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NFκB Signaling Directs Neuronal Fate Decision

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1. Introduction

During neural induction, the ectoderm stem cells overlying the notochord of the mesoderm convert into neuroepithelial cells (NECs) that proliferate/differentiate rapidly to form neural plate in response to diffusible inhibitory signals (neural inducer) produced from the notochord. Neural plate folds to form neural groove, which fuses to form neural tube. Within the neural tube, NECs undergo asymmetric dividing to generate neural stem cells (NSCs, or called radial glia cells) due to the expression of B-cell translocation gene 2 (BTG2) [1, 2, 3, 4]. NSCs differentiate sequentially into neural progenitor cells (NPCs) and various lineage-restricted neural blast cells, which include neuroblast and glioblast. These neural blast cells migrate to the target region where they mature and integrate into the existing neural network [5]. 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 [6, 7]. It remains largely unclear at which step the fate of neuronal lineage has been decided, from embryonic stem (ES) cells to NECs, to NSCs and to terminally-differentiated neurons. The transcriptional factor NFκB plays a pivotal role in inflammation, immunity, cancer and neural plasticity [8, 9]. Constitutive and inducible activation of NFκB has been reported in many types of human tumors and chronic diseases including neurodegenerative diseases [10, 11, 12, 13, 14]. However, moderate activation of NFκB signaling on many physiological conditions may benefit the whole process of neuronal fate decision, including neurodevelopment and adult neurogenesis [15].

2. NFκB initiates and maintains neuronal fate decision from neural stem cells

NFκB is activated through a series of signaling cascades (Figure 1). The NFκB family contains 5 members including RelA(p65), RelB, c-Rel, p50/p105 (NFκB1) and p52/p100 (NFκB2),

which form various combination of homodimers or heterodimers [8, 16]. In non-stimulated cells, the NFκB dimer is sequestered in the cytoplasm by the Inhibitor of NFκB (IκB), which include at least 8 members. 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 phosphorylation of IκB is regulated by the IκB kinase (IKK) that is activated by its upstream IKK kinases. The classical IKK complex contains 2 catalytic subunits IKK1/2 or IKKα/β and 1 regulatory subunit IKKγ [8, 16]. Three distinct signaling pathways for NFκB activation have been identified: classical (canonical), non-classical (non-canonical, alternative) and atypical pathways, all of them rely on sequentially activated kinases (Figure 1) [17]. The classical pathway involves the activation of classical IKK complex [9]. This pathway generally regulates the activation of classical 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, etc. 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$^{β-TrCP}$. 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 involves TNF receptor associated factor 3 (TRAF3)-mediated activation of the NFκB-inducing kinase (NIK) and IKKα [18, 19]. Activated IKKα phosphorylates p100 on specific serine residues. After phosphorylation, p100 is ubiquitinated by SCF$^{β-TrCP}$ 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, such as Lymphotoxin (LT) β, B-cell activation factor (BAFF), CD40 ligand (CD40L). The function of classical pathway has been well investigated but non-classical pathway remains in its infancy. In the following discussion, the role of NFκB signaling in the nervous system relates primarily to classical pathway.

In adult nervous system, NFκB signaling plays a sword-edge role after injuries or diseases [15, 20, 21, 22, 23]. The final outcome is attributable to the cell types, disease stages, and target genes. In most cases, NFκB signaling in immune cells, microglia/macrophage and astrocytes is neurodestructive due to overwhelming production of inflammatory mediators and neurotoxic molecules [22, 23]. However, neuronal NFκB signaling is neuroprotective via its crucial role in maintaining neuronal survival, synaptogenesis, neural plasticity, learning and memory [22, 23, 24, 25]. Recent studies demonstrate a striking enrichment of phosphorylated IκBα and IKK in the axon initial segment [26, 27] and the nodes of Ranvier [28], suggesting a novel role of NFκB signaling in regulating axonal polarity and initial axonal formation.

