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NFκB signaling regulates embryonic and adult neurogenesis

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Abstract

Both embryonic and adult neurogenesis involves the self-renewal/proliferation, survival, migration and lineage differentiation of neural stem/progenitor cells. Such dynamic process is tightly regulated by intrinsic and extrinsic factors and complex signaling pathways. Misregulated neurogenesis contributes much to a large range of neurodevelopmental defects and neurodegenerative diseases. The signaling of NFκB regulates many genes important in inflammation, immunity, cell survival and neural plasticity. During neurogenesis, NFκB signaling mediates the effect of numerous niche factors such as cytokines, chemokines, growth factors, extracellular matrix molecules, but also crosstalks with other signaling pathways such as Notch, Shh, Wnt/β-catenin. This review summarizes current progress on the NFκB signaling in all aspects of neurogenesis, focusing on the novel role of NFκB signaling in initiating early neural differentiation of neural stem cells and embryonic stem cells.

Keywords

neural stem cells; transcriptional factors; NFκB; neurogenesis; embryonic stem cells; signal transduction

Introduction

Neurogenesis is a process of neural cell formation and includes three terms based on the lineage differentiation into neurons, astrocytes and oligodendrocytes: neuronogenesis, astrocytogenesis and oligodendrocytogenesis. Neurogenesis occurs not only during embryonic and perinatal development but also in adult nervous system including central (Conti and Cattaneo, 2010; Ming and Song, 2011), peripheral (Le Douarin et al., 2008; Pardal et al., 2010) and enteric nervous system (Heanue and Pachnis, 2007; Metzger, 2010). Defects or impairments in embryonic and neonatal neurogenesis contribute significantly to a large range of neuropsychiatric diseases including intellectual disability (mental retardation), autism spectrum disorders, childhood-onset schizophrenia, epilepsy, pediatric bipolar disorder, attention-deficit hyperactivity disorder, as well as genetic or neurodevelopmental disorders such as Fragile X syndrome, Rett syndrome, Down syndrome, Hirschsprung's disease (Heanue and Pachnis, 2007; Vaillend et al., 2008; Ma et al., 2009; Schäfer et al., 2009; Kishi and Macklis, 2010; Callan and Zarnescu, 2011). Adult neurogenesis is a relatively new concept and abnormal adult neurogenesis plays an important role in the pathogenesis of many cognitive/mood dysfunction in adult such as depression (Hanson et al., 2011), schizophrenia (Inta et al., 2011), epilepsy (Andres-Mach et al., 2011), stroke (Zhang et al., 2011), HIV-associated neurocognitive disorders (Okamoto et al., 2007; Kaul, 2008) and neurodegenerative diseases including Alzheimer's disease (Mu and Gage, 2011),

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Parkinson's disease (van den Berge et al., 2011), multiple sclerosis (Huehnchen et al., 2011; Tepavčević et al., 2011), and others (Winner et al., 2011; Curtis et al., 2012).

Both embryonic and adult neurogenesis includes the self-renewal/proliferation, survival, migration and lineage differentiation of neural stem/progenitor cells (NSCs/NPCs). For better understanding, neurogenesis can be divided into early, middle and late phases though they are indistinguishable in most cases. Early neurogenesis includes self-renewal/proliferation of NSCs/NPCs and cell fate commitment. Middle neurogenesis covers the migration of lineage-restricted cells (neuroblast or glioblast) and terminal differentiation. Late neurogenesis includes the maturation and functional integrity of nascent cells. The duration of each phase depends upon the neurogenic region, developmental stage, and species. The progression from the early to late neurogenesis is tightly regulated by intrinsic and extrinsic factors and complex signaling pathways (Ma et al., 2009; Pathania et al., 2010). At the early stage, NSCs represent a very small population of quiescent, slow dividing cells while NPCs represent a large population of amplifying, rapid dividing cells (Encinas and Sierra, 2012). NSCs are the most primitive and normally quiescent neural precursor cells and are exceptionally sensitive to cosmic radiation (Encinas et al., 2008). Distinguishing NSCs from NPCs both *in vitro* and *in vivo* remains a big challenge (Bonaguidi et al., 2011; Siebzehnrubl et al., 2011).

Neurogenesis is regulated on various conceptual levels, from behavior, systemic response, specific nervous system activity, niche factors to intracellular/molecular regulation. Although many extrinsic factors and intrinsic epigenic/transcriptional proteins to regulate both embryonic and adult neurogenesis have been identified (Zhao et al., 2008; Conti and Cattaneo, 2010), the signaling pathways and molecular mechanisms remain poorly understood. In particular, what factors control the initiation of NSC differentiation into NPCs? After initial differentiation, what factors guide lineage-specific terminal differentiation? Several signaling pathways such as Wnt/β-catenin, Notch, sonic hedgehog (Shh) as well as transcriptional factors such as Sox2, Pax6, Mash1, TLX, Hes1/5, NeuroD, Tbr2, etc. in neurogenesis have been identified (Ma et al., 2009; Hodge and Hevner, 2011), but little is known about the signaling of nuclear factor κB (NFκB) during neurogenesis (Schölzke and Schwaninger, 2007; Widera et al., 2008; Kaltschmidt and Kaltschmidt, 2009; Gutierrez and Davies, 2011; Zhang et al., 2011). Recently, inflammatory mediators including cytokines, chemokines, growth factors, adhesion molecules, are receiving increased attentions in the field of embryonic and adult neurogenesis because inflammatory and immune responses are known to play critical roles in various diseases and injuries of the nervous system (Das and Basu, 2008; Taupin, 2008; Widera et al., 2008; Whitney et al., 2009; Teng and Tang, 2010). Most inflammatory mediators act as both sources and targets of NFκB signaling. The role of NFκB signaling in regulating the proliferation/apoptosis of NSCs/NPCs, migration of neuroblast, maturation and plasticity of nascent neurons has been reviewed in several previous publications (Widera et al., 2006b; Schölzke and Schwaninger, 2007; Widera et al., 2008; Gutierrez and Davies, 2011; Zhang et al., 2011). In this review, we will focus on the role of NFκB signaling in regulating selfrenewal and early differentiation of NSCs.

