

Review Article – Submitted 8 June 2007 – Accepted 13 December 2007

Neural stem cells, inflammation and NF- κ B: basic principle of maintenance and repair or origin of brain tumours?

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Keywords: neural stem cells, brain tumours, inflammation, NF-kappaB

This is an Accepted Work that has been peer-reviewed and approved for publication in the *Journal of Cellular and Molecular Medicine*, but has yet to undergo copy-editing and proof correction. See <http://www.blackwell-synergy.com/loi/jcmm> for details. Please cite this article as a "Postprint";10.1111/j.1582-4934.2007.00208.x

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Abstract

Several recent reports suggest that inflammatory signals play a decisive role in the self-renewal, migration and differentiation of multipotent neural stem cells (NSCs). NSCs are believed to be able to ameliorate the symptoms of several brain pathologies through proliferation, migration into the area of the lesion and either differentiation into the appropriate cell type or secretion of anti-inflammatory cytokines. Although NSCs have beneficial roles, current evidence indicates that brain tumours such as astroglomas or ependymomas are also caused by tumour-initiating cells with stem-like properties. However, little is known about the cellular and molecular processes potentially generating tumours from NSCs.

Most pro-inflammatory conditions are considered to activate the transcription factor NF- κ B in various cell types. Strong inductive effects of NF- κ B on proliferation and migration of NSCs have been described. At the same time, NF- κ B is constitutively active in most tumour cells described so far. Chronic inflammation is also known to initiate cancer. Thus NF- κ B might provide a novel mechanistic link between chronic inflammation, stem cells and cancer.

This review discusses the apparently ambivalent role of NF- κ B: physiological maintenance and repair of the brain via NSCs, and a potential role in tumour initiation. Furthermore, it reveals a possible mechanism of brain tumour formation based on inflammation and NF- κ B activity in NSCs.

Neural Stem Cells

During mammalian central nervous system (CNS) development, multipotent cells undergo division, cell fate specification and maturation. These neural stem cells (NSCs) are commonly defined as undifferentiated cells with the ability to proliferate, exhibit self-renewal, generate a large number of progeny including the principal phenotypes of nervous tissue, and retain their differentiation potential over time. Within the adult brain NSCs are mainly located in the subventricular zone (SVZ) and the dentate gyrus of the hippocampus.

NSCs are believed to have the capacity to replace lost cells within the CNS, thus offering a potential starting point for therapy of neurodegenerative diseases such as Parkinson's and Alzheimer's disease [1,2]. They also provide a promising method for treating brain cancers by delivering chemotherapeutic agents directly to the tumour cells (reviewed in [3]). On the other hand, multipotent subsets of NSCs such as radial glia are believed to generate all the phenotypically diverse cells that populate brain tumours (for review see [4]).

NF- κ B

The transcription factor NF- κ B plays a pivotal role in a variety of biological processes including innate and adaptive immunity (reviewed in [5]), neuroprotection and degeneration (reviewed in [6] and [7]), learning and memory formation and pathological tumour malignancies (reviewed in [8] and [9]). In particular NF- κ B has distinct functions in multiple immune cell types via the regulation of target genes essential for cell proliferation, survival, effector functions and cell trafficking [10-12].

In the nervous system NF- κ B is known to mediate either neuroprotection or apoptosis in a stimulus depending manner [13]. Concerning memory formation NF- κ B regulates spatial memory formation, synaptic transmission, and plasticity through protein kinase A/CREB signalling as demonstrated in a forebrain neuronal conditional NF- κ B-deficient mouse model [14].

The NF- κ B protein family comprises p50, p52, p65, RelB and c-Rel, which form different heterodimeric complexes (reviewed in [15]). The most common NF- κ B dimer within the CNS, p50-p65, exists as an inactive cytoplasmic complex bound to inhibitory proteins of the I κ B family (see [6] for review). The trimeric NF- κ B-I κ B complex can be activated by several stimuli such as inflammatory cytokines, neurotransmitters, mitogens and growth factors (reviewed in [16] and [6]).

TNF- α

Tumour necrosis factor-alpha (TNF- α) is one of the best-characterized mediators of inflammation. Among the cells of the haematopoietic system, TNF- α is mainly secreted by macrophages, monocytes, neutrophils, T-cells and NK-cells after stimulation with bacterial

lipopolysaccharides (LPS). In the event of pathological alterations within the CNS, TNF- α is secreted by astrocytes and microglial cells [17,18]. TNF- α synthesis is induced by several different stimuli including interferons (IFN), interleukin 2 (IL2) and GM-CSF, whereas it is inhibited by IL6, TGF- β 2 and dexamethasone [19].