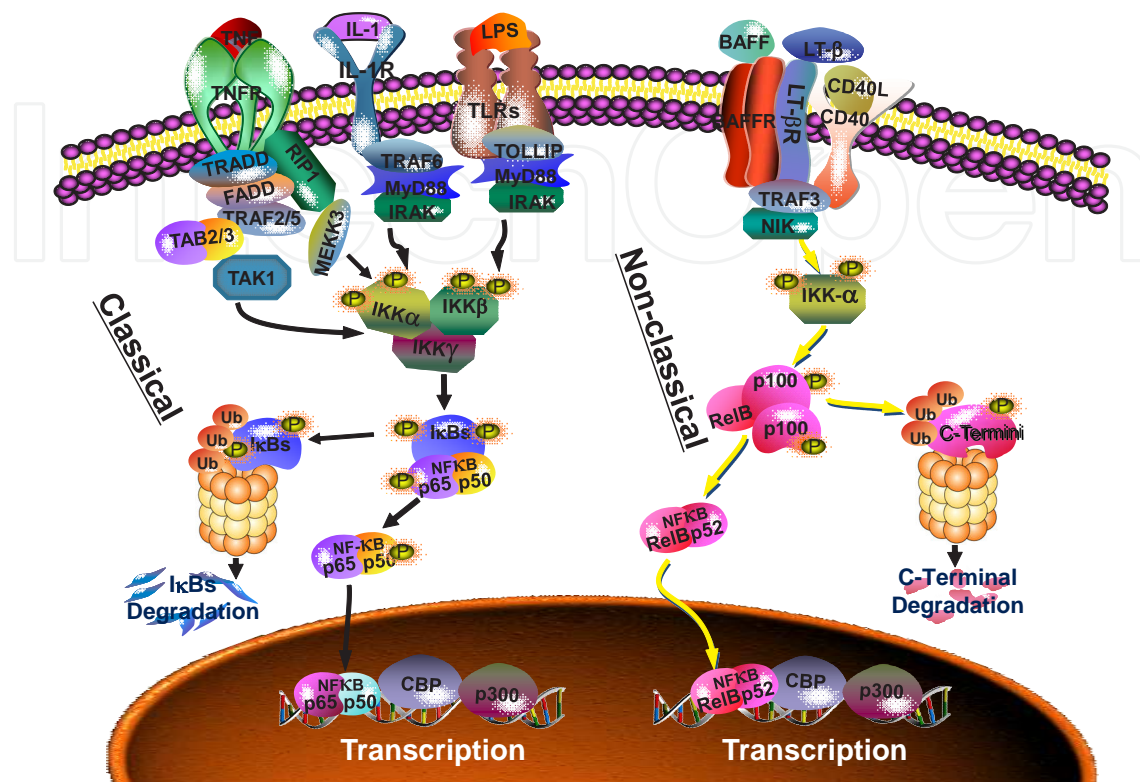In a mouse inducible IκBα transgenic model, NFκB in NSCs/NPCs is necessary for axogenesis and maturation [21].

Figure 1. Classical and non-classical signaling pathways of NFκB activation.

In the zones of active neurogenesis in both postnatal and adult mouse brain, various members of the NFκB family are highly expressed [29], indicating for the first time that NFκB is actively involved in the proliferation, migration and differentiation of adult NSCs/NPCs [30, 31]. The presence of NFκB in adult neurogenic zone is further validated by the studies using immunofluorescent microscopy [32, 33]. Direct evidence for the *in vivo* effect of NFκB signaling on the proliferation of NSCs/NPCs derives from p65 and p50 double knockout mice [34] as well as overexpression of super inhibitor IκBα mutant in NSCs/NPCs [35, 36, 37, 38]. Little is known about the role of NFκB signaling in regulating neural differentiation of NSCs/NPCs. A recent study demonstrates that 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 [30]. In p50-deficient mice, the neuronal differentiation of adult hippocampal NSCs is reduced by 50% while the proliferation does not change [39]. In our recent study, we demonstrate that NFκB signaling regulates the early differentiation of NSCs [32]. During early differentiation of NSCs, NFκB signaling becomes activated [32]. Addition of TNFα to activate NFκB signaling under proliferation conditions induces neural differentiation of NSCs/NPCs [32, 40, 41]. TNF-like weak inducer of apoptosis (TWEAK) induces neuronal differentiation of NSCs/NPCs, under proliferation condition, through NFκB-dependent down-regulation of Hes1 that prevents neuronal differentiation

[42]. Selective inhibition of classical NFκB signaling by various pharmacologic inhibitors, small interfering RNA and NSC-specific transgene dominant-negative IκBα 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 [32]. The critical role of NFκB in the initial differentiation step of NSCs highlights a novel molecular mechanism for neurogenesis. We hypothesize that moderate activation of NFκB signaling promotes NSC differentiation into NPCs and maintains a continuous source for adult neurogenesis under physiological conditions. However, persistent and repeated overactivation of NFκB signaling in NSCs may exhaust NSC pool and thus lead to reduced neurogenesis as seen in aging patients [43, 44] and chronic stress [45].