Signaling pathways of NFκB activation

The transcriptional factor NFκB plays a pivotal role in inflammation, immunity, cancer and neural plasticity (Häcker and Karin, 2006; Perkins, 2007). Constitutive and inducible activation of NFκB has been reported in many types of human tumors and chronic diseases (Wong and Tergaonkar, 2009; Boyce et al., 2010; Lin et al., 2010; Mancino and Lawrence, 2010). Like other signaling transduction pathways, NFκB is activated through a series of signaling cascades. The NFκB family contains 5 members including RelA(p65), RelB, c-

Rel, p50/p105 (NFκB1) and p52/p100 (NFκB2), which form various combinations of homodimers or heterodimers (Chen and Greene, 2004; Perkins, 2007). All contain REL homology domain (RHD, 300 aa) responsible for DNA binding, dimerization, IκB binding and nuclear translocation. The class I (p65, RelB, c-Rel) contains transactivation domain (TAD) and thus has intrinsic ability to activate transcription. The class II (p50 and p52) lacks TAD and thus their homodimers generally repress transcription of target genes but their heterodimers with class I have transcriptional activity. In non-stimulated cells, the NFκB dimer is retained in the cytoplasm by the inhibitor of NFκB (IκB). Upon stimulation, IκB is degraded via a phosphorylation-dependent proteasome-mediated mechanism and the released NFκB is translocated to the nucleus where it binds to the κB-sites and regulates the transcription of target genes. The degradation of IκB is regulated by the IκB kinase (IKK) that is activated by its upstream IKK kinases (Fig. 1). The IκB family contains 8 members including the classical inhibitors IκBα, IκBβ, IκBγ (p105), IκBδ (p100) and IκBε, as well as the atypical regulators Bcl-3, IκBξ and IκBns. All of them are characterized by the hallmark 5–7 ankyrin-repeats that mediate the interaction with NFκB. The classical IKK complex contains 2 catalytic subunits IKK1/2 or IKKα/β and 1 regulatory subunit IKKγ (Chen and Greene, 2004; Perkins, 2007).

Three distinct signaling pathways for NFκB activation have been identified: classical (canonical), non-classical (non-canonical, alternative) and atypical pathways (Viatour et al., 2005), all of them rely on sequentially activated kinases (Fig. 2). The classical pathway is a well-established original pathway and is crucial for the activation of innate immunity and inflammation. It involves the activation of the classical IKK complex (Häcker and Karin, 2006). This pathway generally regulates the activation of NFκB complexes (e.g. p65/p50), in response to a wide range of stimuli such as pro-inflammatory cytokines tumor necrosis factor α (TNFα) and interleukin (IL) 1β, Toll-like receptor agonists (LPS), antigens, or viruses (HTLV1, EBV). The activated IKK complex phosphorylates IκB members (IκBα, IκBβ, IκBε and p105) on a consensus motif DSGFxS (e.g. Ser-32/Ser-36 for IκBα and Ser-19/Ser-23 for IκBβ) and the phosphorylated serines act as binding site for β-TrCP, the substrate recognition subunit of a Skp1-Cullin-F-box (SCF)–type E3 ubiquitin-protein ligase complex, named $SCF^{\beta\text{-}TrCP}$. This process, then, leads to the ubiquitination on specific lysine and the ubiquitinated IκBs are directed to 26S proteasome for full degradation, leaving free NFκB complexes to enter into the nucleus. The kinetics of phosphorylation and degradation of IκBβ or IκBε are much slower than that of IκBα and may reflect different substrate specificities of the IKK complex. The non-classical pathway is critical for the secondary lymphoid organ development, maturation of B cells and adaptive humoral immunity. It involves TRAF3-mediated activation of the NFκB-inducing kinase (NIK) and IKKα (Razani et al., 2011; Sun, 2012). Activated IKKα phosphorylates p100 on specific serine residues. After phosphorylation, p100 is ubiquitinated by $SCF^{\beta\text{-}TrCP}$ E3 ligase and cleaved by 19S proteasome, instead of completely degraded by 26S proteasome, to generate the NFκB subunit p52. This process is generally slower than the activation of the classical pathway and leads to a delayed activation of nuclear p52-containing complexes, such as RelB/p52. The mechanisms of p52 generation are either constitutive (by cotranslational processing) or inducible (by post-translational cleavage). The non-classical pathway is triggered by some particular members of TNF family (Lymphotoxin β, B cell activation factor, CD40 ligand). Early studies demonstrated that almost all inducers of NFκB lead to activation of the classical IKKα/β/γ complex. Additional IKK complex, NIK/IKKα (Woronicz et al., 1997; Senftleben et al., 2001) and IKKβ/IKKγ (Quirling et al., 2004), has been identified. NIK/IKKα mediates the non-classical NFκB pathway while IKKβ/IKKγ subcomplex remains functional for the classical NFκB pathway. Our studies identified a novel NFκB signaling regulator, NIBP (NIK-and IKKβ binding protein) that forms a novel subcomplex comprised of NIK-NIBP-IKKβ without IKKα and IKKγ (Hu et al., 2005). Such subcomplex may represent a novel signaling pathway of NFκB activation and regulate

protein transport and subcellular trafficking (Cox et al., 2007; Kümmel et al., 2008; Zong et al., 2011; Westlake et al., 2011; Zong et al., 2012).