In eukaryotes, members of the TNF receptor superfamily play pivotal roles in several biological processes like haematopoiesis, protection from bacterial infection, and immune surveillance [19-24].

On the other hand, dysregulation of TNF and its superfamily members leads to various pathological symptoms like diabetes (Type II), heart failure, arteriosclerosis, tumourigenesis and tumour metastasis [25-28].

Activation of this family of receptors leads to activation of multiple signal transduction pathways including NF- κ B signalling [29].

NF- κ B activation via TNF- α

NF- κ B can be activated by a wide range of stimuli including endotoxins (e.g. lipopolysaccharides), hypoxia, cytokines or bacterial and viral infection (see [16] for review). During inflammation, the activation of NF- κ B is mediated mainly by TNF- α . In this canonical NF- κ B activation pathway, the TNF ligand binds to the receptor, thereby transducing the signal to the I κ B kinase (IKK) complex. This complex in turn leads to phosphorylation, ubiquitinylation and finally proteasomal degradation of the inhibitory I κ B (reviewed in [6]). NF- κ B is thereby released, enabling it to be translocated to the nucleus where it binds to specific promoter regions on the DNA, and finally the target genes are transcribed (see NF- κ B target genes affecting NSCs and tumour formation).

Inflammation, NF- κ B and neural stem cells

Brain inflammation is a complex phenomenon. In addition to the well-described neurodegenerative effect of inflammation, several studies suggest that inflammatory signals influence NSCs in respect of proliferation, migration and differentiation leading either to functional integration and improvement of the symptoms of inflammation or to secretion of anti-inflammatory cytokines by the NSCs [15,30-39].

As described above, much inflammatory signal transduction can be considered an innate immune response triggered by TNF [40,41]. The transcriptional profile of TNF-treated astrogloma cells has been investigated by Schwamborn et al as a model for brain inflammation [42]. In this study, more than 800 TNF-regulated genes have been found and analysed by microarray analysis. Macrophage Chemoattractant Protein 1 (MCP-1) gene expression was demonstrated to be strongly up-regulated and secreted into the medium as showed by immunocytochemistry and ELISA.

It is well known that NSCs express various chemokine receptors as a result of brain pathology (for review see [43] and [15]). In addition to MCP-1, expression of stromal derived factor 1 α (SDF1- α) [34], stem cell factor (SCF) [33] and vascular endothelial growth factor has been reported [44]. Subsequent experiments provided strong evidence that MCP-1 induces NSC migration [35].

In view of the well characterized TNF secretion in the course of inflammatory diseases and the very potent induction of NSC migration by MCP-1, it has been proposed that in pathological situations like neuroinflammation these cells migrate from the SVZ to the area of the lesion. Belmadani et al showed that in hippocampal slice cultures eGFP-labeled neural progenitors migrate toward injected inflammatory stimuli and that chemokines are the major regulators of this process [38].

Functional chemokine signalling strongly depends on expression of the relevant receptors.

Robust *in vivo* expression of chemokine receptors in neurogenic regions of the brain has been recently demonstrated [45]. In this report, Tran and colleagues clearly showed the expression of CCR1, CCR2 (the cognate MCP-1 receptor), CCR5, CXCR3 and CXCR4 on NSCs in the dentate gyrus of the hippocampus, SVZ and olfactory bulb. These findings accord with a model proposed by Muller et al. stating that NSCs are attracted by inflammation, reactive astrocytosis and angiogenesis [43].

Thus, NSCs are exposed after migration to TNF at the area of inflammation. In this context, it is noteworthy that TNF-induced NF- κ B activity results in increased proliferation of NSCs ([31,32]). After migration and proliferation, NSCs may participate in the repair process. In accordance with this hypothesis, Pluchino et al. showed that NSCs are able to promote neuroprotection during CNS inflammation [30]. This phenomenon might be explained either by secretion of neuroprotective cytokines or by functional integration of the proliferated NSCs. In addition, the transplanted NSCs exerted immune-like functions by inducing apoptosis of blood-borne CNS-infiltrating encephalitogenic T cells [30].