To further test this hypothesis, we generated double transgenic mice expressing constitutively active form of IKKβ (IKKβ^{CA}) [46, 47] driven by the promoter of glial fibrillary acid protein (GFAP) by crossbreeding GFAP-Cre mice (Jackson Lab, 004600) with Rosa26-Stop^{Floxed}-IKKβ^{CA} mice (Jackson Lab, 008242). *In vitro* studies using the NSCs/NPCs cultured from the brain of GFAP-IKKβ^{CA} mice validated the over-activation of NFκB signaling (Figure 2), the loss of NSCs during passage as determined by the reduced number of GFAP$^+$/Nestin$^+$ NSCs (Figure 3) as well as the inhibition of NSC selfrenewing and tripotential capacity (Figure 4) [32]. The *in vivo* effect of persistent over-activation of NFκB on GFAP$^+$ NSCs and their progeny in brain neurogenic zones of adult animals and their correlations with aging are currently under investigation.
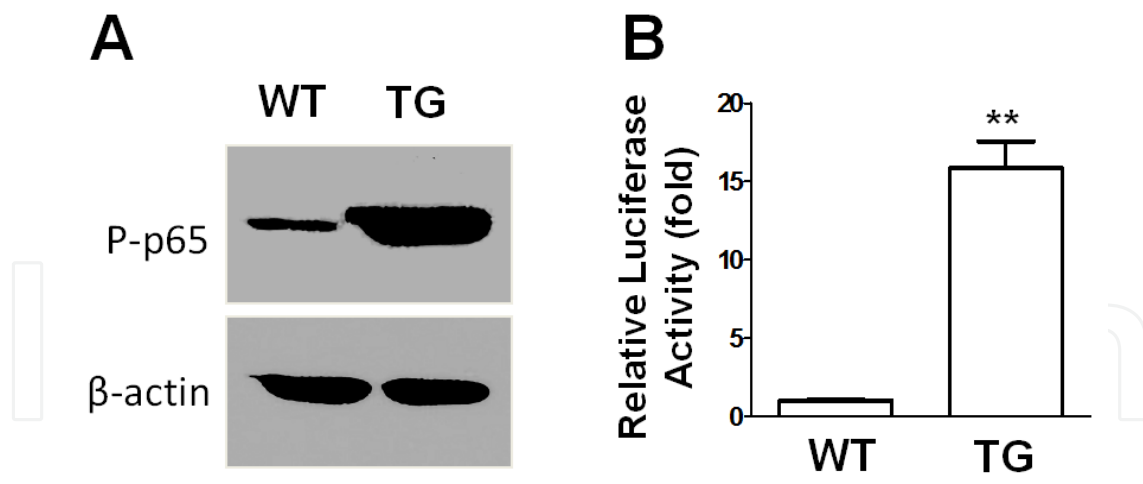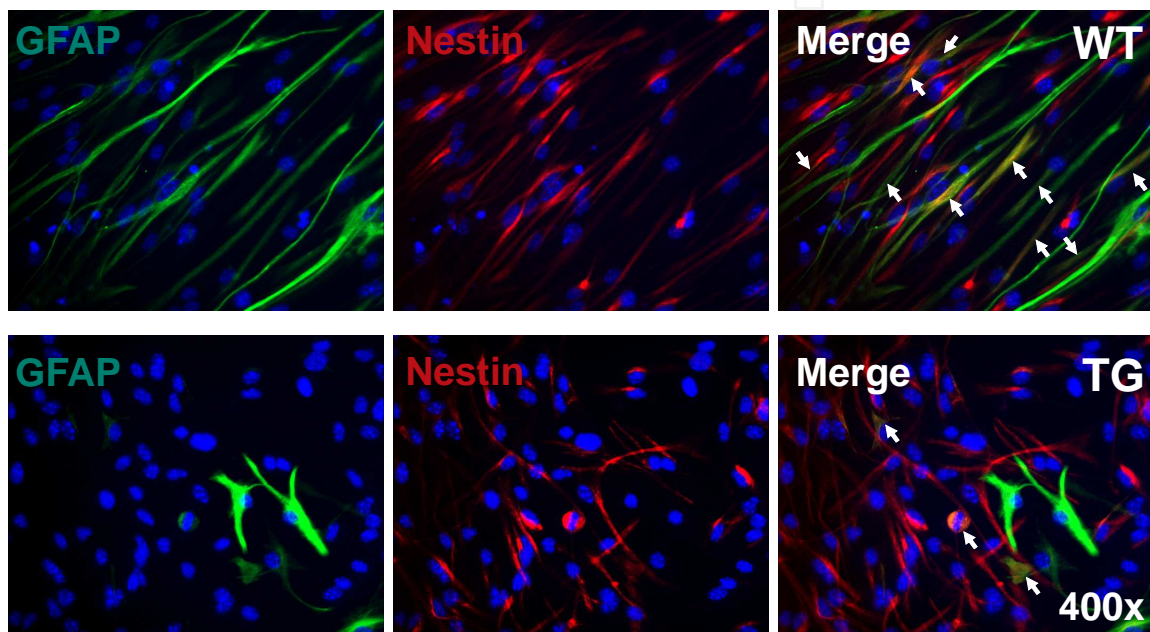

