic factor in ischemia, at least in vitro [62, 74]. In contrast, an earlier study using a model with a different astrocyte-specific dominant-negative I κ B α transgene did not find any consequences of astroglial NF- κ B inhibition for the pathogenesis of cerebral ischemia [75].

A reduction of the expression of the oxidative stress promoting enzyme iNos by astroglial NF- κ B inhibition in GFAP-I κ B α -dn mice was also found in a model of hepatic encephalopathy [76]. In this model, astroglial NF- κ B inhibition had a protective effect due to a prominent reduction of astrocyte swelling and edema formation [76].

These findings, as the described similar findings in EAE/optic neuritis [63], indicate that astroglial NF- κ B signaling increases oxidative stress, which might contribute to the pathogenesis of a range of neuroinflammation-associated neuropathological conditions.

Classical chronic neurodegenerative disorders like AD, PD or ALS are also associated with neuroinflammatory processes, which are believed to contribute to the pathogenesis of these diseases. However, only few studies so far have addressed the role of astroglial NF- κ B signaling in models of chronic neurodegeneration.

One study found that A β can activate NF- κ B in astrocytes, resulting in C3 induction [70]. Further, this study showed that in AD C3 levels are elevated, and that inhibition of the C3 receptor C3aR can revert memory deficits in a mouse model of AD [70]. This suggests that astroglial NF- κ B activation via C3 induction might contribute to AD pathogenesis. However, a direct link of astroglial NF- κ B activation and disease pathogenesis in AD has yet to be demonstrated.

To study the role of astroglial NF- κ B signaling in PD, we have analyzed the consequences of enhanced NF- κ B activation in astrocytes in GFAP.tTA/tetO.IKK2-CA mice for neurodegeneration in the MPTP model of PD [64]. In this paradigm, astroglial NF- κ B activation did not affect the degeneration of dopaminergic neurons in the substantia nigra, despite inducing prominent neuroinflammation in this brain region [64]. This argues against a prominent role of astroglial NF- κ B signaling in PD pathogenesis. However, the mechanism of degeneration in this toxin-induced dopaminergic neurodegeneration model differs from the mechanism of degeneration in PD, therefore studies in other models of PD should be undertaken to further elucidate the role of astroglial NF- κ B signaling in PD.

Finally, one study inhibited astroglial NF- κ B signaling in a mouse model of ALS, using another independent GFAP-I κ B α -dn transgenic mouse line [77]. Rather unexpectedly, despite the well documented contribution of astrocytes to ALS pathogenesis and a delayed onset of astrogliosis and microgliosis in this model, no alterations in disease onset or progression were found in this model [77]. This argues against a prominent contribution of astroglial NF- κ B signaling to astrocyte dysfunction and neurodegeneration in ALS.

In conclusion, although astrocytes have crucial functions in neuroinflammation and neuronal homeostasis, and neuroinflammation and astrocyte dysfunction are widely accepted as pathogenic mechanisms in chronic neurodegeneration, direct evidence for the contribution of astroglial NF- κ B signaling to the pathogenesis of these disorders is scarce. Given the huge socioeconomic impact of these disorders, and the prominent role of astroglial NF- κ B signaling on the pathogenesis of other neurological disorders, further studies should address the role of astroglial NF- κ B signaling in chronic neurodegeneration in more detail.

6. Other signaling pathways regulating pathophysiological responses of astrocytes: an overview

Although we have focused here on the role of NF- κ B signaling in the regulation of pathophysiological responses of astrocytes, several other signaling pathways have been implicated in these responses. Interestingly, many pathways involved in astrocyte reactivity are also required for astrocyte differentiation in development. Activation of these pathways in pathological conditions seems to promote a partial de-differentiation of astrocytes, resembling more immature stages of astrocyte differentiation with increased proliferative and lineage potential.

One of these key developmental pathways contributing to astrocyte reactivity is the JAK/STAT3 pathway, which is activated by cytokines of the IL-6 family, like IL-6, LIF and CNTF [78, 79]. This pathway is closely interconnected with the NF- κ B pathway, as, for example, IL-6 is induced in many inflammatory conditions, also by NF- κ B activation in astrocytes [58]. Vice versa, JAK/STAT3 signaling induces target genes that are also induced by NF- κ B signaling, like CXCL10 and LCN2 [78]. STAT3 activation in the context of pathological conditions was shown to be a crucial driver of astrocyte hypertrophy and GFAP induction, two major hallmarks of astrogliosis [78]. Indeed, STAT3 directly regulates GFAP expression, in cooperation with SMAD transcription factors, which are activated by BMP and TGF β signaling, another signaling system implicated in astrogliosis [80].

Interestingly, while both NF- κ B and STAT3 signaling promote astroglial scar formation in SCI, STAT3 regulated aspects of astroglial scar formation seem to promote repair and regeneration [20], whereas NF- κ B regulated aspects rather interfere with repair processes [56, 71]. This indicates that different types of astroglial scars exist, which are regulated by different molecular mechanisms and which can influence regeneration in different ways. Therefore, future studies should further investigate these mechanisms, as this might open up new strategies to promote regeneration after CNS damage, by converting astroglial scars to more pro-regenerative states.