In summary, the function of NF- κ B in NSCs during acute inflammation consists in the increase of proliferation and in migration.

Inflammation, NF- κ B and cancer

Inflammation is prerequisite for wound healing, elimination of infections and regeneration after pathological situations via, *inter alia*, the migration, proliferation and differentiation of stem cells (see above). On the other hand, cancer is associated with maladaptive chronic inflammation.

In the 19th century, Rudolf Virchow hypothesized that chronic inflammation may cause several malignancies including cancer [46-48]. Interestingly, one of the most prominent inflammatory cytokines – TNF- α (see above) - is known to activate NF- κ B strongly

in several experimental cancer models and to act as a potent tumour promoter (reviewed in [9]). Brain tumours were demonstrated to express TNF receptors like TNFRI, TNFRII, DR6, Fas or Fn14 and the TNF receptor associated signalling molecules consisting of TRAIL-R1, TRAIL-R2, TRAIL, TRAF1, TRAF2 and TANK/I-TRAF [49-56]. In addition brain tumours express the chemokine receptors CXCR4, CCR1, CCR3, CCR5 and CCR2 [57-59].

The role of NF- κ B in cancer development and progression has been extensively discussed ([8,16,60-67]). In particular, the activation of NF- κ B blocks apoptosis via modulation of anti-apoptotic target genes such as c-IAP, bcl-2 and bcl-xL and mediates tumour cell proliferation via up-regulation of targets like cyclin-D1 and c-myc [51,68-76].

It also induces resistance to chemotherapeutic agents. In fact, numerous genes involved in tumour initiation, promotion and metastasis are regulated by the NF- κ B pathway (for review see [63], [16]). NF- κ B is constitutively active in most tumour specimens described to date (reviewed in [16] and [9]).

NSCs and brain cancer

Cancer is defined as a progressive disease, typically requiring initial mutations in proliferating cells. Physiologically, proliferation is tightly controlled and restricted to only a few cell types, including stem cells. In this context it is noteworthy that the “immortal strand hypothesis” postulates that during the process of self-renewing primitive stem cells retain DNA strands with the fewest mutations acquired during DNA replication [77]. These stem cells remain primitive and divide slowly in asymmetric manner. The second one, more differentiated daughter cell, e.g. NSC divides fast. Thus, amplifying NSCs potentially have time to accumulate genetic mutations leading to tumour formation [78].

Recent studies on brain tumours have revealed stem-cell-like tumour cell populations. Uchida et al. described Nestin and Musashi-1 expressing cells within an infant brain tumour; this tumour was also positive for several immature neuronal and astrocytic markers [79]. Nestin - an intermediate filament [80], and Musashi, a RNA binding protein [81,82] are very well described markers for NSCs.

Hemmati et al. [83] isolated tumorigenic cells with stem cell properties from pediatric brain tumours. These neurosphere-forming, multipotent and self-renewing cells could differentiate into neural and glial lineages. Similarly, Tunici et al. [84] reported neurosphere-forming tumour cells with neural stem/precursor cell properties. Recently, Lee and colleagues found that TSCs derived directly from glioblastomas harbour extensive similarities to normal stem cells if they are cultured in bFGF- and EGF-containing media [85-87]

These similarities include the formation of neurosphere-like structures in vitro, self-renewal, terminal differentiation into glial and neuronal lineage and of gene expression profile similar to NSCs.

TSCs have also been detected in brain tumours such as ependymomas, glioblastomas and medulloblastomas (see [88] for review). Some reports provide evidence that neuroblastomas - embryonic cancers of the neural crest - contain stem cell populations as well (see [89] for review). Moreover, Taylor et al. [90] discussed radial glia as potential stem cells for ependymomas in a recent review.

In summary, similarities between stem cells and cancer stem cells have been demonstrated in cell signalling pathways, differentiation and drug resistance [91-93].

During inflammation, stem cells are believed to switch from asymmetrical divisions that give rise to differentiated progeny to rapid symmetrical divisions resulting in an increased number of undifferentiated stem cells (reviewed in [94]). Several reports show that the molecular pathways regulating asymmetrical division in stem cells control the orientation of the mitotic spindle [95,96]. The switch from asymmetrical to symmetrical cell division may increase the likelihood of aneuploidy – a frequently observed phenomenon in tumour cells.