Figure 2. Over-activation of NFκB signaling in brain neural stem/progenitor cells from GFAP-Cre-IKKβ^{CA} mice determined by Western blot analysis (A) and adenovirus-mediated NFκB-luciferase reporter assay (B). *A*. Whole cell lysates of primary neurospheres cultured from brain subventricular zones (SVZ) of littermate wild-type (WT) or transgenic (TG) adult mouse were immunoblotted with antibodies against phosphorylated p65 (Ser-536) or β-actin (as loading control). *B*. Dissociated neural stem/progenitor cells were plated on 96-well plate and infected with adenovirus carrying NFκB *firefly*-luciferase at 50 multiplicity of infection (MOI) for 24 h. Luciferase activity was measured with *OneGlo™* luciferase assay and cell viability was determined with *CellTiter-Glo™* luminescent assay. Data are expressed as relative fold change after cell number normalization. ** p<0.01 indicates statistical significance from WT control.

Figure 3. Over-activation of NFκB signaling in cultured brain neural stem/progenitor cells from GFAP-Cre-IKKβ^{CA} mice reduced the number of GFAP+/Nestin+ neural stem cells (Arrow). Passage 2 neurospheres cultured from brain subventricular zones (SVZ) of littermate wild-type (WT) or transgenic (TG) 5-week-old mouse were dissociated into single cells. Cells were plated in matrigel-coated 8-well chamber slide and cultured under proliferation media containing 20 ng/mL of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) for 3 d. After fixation for 10 min at room temperature with 4% paraformaldehyde, the cells were immunostained simultaneously with goat anti-GFAP polyclonal antibody and mouse anti-Nestin monoclonal antibody followed by donkey anti-goat *Alexa Fluor*® 488 and donkey anti-mouse *Alexa Fluor*® 594 secondary antibodies. The nuclei were counterstained with Hoechst 33258.