Most stimuli activate NFκB through IKK-mediated IκB phosphorylation on N-terminal serine residues. A third signaling pathway for NFκB activation is classified as atypical because it is independent of IKK (Fig. 2). Although the phosphorylation and proteasome-mediated degradation of IκB are involved, the phosphorylation sites are different. One atypical pathway is triggered by DNA damage such as UVor doxorubicin, leading to IκBα degradation via the proteasome, but the targeted serine residues are located within a C-terminal cluster, which is recognized by the p38 MAP kinase-activated casein kinase 2 (CK2) (Kato et al., 2003; Huillard et al., 2010). Another atypical pathway is stimulated by oxidative stress, which involves the activation of NADPH oxidase (NOX), generation of superoxide and hydrogen peroxide (H_2O_2) that leads to NFκB activation via phosphorylation of IκBα on the N-terminal Tyr-42 residue (Gloire et al., 2006). The upstream kinases for tyrosine phosphorylation of IκBα remain unclear, and the spleen tyrosine kinase (Syk) may be involved (Gallagher et al., 2007).

NFκB signaling in embryonic neurogenesis (neurodevelopment)

During early embryonic development, a subset of cells in the ectoderm overlying the notochord of the mesoderm proliferate/differentiate and become neural plate in response to the diffusible inhibitory signals (neural inducer) produced from the notochord. Neural plate folds to form the neural groove, which fuses to form the neural tube. Within the neural tube, NSCs (radial glia cells) derive from neuroepithelial cells (NECs) and differentiate sequentially into NPCs and various lineage-restricted precursor cells (RPCs), which include neuroblast and glioblast. These RPCs migrate to the marginal zone and beyond to assume their terminal fate. The generation of different lineage occurs in a temporally distinct yet overlapping pattern. In rodents, neuronogenesis peaks at embryonic day (E) 14, astrocytogenesis at postnatal day (P) 2, and oligodendrocytogenesis at P14 (Wang and Bordey, 2008; Sauvageot and Stiles, 2002).

The self-renewal and cell fate decision of NSCs during embryonic neurogenesis are regulated by various transcription factors and their signaling pathways including the nuclear hormone receptor TLX (tailless), the high-mobility-group transcription factor Sox2, the basic helix-loop-helix transcriptional factor Hes (hairy and enhancer of split), the tumor suppressor phosphatase Pten (phosphatase and tensin homolog deleted on chromosome 10), and the *Drosophila* membrane-associated protein Numb homologs, Numb and Numblike (Shi et al., 2008). The Hes family plays key but opposing role in regulating neurodevelopment. Hes1 and Hes5 are activated by Notch signaling and repress the expression of proneuronal factors such as Mash1, Neurogenin, Math and NeuroD (Cau et al., 2000; Kageyama et al., 2008). In contrast, Hes6 promotes neuronal differentiation but inhibits astrocyte differentiation (Fior and Henrique, 2005; Vilas-Boas and Henrique, 2010).

NFκB is essential for embryonic development because p65 knockout mice died on E15 and p65/p50 or p65/c-rel double knockout mice died on E13 due to liver degeneration (Beg et al., 1995; Grossmann et al., 1999). Such embryonic lethality precluded further investigation on the role of NFκB in late embryonic brain development. Additional knockout of TNF receptor 1 (TNFR1) in these p65 null mice rescued embryonic lethality (Alcamo et al., 2001), providing an opportunity to investigate the role of NFκB signaling in regulating embryonic neurogenesis (Young et al., 2006). However, the distribution pattern of NSCs/NPCs and cell lineage analysis in neurogenic zones of these mutants have not yet been examined. IKKα/IKKβ double knockout mice died on E12 due to apoptosis of NECs leading to impairments in neurogenesis (Li et al., 2000). In *Drosophila* (Chen et al., 2000; Ayyar et

al., 2007; DeLotto et al., 2007; Reeves and Stathopoulos, 2009) and *Xenopus laevis* (Lake et al., 2001), the graded activation of NFκB/c-rel protein in dorsal region determine the dorsal-ventral patterning during the very early embryonic development. During mouse embryogenesis, virtually all members of the NFκB pathway are expressed in embryonic, trophoblastic, and uterine cells (Torchinsky and Toder, 2004). NFκB may protect the embryos exposed to embryopathic stresses, possibly through its anti-apoptotic effect (Torchinsky and Toder, 2004).