STAT3 signaling also contributes to the proliferative response of astrocytes observed after acute injury [78], a response which is also regulated by Sonic hedgehog (SHH) signaling [21]. Interestingly, this proliferative response seems to be directly linked to the acquisition of NSC-like properties of astrocytes after injury, which similar to NSCs and immature astrocytes, can form multipotent neurospheres *in vitro* [21, 81]. This indicates that astrocytes after injury can partially de-differentiate, and can regain increased lineage plasticity, including the potential to generate new neurons. Indeed, recent studies have demonstrated that at least in the striatum, some astrocytes can generate neurons *in vivo* after cell cycle re-entry in response to ischemic or excitotoxic injury [25, 26]. In ischemic injury, this reactivation of proliferation and subsequent neurogenesis was associated with reduced Notch signaling [25], another pathway which is required for astrocyte differentiation and maturation, and which is also controlling NSC quiescence [82, 83].

This study further showed that genetic activation of Notch signaling can suppress this proliferative and neurogenic response in ischemia [25]. Vice versa, inhibition of Notch signaling in astrocytes by conditional RBPJ deletion is sufficient to elicit a neurogenic response in some striatal astrocytes [25]. These results indicate that Notch signaling is crucial to maintain the mature, quiescent state of astrocytes, and that downregulation of Notch signaling promotes a de-differentiation response of astrocytes in pathological conditions.

It will be important to further dissect the mechanisms governing these neurogenic de-differentiation responses of astrocytes, which might open up new strategies for regenerative medicine. This could allow enhancing endogenous neuronal replacement in neurodegenerative conditions and improving the efficiency of neuronal reprogramming of astrocytes.

7. Conclusions and future directions

As we have described in this chapter, astrocytes are functionally diverse and plastic cells that are highly responsive to changes in the CNS microenvironment.

In most CNS pathologies, including acute injuries, autoimmune/inflammatory disorders like multiple sclerosis, and chronic neurodegenerative diseases like Alzheimer's disease, astrocytes show prominent pathophysiological responses, often rather superficially described with the unifying terms astrogliosis or astrocyte reactivity. These responses share common features, but include also many distinct aspects in different CNS pathologies, and can have important protective or pathogenic consequences in these pathologies.

Therefore, understanding the precise mechanisms as how these responses are controlled and how they influence CNS development, homeostasis and pathology, is highly relevant for translational and clinical neuroscience.

A large spectrum of extracellular signals activating several intracellular signaling pathways regulates the pathophysiological responses of astrocytes. One central signaling hub integrating many of these extracellular signals is the IKK/NF- κ B signaling pathway. A number of studies summarized here have established that the IKK/NF- κ B pathway in astrocytes is a key regulator of neuroinflammatory responses. These studies also demonstrated that astroglial IKK/NF- κ B activation interferes with normal CNS development and homeostasis and contributes to the pathogenesis of various CNS disorders in mouse models.

These findings have important implications for the development of new strategies for the treatment of CNS disorders. Although pharmacological targeting of the IKK/NF- κ B pathway has proven to be difficult due to its broad spectrum of functions, it might be an option for some very specific conditions, where a transient inhibition of a particularly strong inflammatory response might be beneficial, for example, in acute stages of autoimmune disorders or injury. In addition, the further investigation of the effector pathways of IKK/NF- κ B signaling in astrocytes will hopefully identify specific aspects of this broad response that can be targeted with more selective approaches. Such approaches could include, for example, the inhibition of specific chemokines or the complement system, the prevention of the morphological changes of astrocytes that might cause disruption of the blood-brain-barrier or neuronal support functions, or the restoration of neurotransmitter uptake by astrocytes. Another important, unsolved question is, in which conditions astroglial NF- κ B activation is actually beneficial. In most conditions investigated so far, astroglial NF- κ B activation seems to have detrimental effects, but as this response is evolutionary conserved, it should have beneficial effects in some circumstances. One could speculate that acute CNS infections might require astroglial NF- κ B activation to allow a rapid and strong response to stop spreading of the pathogens and to allow their efficient clearance. However, this has not been experimentally demonstrated yet.

As only shortly summarized here, also other signaling pathways have important functions in the regulation of astroglial responses to pathological insults, which, except for JAK/STAT signaling,

have received only relatively limited attention so far. The functions of these pathways in astrocytes should be investigated in more detail in future studies, and the functional interaction of these pathways with each other has to be elucidated. Manipulation of the balance of these pathways might allow to improve regenerative responses of astrocytes, as indicated, for example, by the detrimental versus beneficial roles of NF- κ B and STAT3 signaling in astroglial scars for regeneration in spinal cord injury models.

Finally, the investigation of the mechanisms which regulate the only recently recognized neurogenic responses of astrocytes, offers an exciting perspective for regenerative medicine. It might uncover approaches to stimulate endogenous replacement of lost neurons, which is an important mechanism of CNS repair in lower vertebrates, but has been largely lost in mammals.

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