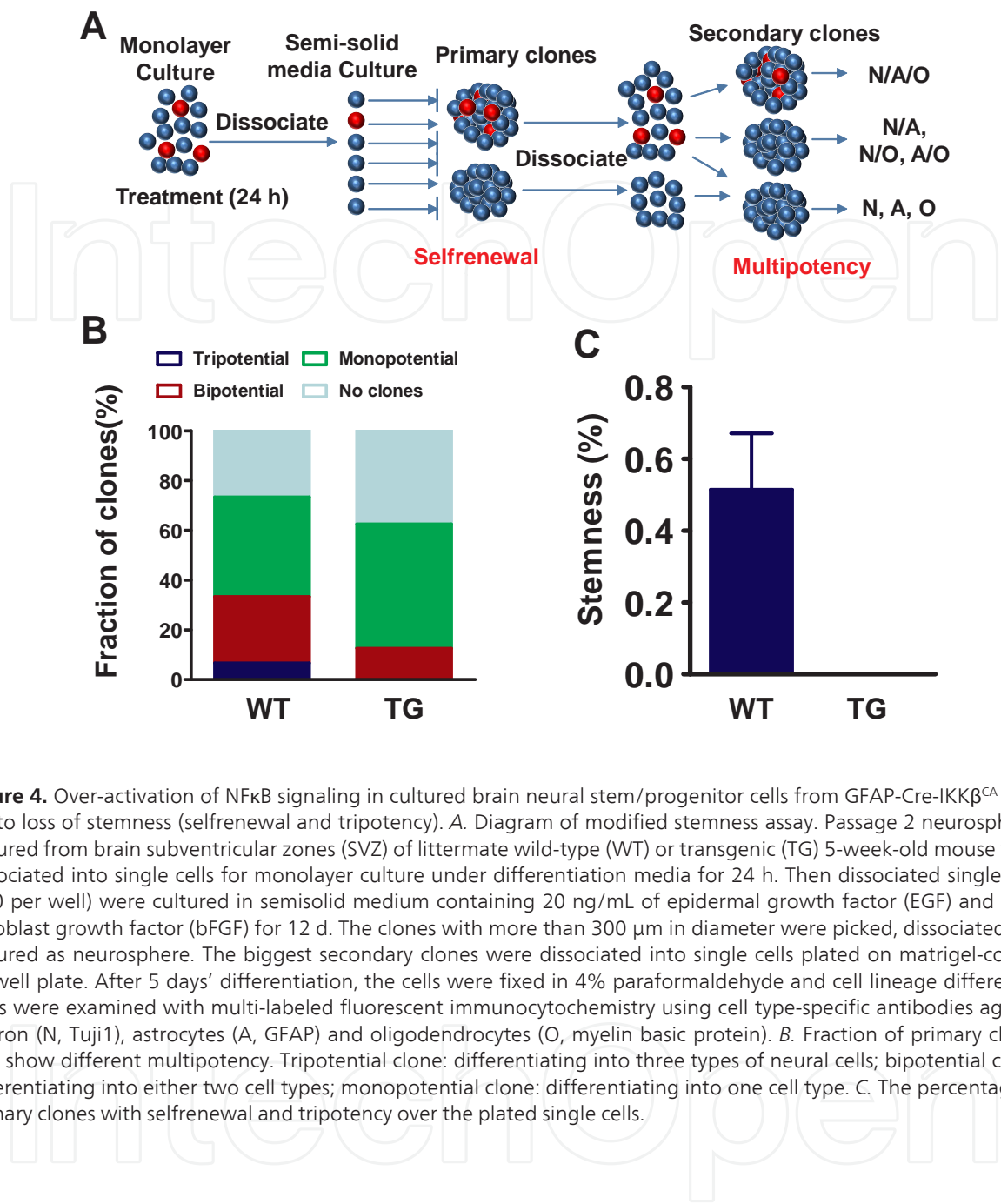
Figure 4. Over-activation of NFκB signaling in cultured brain neural stem/progenitor cells from GFAP-Cre-IKKβ[CA] mice led to loss of stemness (selfrenewal and tripotency). *A.* Diagram of modified stemness assay. Passage 2 neurospheres cultured from brain subventricular zones (SVZ) of littermate wild-type (WT) or transgenic (TG) 5-week-old mouse were dissociated into single cells for monolayer culture under differentiation media for 24 h. Then dissociated single cells (500 per well) were cultured in semisolid medium containing 20 ng/mL of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) for 12 d. The clones with more than 300 μm in diameter were picked, dissociated and cultured as neurosphere. The biggest secondary clones were dissociated into single cells plated on matrigel-coated 96-well plate. After 5 days' differentiation, the cells were fixed in 4% paraformaldehyde and cell lineage differentiations were examined with multi-labeled fluorescent immunocytochemistry using cell type-specific antibodies against neuron (N, Tuji1), astrocytes (A, GFAP) and oligodendrocytes (O, myelin basic protein). *B.* Fraction of primary clones that show different multipotency. Tripotential clone: differentiating into three types of neural cells; bipotential clone: differentiating into either two cell types; monopotential clone: differentiating into one cell type. *C.* The percentage of primary clones with selfrenewal and tripotency over the plated single cells.