Although little is known regarding the role of NFκB in the early step of embryonic neurogenesis, several lines of evidence demonstrate that NFκB is implicated in early differentiation of other stem cells. During murine spermatogenesis, NFκB is activated in a stage-specific manner (Lilienbaum et al., 2000). During oocyte maturation and early embryonic development, NFκB is activated (Nishikimi et al., 1999; Paciolla et al., 2011). In *Drosophila melanogaster*, the mRNA of the p65 homolog, named Dorsal, is maternally expressed and is concentrated in the egg cortex (Chen et al., 2000). In *Xenopus*, NFκB activation is observed during oocyte maturation (Dominguez et al., 1993) and in late blastulae and gastrulae (Richardson et al., 1994). In mouse embryos, NFκB activation is crucial to engage development beyond the 2-cell stage (Nishikimi et al., 1999). NFκB mediates the neurogenic effect of erythropoietin in neurosphere cultures from E14 mouse ganglionic eminence (Shingo et al., 2001). Neural induction from cultured embryonic stem (ES) cells or induced pluripotent stem (iPS) cells has been established (Osakada and Takahashi, 2011; Denham et al., 2012), but the signaling mechanisms remain largely unknown. Such induction is an excellent *in vitro* model to recapture the embryonic neurogenesis. The signaling pathways identified during endogenous embryonic morphogenesis and neurogenesis can be applied to the neural induction and patterning, such as bone morphogenetic protein (BMP), fibroblast growth factor (FGF), Wnt, Shh and Notch signaling. We speculate that NFκB signaling play an important role in the neuronal induction from ES or iPS cells. Recently, it has been shown that murine and human ES cells possess a low level of NFκB activity that increases significantly during the differentiation process (Kang et al., 2007; Kim et al., 2008; Torres and Watt, 2008). In human ES cells, the classical NFκB pathway regulates differentiation while the non-classical pathway maintains pluripotency (Yang et al., 2010). The transcription factor Nanog is essential in maintaining pluripotency of ES cells (Mitsui et al., 2003). During ES cell differentiation, endogenous NFκB activity and target-gene expression increased. NFκB inhibition increased expression of pluripotency markers. Nanog binds to NFκB proteins, inhibits NFκB activity and cooperates with Stat3 to maintain pluripotency (Torres and Watt, 2008). ES cell-specific miR-290 maintains the pluripotency and self-renewal of ES cells through repressing NFκB classical signaling (Lüningschrör et al., 2012). Forced expression of p65 causes loss of pluripotency, promotes differentiation of ES cells, and leads to an epithelial to mesenchymal transition. These data define p65 as a novel target gene of miR-290 cluster and provide new insight into the function of ES cell-specific miRNAs (Lüningschrör et al., 2012). Taken altogether, NFκB signaling is activated and required during the early differentiation of various stem cells including ES/iPS, hematopoietic (Xiao et al., 2009; Montano-Almendras et al., 2012), mesenchymal (Hess et al., 2009; Cho et al., 2010) and cancer stem cells (Reikvam et al., 2009; Nogueira et al., 2011).

NFκB signaling in adult neurogenesis

NFκB signaling is well known to regulate cell survival or apoptosis in many cell types, depending upon the generation of its target genes. In adult nervous system, inflammation-related NFκB signaling plays a sword-edge role after injuries or diseases. Neuronal NFκB signaling is neuroprotective via its crucial role in maintaining neuronal survival, synaptogenesis, neural plasticity, learning and memory (Fridmacher et al., 2003; Mattson

and Meffert, 2006; Camandola and Mattson, 2007; Boersma et al., 2011). A striking enrichment of phosphorylated IκBα and IKK is observed in the axon initial segment (Schultz et al., 2006; Sanchez-Ponce et al., 2008) and the nodes of Ranvier (Politi et al., 2008), suggesting a novel role of NFκB signaling in regulating axonal polarity and initial axonal formation. In the zones of active neurogenesis in both postnatal and adult mouse brain, various members of the NFκB family are highly expressed (Denis-Donini et al., 2005), indicating for the first time that NFκB is actively involved in the proliferation, migration and differentiation of adult NSCs/NPCs (Rolls et al., 2007; Widera et al., 2008). The presence of NFκB in adult neurogenic zone is further validated using immunofluorescent microscopy (Meneghini et al., 2010; Zhang et al., 2012b). Early studies using κB-dependent lacZ transgenic mice show that NFκB activation in the central nervous system starts on day E12.5 and major changes are not observed until after birth, when the structures start their final maturation processes, but details about neurogenic zones are not reported (Schmidt-Ullrich et al., 1996). Recent studies in the hippocampal subgranular zone of adult NFκB lacZ reporter mice have identified the activation of NFκB signaling in NSCs instead of NPCs (Koo et al., 2010), suggesting a potential role of NFκB signaling in early neurogenesis. Direct evidence for the *in vivo* effect of NFκB signaling on the proliferation of NSCs/NPCs derives from p65 and p50 double knockout mice (Young et al., 2006) as well as overexpression of super inhibitor IκBα mutant in NSCs/NPCs (Wu et al., 2000; Widera et al., 2006a; Rubio-Araiz et al., 2008; Zhu et al., 2008).