Interestingly, Diamandis et al. [97] demonstrated in a recent report that small molecules known to affect neurotransmission pathways inhibit the proliferation of NSC also have inhibitory effects on brain cancer stem cell proliferation.

NF- κ B target genes affecting NSCs and tumour formation

In this review we focus on NF- κ B targets regulating cell-cycle, anti-apoptosis, cellular ageing and multidrug-resistance.

Several tumour specimens like malignant astrocytomas, especially glioblastomas show elevated levels of the c-myc proto-oncogene [51]. c-myc is a well described NF- κ B target with functional κ B-binding site in its promoter region [98,99]. In addition, in their study Bouragel-Rey and colleagues demonstrated that activated NF- κ B strongly induces c-myc [100]. Recently, Faria and colleagues showed a positive correlation between c-Myc expression and the histopathological grade and the proliferative status of astrocytic tumours [101].

Also many human medulloblastomas express significantly elevated levels of myc oncogenes correlated with worse clinical outcome [102-104]. The c-Myc oncoprotein is well described to be a potent mitogen for neural precursors *in vitro and in vivo* [105].

In a recent study Xiaohua et al showed that in neural stem cells an elevated expression of c-Myc and REST/NRSF, a transcriptional repressor of neuronal differentiation causes cerebellar tumours [106]. Additionally, c-Myc enhances sonic-hedgehog induced medulloblastoma formation from nestin-expressing neural progenitors [107]. Interestingly, TNF- α stimulated rat NSCs showed highly elevated c-Myc expression compared to untreated control (Widera et al. unpublished data).

All these data suggest that c-myc to be one of the NF- κ B target genes responsible for

induction of tumours from NSCs in inflammatory situations.

A further NF- κ B target gene known to trigger proliferation of tumour cells is cyclin D1. Cyclin D1 has two NF- κ B binding sites in the promoter region. The stimulation of the transcription of cyclin D1 by NF- κ B results in increased proliferation of several cell types (reviewed in [108]). Similar to c-myc, Cyclin D1 is widely up-regulated in several brain tumours like meningiomas, olfactory neuroblastomas and gliomas and is closely related to oncogenesis, proliferation of tumour cells and worse clinical prognosis [76,109,110].

In contrast loss of cyclin D1 suppresses medulloblastoma formation [111]. The NF- κ B induced up-regulation of Cyclin D1 has been identified as one of the crucial events in cell cycle progression of tumour cells [75,112].

In NSCs, Cyclin D1 seems to act in a similar manner. TNF- α treated rat NSCs show highly up-regulated Cyclin D1 expression and significantly increased proliferation compared to control cells [31]. This finding is in accordance with the hypothesis that inflammation activates the transcription factor NF- κ B resulting in transcription of target genes which induce proliferation. In contrast, dexamethasone induced ubiquitination of Cyclin D1 or downregulation of Cyclin D1 by GATA2 led to decreased proliferation of NSCs [113,114]. Thus, cyclin D1 seems to be another NF- κ B target gene potentially responsible for tumour formation and progression.

In addition to the deregulated cell cycle control, several pathways regulating apoptosis are also disrupted in brain tumours. Thus, malignant tumours often show intense resistance to apoptosis. NF- κ B is known to directly activate the apoptosis inhibitors Bcl-xL and Bcl-2. In tumours a positive correlation between high expression of NF- κ B and up-regulated levels of the target genes Bcl-xL and Bcl-2 has been demonstrated [69]. This phenomenon might partially explain the apoptosis resistance of tumours through NF- κ B driven induction of anti-apoptotic genes like Bcl-xL and Bcl-2.

One problem of many brain malignant tumours is their resistance to chemotherapy [115]. This observable fact can be explained by the expression of ATP-binding cassette (ABC) drug efflux transporters (reviewed in [116] and [117]). Mutch and colleagues clearly demonstrated that the ABC transporter ABCB2 contains a functional NF- κ B binding site in its promoter region [118]. Cells expressing ABCG2 are known to exclude Hoechst in flow cytometry, have been called side population (SP) cells [119]. Furthermore, it has been demonstrated that putative stem cells from solid tissues may also possess this SP phenotype [120].

A robust expression of ABC transporters ABCA2, ABCA3, ABCB1 and ABCG2 in NSCs has been described (reviewed in [121]). This fact suggests a potential role of these NF- κ B targets in tumour biology.