3. Regulation of proneuronal genes by NFκB signaling

At each step of neurogenesis, cells undergo symmetric and asymmetric dividing to maintain stemness and generate daughter progeny. The self-renewal and neuronal fate decision of NECs/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 [48]. Neuronal fate decision also relies on the intrinsic proneuronal genes in NECs/NSCs/NPCs [49]. The proneuronal factors specify distinct neuronal identities in different regions of the nervous system [49, 50]. Transcriptional activation and epigenic modification of the proneuronal genes are essential for neuronal lineage progression [51]. Little is known about the effect of NFκB signaling on the expression or function of proneuronal factors during neurogenesis. 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 [52, 53, 54]. In contrast, Hes6 promotes neuronal differentiation but inhibits astrocyte differentiation [55, 56]. Notch signaling is regulated by NFκB signaling, and thus it is speculated that NFκB signaling may regulate the expression of proneuronal genes during neural induction and neurogenesis [57, 58, 59]. The tripartite motif-containing protein 32 (Trim32) promotes asymmetric dividing and neuronal differentiation of NSCs/NPCs by regulating protein degradation and microRNA activity [60, 61], and enhancing retinoic acid receptor-mediated transcription [62]. Our studies demonstrated that NFκB inhibition blocks the asymmetric distribution of Trim32 and maintain NSC selfrenewal [32], implying that NFκB signaling may initiate neuronal differentiation through suppressing Trim32 function.

4. Regulation of neural induction and neural plate patterning by NFκB signaling

NFκB signaling is essential for embryonic development (http://www.bu.edu/nf-kb/gene-resources/gene-knockouts/) because p65 knockout mice died on E15 and p65/p50 or p65/c-rel double knockout mice died on E13 due to liver degeneration [63, 64]. 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 [65], providing an opportunity to investigate the role of NFκB signaling in regulating embryonic neurogenesis [34]. 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 [66].

Several lines of clinical studies identified the correlation of NFκB signaling defects to various neurodevelopmental disorders. Among 6 genes associated with nonsyndromic autosomal-recessive mental retardation [67, 68, 69], two, NIK- and IKKβ-binding protein (NIBP) [67, 68, 69] and coiled-coil and C2 domain-containing protein 2A (CC2D1A) [70, 71], have been shown to regulate NFκB signaling through the classical IKKβ pathway, implying the important role of NFκB signaling in mental retardation and possibly other neurodevelopmental diseases. In autism spectrum disorders, activation of NFκB signaling is significantly increased [72, 73, 74], although the role and mechanism of the activated NFκB signaling remain to be determined.

During neural induction, the ectodermal epithelial cells transit into NECs due to the inhibition of bone morphogenetic protein (BMP) signaling by the neural inducer (Chordin, Noggin and Follistatin). In this original "default model", high activity of BMP signaling defines epidermis, while absence of BMP specifies neural plate [75, 76, 77]. However, this model can no longer explain the complicate process of neural induction, which involves additional signaling pathways such as Wnt/β-catenin, FGF, Sox2, and Notch signaling [77, 78, 79, 80, 81, 82]. NFκB signaling is shown to inhibit BMP signaling in oesteoblastogenesis [83, 84]. We speculate that NFκB may regulate neural induction. Previous studies showed that the graded activation of NFκB/c-rel protein in the dorsal region determine the dorsal-ventral patterning in Drosophila [85, 86, 87, 88] and Xenopus laevis [89]. During mouse embryogenesis, virtually all members of the NFκB pathway are expressed in embryonic, trophoblast, and uterine cells [90]. It is proposed that NFκB may protect the embryos exposed to embryopathic stresses, possibly through its anti-apoptotic effect [90]. However, there is no direct evidence for the role of NFκB signaling in the *in vivo* neural induction (Figure 5).

5. Importance of NFκB signaling in mediating early differentiation of ES/iPS

In vitro neural induction from cultured ES cells or induced pluripotent stem (iPS) cells has been established [80, 82, 91, 92], but the signaling mechanisms remain largely unknown. Such induction is an excellent *in vitro* model to recapture the *in vivo* neural induction and embryonic neurogenesis [80]. The signaling pathways identified during endogenous embryonic morphogenesis can be applied to the neural induction and patterning, such as BMP, FGF, Wnt, Shh and Notch signaling [77, 78, 79, 80, 81, 82]. We speculate that NFκB signaling, through crosstalk with these signaling pathways, play an important role in the neuronal induction from ES or iPS cells (Figure 5) [80].