Little is known about the role of NFκB signaling in regulating neural differentiation of NSCs/NPCs. In PC12 cells, both NIK and IKKβ and their binding protein NIBP are required for nerve growth factor-induced neuronal differentiation via NFκB signaling (Foehr et al., 2000; Azoitei et al., 2005; Hu et al., 2005), though several other signaling pathways are also involved (Wooten et al., 2000; Azoitei et al., 2005). In neuroblastoma cells, NFκB promotes neuronal differentiation (Feng and Porter, 1999). Toll-like receptor 2 (TLR2) induces neuronal differentiation via protein kinase C (PKC)-dependent activation of NFκB whereas TLR4 inhibits proliferation and neuronal differentiation of NPCs (Rolls et al., 2007). In p50-deficient mice, the neuronal differentiation of adult hippocampal NSCs is reduced by 50% while the proliferation does not change (Denis-Donini et al., 2008). In our recent study, we demonstrate that NFκB signaling regulates the early differentiation of NSCs (Zhang et al., 2012b). During early differentiation, NFκB signaling becomes active. Addition of TNFα to activate NFκB signaling under proliferation conditions induces neural differentiation of NSCs/NPCs (Lou et al., 2003; Bernardino et al., 2008; Zhang et al., 2012b). TNF-like weak inducer of apoptosis (TWEAK) induces neuronal differentiation of NSCs/NPCs, under proliferation condition, through NFκB-dependent downregulation of Hes1 that prevents neuronal differentiation (Schölzke et al., 2011). Selective inhibition of canonical NFκB signaling by various pharmacologic inhibitors, shRNA and NSC-specific transgene dnIκBα retain the tripotential ability of differentiation and restore or enhance self-renewal capability of NSCs, suggesting that NFκB signaling is essential for early neural differentiation (Zhang et al., 2012b). The critical role of NFκB in the initial differentiation step of NSCs highlights a novel molecular mechanism for neurogenesis. Under physiologic conditions, moderate activation of NFκB signaling promotes NSC differentiation into NPCs and maintains a continuous source for adult neurogenesis. In a mouse inducible IκBα transgenic model, NFκB in NSCs/NPCs is necessary for axogenesis and maturation (Imielski et al., 2012). However, persistent and repeated overactivation of NFκB signaling in NSCs may exhaust the NSC pool and thus lead to reduced neurogenesis as seen in aging patients (Villeda et al., 2011; Artegiani and Calegari, 2012; Encinas and Sierra, 2012) and chronic stress (Koo et al., 2010).

Cytokine-induced regulation of NFκB signaling during neurogenesis

Several cytokines have been shown to regulate neurogenesis, such as TNFα, IL-1β, IL-6, TWEAK, and IFNγ (Das and Basu, 2008; Whitney et al., 2009; Schölzke et al., 2011; Yirmiya and Goshen, 2011), and most of them stimulate NFκB signaling. TNFα is extensively studied in affecting neurogenesis but the reports remain controversial. The enhancing effect of TNFα on neuronal differentiation is first reported in rat mesencephalic NSCs (Lou et al., 2003). TNFα stimulation promotes the reaggregation of 3D neurospheres *in vitro* (Widera et al., 2006c). TNFR1-derived peptide promotes neuronal differentiation of the hippocampal NSCs (Kajiwara et al., 2005). However, TNFα has no effect on neuronal differentiation and neurite outgrowth of murine adult NSCs/NPCs (Wong et al., 2004; Keohane et al., 2010) and mouse ES-derived NPCs (Ideguchi et al., 2008). Other data suggest that TNFα promote gliogenesis but not neuronogenesis in the NSCs/NPCs (Ricci-Vitiani et al., 2006; Ideguchi et al., 2008; Johansson et al., 2008; Peng et al., 2008). Recent study demonstrates that TNFα-induced neuronal differentiation in NSCs/NPCs is dose-dependent (Bernardino et al., 2008). These opposite results regarding the effects of TNFα on neural differentiation may have resulted from the use of different protocols (culture media, coating matrix, and exposure time), passage numbers, brain regions, species, or doses (Keohane et al., 2010). In addition, these reports have targeted the late stages (from NPCs to RPCs and terminal cells) of neural differentiation. Using stemness assay and pharmacological approach, we demonstrate that TNFα treatment under proliferation conditions induced neural differentiation through NFκB activation at a very early stage of neurogenesis. We also confirmed previous reports (Bernardino et al., 2008; Keohane et al., 2010) showing that TNFα controls the survival and neuronal differentiation of neural cells at some late stages during neural differentiation. The neurogenic effects of inflammatory cytokines highlight the important role of inflammatory and immune responses in early neurogenesis after injury or diseases of the nervous system (Rolls et al., 2007).

IL-1β, another major proinflammatory cytokine, also plays an important role in neurogenesis. Several lines of evidence implicate that IL-1β mediates stress-induced depression via inhibiting adult neurogenesis (Ben Menachem-Zidon et al., 2008; Goshen et al., 2008; Koo and Duman, 2008; Goshen and Yirmiya, 2009). Blockade of IL-1β signaling could be a novel therapeutic approach for the treatment of depression (Koo and Duman, 2009). Further studies demonstrate a critical role of NFκB signaling in mediating IL-1β-induced antineurogenic effect by exhausting NSC pool (Koo et al., 2010). IL-1β treatment decreases the proliferation and self-renewal of proliferating NSCs/NPCs cultured from embryonic rat hippocampus, but inhibits neuronal differentiation and promotes astroglial differentiation (Green et al., 2012), consistent with the effect of TNFα (Ricci-Vitiani et al., 2006; Ideguchi et al., 2008; Johansson et al., 2008; Peng et al., 2008).

Increasing evidence shows that another cytokine, IL-6, inhibits neuronogenesis but promotes gliogenesis both *in vitro* and *in vivo* (Okano, 2006; Nakanishi et al., 2007; Ideguchi et al., 2008; Johansson et al., 2008; Mukaino et al., 2008; Islam et al., 2009). However, interferon-γ is shown to inhibit the proliferation but promote neuronal differentiation of NSCs (Ben-Hur et al., 2003;Wong et al., 2004; Ideguchi et al., 2008; Johansson et al., 2008; Lum et al., 2008).