Summary

Inflammatory signals and conditions have been described as inducing NSC proliferation via activation of the NF- κ B pathway [31,122-124]. Physiologically, NSCs proliferate slowly and asymmetrically or rest in the G0-Phase of the cell cycle. In an inflammatory environment, they start to proliferate rapidly and symmetrically [94]. This may be attributable to the release of pro-inflammatory cytokines such as TNF- α from the injured tissue. In addition, the expression of mitogens like FGF-2 is increased in inflammation [125]. The expression of FGF and FGF receptors seems to be crucial for symmetrical division of embryonic and neural stem cells (self-renewal) [60-62]. Recently, evidence was provided that FGF-2 activates NF- κ B [63]. In addition, FGF-2 acts in an anti-apoptotic and pro-proliferative manner through activated NF- κ B [64,65].

After attenuation of the acute phase of the inflammation and a decrease in local concentration of pro-inflammatory signals NSCs decrease their rate of proliferation and proceed either to slow proliferation or to the resting state (G0-Phase) (see Fig 1).

In contrast, during chronic inflammation, NSCs are permanently exposed to proliferation signals. Fast proliferation holds a much higher risk of mutation than slow cell division. These fast symmetric divisions may promote the expansion of NSCs and lead to aneuploidy (see Fig. 2). In rapidly-proliferating NSCs, an initial mutation may be followed by additional mutations that ultimately lead to transformation. If the mutations occur in proto-oncogenes coding e.g. for signalling molecules activating NF- κ B, constitutive activity may lead to growth factor-independent proliferation of the transformed NSCs.

In fact, subsets of adult NSCs isolated from a long term culture might become independent of exogenous growth factors. Such growth factor independent cells still expressed typical stemness markers as well as migratory activity, identifying them as stem cells. Moreover these cells showed a constitutively high NF- κ B activity and an aberrant, polyploid DNA content (Kaus et al., unpublished data).

From our point of view, NF- κ B may be one of the most important regulators of brain tumour development via NSCs and later via TSCs. A primary physiological function of NF- κ B may be to regulate stem cell proliferation via transcriptional regulation target genes like c-myc or cyclin D1 and their migration and differentiation. On the other hand, pathologically high activity of NF- κ B during chronic inflammation may cause tumour initiation, progression and metastasis.

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Figure legends

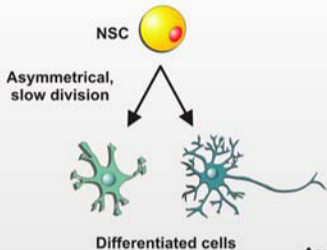
Fig. 1

NSC division in physiological situation and in acute inflammation. Physiologically, NSCs proliferate slowly and asymmetrically generating more committed precursors or differentiated cells. In an inflammatory environment, NSCs might start to proliferate rapidly and symmetrically in response to pro-inflammatory cytokines such as TNF- α . The pro-inflammatory stimuli activate the transcription factor NF- κ B. After acute inflammation is attenuated, NF- κ B becomes deactivated and NSCs switch back to the asymmetrical mode of division.

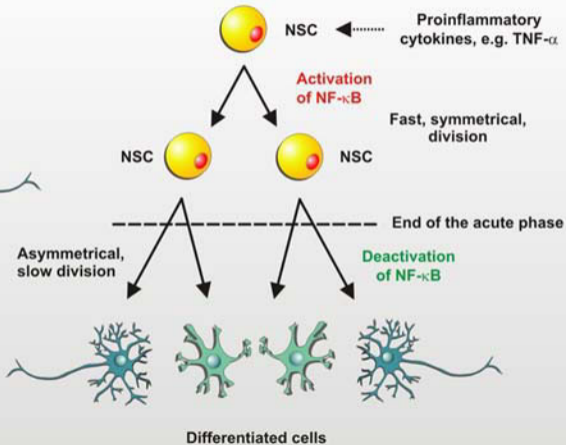
Fig. 2

Model for the correlation between chronic inflammation, symmetric division of NSCs and cancer. In chronic inflammation, NSCs are permanently exposed to proliferation-inducing stimuli such as TNF- α . The ensuing rapid proliferation entails a much higher risk of mutation than slow cell division. Initial mutations could easily be propagated as a result of the fast symmetric division. Secondary mutations then may lead to constitutive NF- κ B activity, aneuploidy and finally to cancer.

Physiological situation



Acute inflammation



Chronic inflammation