During murine spermatogenesis, NFκB is activated in a stage-specific manner [93]. During oocyte maturation and early embryonic development, NFκB is activated [94, 95]. In Drosophila melanogaster, the mRNA of the p65 homologue, named Dorsal, is maternally expressed and is concentrated in the egg cortex [85]. In Xenopus, NFκB activation is observed during oocyte maturation [96] and in late blastulae and gastrulae [97]. In zebrafish, NFκB signaling regulates notochord differentiation via activating the expression of no tail (ntl) gene [98]. In mouse embryos, NFκB activation is crucial to engage development beyond the 2-cell stage [94]. NFκB mediates the neurogenic effect of erythropoietin in neurosphere cultures from E14 mouse ganglionic eminence [99]. 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 [100, 101, 102]. In human ES cells, the classical NFκB pathway regulates differentiation while the non-classical pathway maintains pluripotency [103]. The transcription factor Nanog is essential in maintaining pluripotency of ES cells [104]. During ES cell differentiation, endogenous NFκB activity and target-gene expression are increased (Figure 5) [101, 102, 105]. NFκB inhibition increases expression of pluripotency markers [106, 107]. Nanog binds to NFκB proteins, inhibits NFκB activity and cooperates with Stat3 to

maintain pluripotency [100]. ES cell-specific miR-290 maintains the pluripotency and self-renewal of ES cells through repressing classical NFκB signaling [107]. Forced expression of p65 causes loss of pluripotency, promotes differentiation of ES cells, and leads to an epithelial to mesenchymal transition [107]. 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 [107]. Taken altogether, NFκB signaling is activated and required during the early differentiation of various stem cells and embryogenesis (Figure 5).
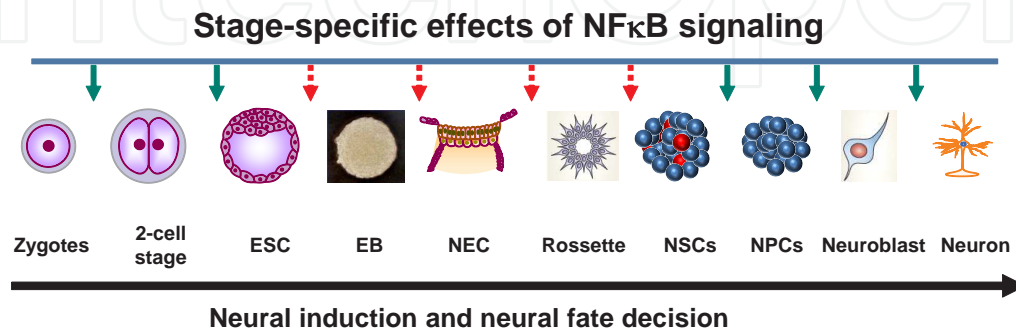

Figure 5. Potential regulatory sites of NFκB signaling during neuronal cell fate decision. Solid green arrows indicate the sites supported by limited reports, while the dotted red arrows indicate the stages that need experimental supports. ESC, embryonic stem cells; EB, embryoid body; NEC, neural epithelial cells; NSCs, neural stem cells; NPCs, neural progenitor cells.

6. Promotion of iPS reprograming by pharmacological or genetic inhibition of NFκB signaling.

Various somatic cells have been successfully reprogramed into the ES-like pluripotent stem cells by a combination of factors or a single factor [108, 109]. During the reprogramming process, the classical NFκB signaling is inhibited [103, 106, 107]. Therefore, we speculate that NFκB inhibition might directly induce or promote the reprograming of iPS. Many specific inhibitors for NFκB signaling have been developed and some of them are applied to clinical trial [110]. In addition, fibroblasts or other somatic cells from transgenic mice deficient in NFκB signaling or clinical patients with mutation of NFκB signaling components can be easily accessible. It will be imperative to use NFκB inhibitors or genetic sources for easy and fast generation of iPS for drug discovery and cell transplantation studies.

7. Concluding remark and future direction

NFκB signaling is a key mediator for numerous niche factors that regulate various stages or phases of neural induction and neurogenesis. The classical pathway of NFκB activation plays important role in regulating selfrenewal/multipotency and early differentiation of

NSCs and ES/iPS cells. During neural induction both *in vitro* and *in vivo*, NFκB signaling is required. However, further studies are needed to determine the expression and function of NFκB signaling during the formation of embryoid body and neural rosette (Figure 5). The upstream regulation and downstream mechanism will be important targets to better understand the essential role of NFκB signaling in initiating early differentiation of both neural induction and neurogenesis. These studies 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 [101, 102, 111]. It will be important to evaluate the different role of three NFκB pathways during neuronal fate decision.

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