Taken together, transient NFκB activation by these cytokines under normal conditions or early stage of injuries or diseases may be beneficial by promoting NSC differentiation for neural repair or maintaining daily neurogenesis. However, chronic NFκB activation may delete the NSC pool, leading to aberrant and insufficient neurogenesis (Koo et al., 2010; Artegiani and Calegari, 2012; Schwarz et al., 2012).

Non-classical and atypical NFκB signaling pathways during neurogenesis

Most studies in terms of neurogenesis target the classical IKKβ/IκBα/p65 pathway of NFκB activation (Widera et al., 2008; Kaltschmidt and Kaltschmidt, 2009). Little is known about the role of non-classical and atypical pathways in neurogenesis. RelB is expressed in migrating neuroblast, c-Rel is present in a few cells located at the edges of the rostral migratory stream, but only the classical p65/p50 is detectable in NSCs/NPCs (Denis-Donini et al., 2005). The p65 knockout mice dies on E15 (Beg et al., 1995), but RelB (Weih et al., 1997), c-Rel (Köntgen et al., 1995) or p50 (Sha et al., 1995) knockout mice are not embryonically lethal. There are no reports on the neurogenic pattern and lineage differentiation in the neurogenic zones of these knockout mice. In NSCs/NPCs, the pigment epithelium-derived factor (PEDF) induces a non-canonical activation of the NFκB pathway, leading to the dismissal of the transcriptional co-repressor N-CoR from specific Notch-responsive promoters (Andreu-Agulló et al., 2009). However, several studies have shown that non-classical pathway plays important role in the differentiation of ES cells and other tissue stem cells. For example, the canonical NFκB pathway regulates differentiation while the noncanonical pathway maintains the pluripotency of human ES cells (Yang et al., 2010). The p100/RelB signaling positively and intrinsically regulates self-renewal of hematopoietic stem/progenitor cell (Zhao et al., 2012). NIK/RelB signaling is required for osteoclast differentiation (Vaira et al., 2008). In mesenchymal stem cells, the non-classical NFκB pathway promotes but the classical pathway inhibits the late and sustained CD69 expression (Saldanha-Araujo et al., 2011). LIGHT, a stimulator for non-classical NFκB pathway, negatively regulates neurite growth from developing sensory neurons via inhibition of classical NFκB pathway (Gavaldà et al., 2009). The mechanisms underlying the different and frequently opposing effects of the classical and non-classical NFκB pathways in stem cell seflrenewal and differentiation remain to be determined. NIBP may act as a switch between two pathways by binding to IKKβ (classical) and NIK (nonclassical) (Hu et al., 2005).

Although there is no direct evidence, we speculate that the atypical NFκB pathway is involved in neurogenesis, because the key components of these atypical pathways have been shown to regulate neurogenesis. NOX-mediated ROS is well known to activate NFκB in various cell types (Gloire and Piette, 2009; Morgan and Liu, 2011). NSCs/NPCs maintain a higher level of ROS compared to differentiated neurons (Le Belle et al., 2011). Endogenous ROS and nitric oxide are essential for the proliferation and differentiation of NSCs/NPCs (Yoneyama et al., 2010; Le Belle et al., 2011). Controlled generation of ROS at low-to-moderate levels stimulates neural differentiation of NSCs/NPCs (Vieira et al., 2011; Kennedy et al., 2012). Numb-interacting protein 1 (Nip1), a component of the ROS-generating Duox system, directs neuronal differentiation of NSCs through ROS generation (Kennedy et al., 2010). The mechanisms underlying ROS-mediated neurogenesis may involve ROS-stimulated signaling pathways such as PI3K/Akt (Le Belle et al., 2011), p38 MAPK (Kim and Wong, 2009), ERK (Kim et al., 2011a), JNK (Yeo and Kang, 2007) and NFκB signaling (Piao et al., 2005; Li et al., 2009; Qin and Crews, 2012). Syk mediates ciliary neurotrophic factor (CNTF)-induced tyrosine phosphorylation of IκBα and promotes neurite growth of developing neurons (Gallagher et al., 2007; Gutierrez and Davies, 2011). Syk is involved in ephrinA-induced promotion of neuritogenesis (Richards et al., 2006; Angibaud et al., 2011). CK2β functions as a positive regulator for NSC proliferation and multipotency (Ziercher et al., 2011) and controls oligodendrocytogenesis (Huillard et al., 2010).

Crosstalk between NFκB and other signaling pathways

Many signaling pathways have been identified to regulate both embryonic and adult neurogenesis, including Notch, Shh, Wnt/β-catenin, etc. (Mu et al., 2010). The functional interaction of these pathways with NFκB signaling has been reported in neuron, microglia, astrocytes and other cells (Cao et al., 2011; Maniati et al., 2011; Zhang et al., 2012a). Such crosstalk may occur also to NSCs/NPCs (Bonini et al., 2011), but experimental evidence is needed. For example, Notch signaling is well known to maintain NSC selfrenewal and multipotency, and thus it is speculated that NFκB signaling may regulate NSC stemness through Notch signaling (Ang and Tergaonkar, 2007; Fujita et al., 2011). PEDF modulates Notch-dependent stemness of mouse NSCs through activation of non-canonical NFκB pathway (Andreu-Agulló et al., 2009). In mouse mesencephalic neural crest cells, NFκB signaling promotes gliogenesis through the interaction with Notch signaling (Fujita et al., 2011). In *Xenopus laevis*, NFκB activates Shh signaling for anterior neural patterning (Lake et al., 2001). In mouse, Shh signaling regulates neural induction from ES cells (Cai et al., 2008) or NSCs (Dave et al., 2011). TLR3 regulates NSC proliferation by modulating Shh signaling (Yaddanapudi et al., 2011), perhaps through activation of NFκB (Kasperczyk et al., 2009). Many studies have demonstrated the importance of Wnt/β-catenin signaling in neurogenesis (Kondo et al., 2011; Pei et al., 2012) and its interaction with NFκB signaling in cancer stem cells (Gavert et al., 2011; Pan et al., 2012) and mesenchymal stem cells (Hyun Hwa et al., 2008; Kim et al., 2011b). However, the crosstalk between NFκB and Wnt/β-catenin signaling during neural induction and neurogenesis need further investigation.

Correlation of NFκB dysfunction to neurodevelopmental and neurodegenerative diseases

The link of NFκB signaling defects to various neurodevelopmental disorders remains to be determined, though many immune and inflammatory responses have been implicated in these diseases and NFκB signaling mediates most actions of these immune/inflammatory factors. Among 6 genes associated with nonsyndromic autosomal-recessive mental retardation (Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009), two, NIBP (Mir et al., 2009; Mochida et al., 2009; Philippe et al., 2009) and CC2D1A (Noor et al., 2008; Zhao et al. 2010), have been shown to regulate NFκB signaling through the classical IKKβ pathway, implying the important role of NFκB signaling in mental retardation. In the cerebellum and front cortex from autism patients and animal model, IKKα expression is significantly increased, but the expression and activity of the classical NFκB signaling components such as IκBα and p65 do not display any significant change (Song et al., 2009), although the role of non-classical and atypical NFκB pathways need further investigation. In schizophrenia patients, NFκB activity is increased in peripheral blood mononuclear cells (Song et al., 2009) and the expression of NFκB-responsive genes is also increased (Hashimoto et al., 2011). Three single nucleotide polymorphism variants of the p65 gene are associated with schizophrenia in a Japanese population (Hashimoto et al., 2011).

NFκB signaling has been widely shown to regulate the pathogenesis of many neurodegenerative diseases such as Alzheimer's (Granic et al., 2009; Mu and Gage, 2011), Parkinson's (Ghosh et al., 2007; Sha et al., 2010), Huntington's (Marcora and Kennedy, 2010) diseases and multiple sclerosis (Huehnchen et al., 2011; Tepavčević et al., 2011), as well as traumatic or ischemic injuries of nervous system (Dong et al., 2011; Zhang et al., 2011). NFκB signaling has been targeted as a therapeutic strategy for neurodegenerative diseases (Camandola and Mattson, 2007; Mattson et al., 2000). On the other hand, adult neurogenesis has been shown to contribute to these neurodegenerative diseases (Mu and Gage, 2011; Winner et al., 2011). NFκB signaling acts as a double-edge sword during neurodegenerative disease, and the outcome depends upon the cell type, environmental

factors and disease stages (Massa et al., 2006; Yang et al., 2007; Teng and Tang, 2010). As discussed above, NFκB signaling regulates all aspects of adult neurogenesis, which may contribute to the development and progression of nervous system injury and diseases.

Concluding remark and future direction

NFκB signaling is a key mediator for numerous niche factors that regulate various stages or phases of embryonic and adult neurogenesis. The classical pathway of NFκB activation plays important role in regulating selfrenewal/multipotency and early differentiation of NSCs, as well as the proliferation/apoptosis of NPCs, migration of neuroblast, maturation and plasticity of nascent neurons. NFκB signaling is also important in regulating the early differentiation of other stem cells such as embryonic stem cells, hematopoietic stem cell, and mesenchymal stem cells. During neural induction both *in vitro* and *in vivo*, NFκB signaling is required. Further investigation of the upstream regulation and downstream mechanism underlying the essential role of NFκB signaling in initiating early differentiation of both neural induction and neurogenesis will open a potential avenue for the development of therapeutics for the treatment of neurodevelopmental disorders and neurodegenerative diseases. Emerging evidence suggests that non-classical and atypical NFκB pathways are implicated in ES cell differentiation. It will be important to evaluate the different role of three NFκB pathways during neurogenesis. NFκB signaling selectively regulates cell fate decision and lineage differentiation. The major barrier for NSC-based transplantation is the predominant gliogenesis *in vivo* when NSCs/NPCs encounter the complicate microenvironmental niches. Thus, selective blockade of gliogenesis and promotion of neuronal differentiation will be an important strategy for stem cell transplantation.

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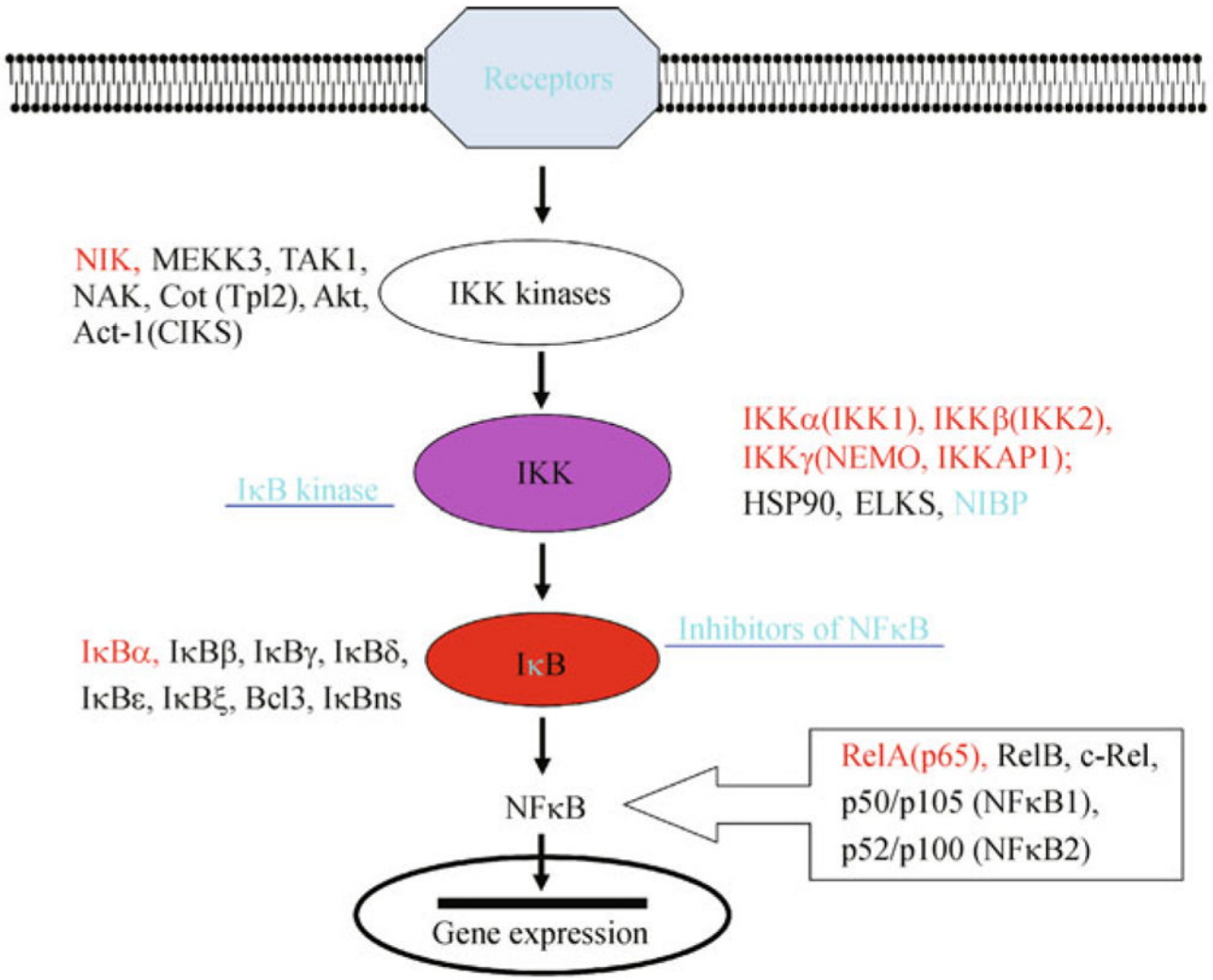

Figure 1.
Signaling cascade of NFκB activation and identified members of each family. The red highlighted text denotes the best-studied original member(s) for each family.

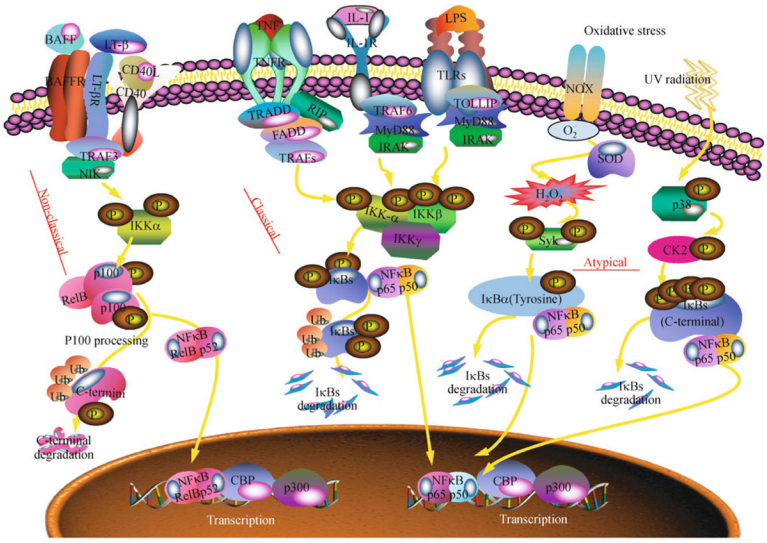

Figure 2.

Signaling pathways of NFκB activation. In the classical pathway, the classical stimulators like TNFα bind to receptor, leading to recruitment of the adaptor molecule TRADD and the signaling proteins TRAF2 and RIP1. TRAF2 recruits the IKK complex that phosphorylates IκBα at serine residue 32 and 36, leading to its ubiquitination and degradation by the proteasome, allowing the release of the classical heterodimer of p65/p50, which then translocate to the nucleus to regulate the transcription of target genes. In the non-classical pathway, NIK-induced phosphorylation of IKKα leads to the phosphorylation of p100 and proteasome-mediated processing of p100 into p52, allowing the nuclear translocation of RelB/p52 to regulate target gene expression. In the atypical pathway, the p38-activated casein kinase 2 (CK2) phosphorylates IκBα at a cluster of serine residues within C-terminal domain, while oxidative stress induces spleen tyrosine kinase (Syk)-mediated phosphorylation of IκBα at tyrosine residue (Y-42) within N-terminal domain.