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 SCFβ-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 SCFβ-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].
[42]. Selective inhibition of classical NFκB signaling by various pharmacologic inhibitors, small interfering RNA and NSC-specific transgene dominant-negative IκBα retain the tripo-tential ability of differentiation and restore or enhance self-renewal capability of NSCs, suggest-ing 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 constitu-tively active form of IKKβ (IKKβCA) [46, 47] driven by the promoter of glial fibrillary acid protein (GFAP) by crossbreeding GFAP-Cre mice (Jackson Lab, 004600) with Rosa26-StopFloxed-IKKβCA mice (Jackson Lab, 008242). In vitro studies using the NSCs/NPCs cultured from the brain of GFAP-IKKβCA 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 ca-pacity (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-IKKβCA mice deter-mined 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 carry-ing 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-IKKβCA 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-IKK β 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 complicated 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 osteoblastogenesis [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 reprogramming 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 reprogramming 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.

Author details

Yonggang Zhang and Wenhui Hu*

*Address all correspondence to: whu@temple.edu

Department of Neuroscience, Temple University School of Medicine, Philadelphia, USA

References

[1] Kowalczyk T, Pontious A, Englund C, et al. Intermediate neuronal progenitors (basal progenitors) produce pyramidal-projection neurons for all layers of cerebral cortex. Cereb Cortex 2009;19:2439-2450

[2] Farioli-Vecchioli S, Saraulli D, Costanzi M, et al. The timing of differentiation of adult hippocampal neurons is crucial for spatial memory. PLoS Biol 2008;6:e246

[3] Kosodo Y, Roper K, Haubensak W, et al. Asymmetric distribution of the apical plasma membrane during neurogenic divisions of mammalian neuroepithelial cells. EMBO J 2004;23:2314-2324

[4] Haubensak W, Attardo A, Denk W, et al. Neurons arise in the basal neuroepithelium of the early mammalian telencephalon: a major site of neurogenesis. Proc Natl Acad Sci U S A 2004;101:3196-3201

[5] Farkas LM, Huttner WB. The cell biology of neural stem and progenitor cells and its significance for their proliferation versus differentiation during mammalian brain development. Curr Opin Cell Biol 2008;20:707-715

[6] Sauvageot CM, Stiles CD. Molecular mechanisms controlling cortical gliogenesis. Curr Opin Neurobiol 2002;12:244-249

[7] Wang DD, Bordey A. The astrocyte odyssey. Prog Neurobiol 2008;86:342-367
[8] Perkins ND. Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat Rev Mol Cell Biol 2007;8:49-62

[9] Hacker H, Karin M. Regulation and function of IKK and IKK-related kinases. Sci STKE 2006;2006:re13

[10] Boyce BF, Yao Z, Xing L. Functions of nuclear factor kappaB in bone. Ann N Y Acad Sci 2010;1192:367-375

[11] Mancino A, Lawrence T. Nuclear factor-kappaB and tumor-associated macrophages. Clin Cancer Res 2010;16:784-789

[12] Lin Y, Bai L, Chen W, et al. The NF-kappaB activation pathways, emerging molecular targets for cancer prevention and therapy. Expert Opin Ther Targets 2010;14:45-55

[13] Wong ET, Tergaonkar V. Roles of NF-kappaB in health and disease: mechanisms and therapeutic potential. Clin Sci (Lond) 2009;116:451-465

[14] Teng FY, Tang BL. NF-kappaB signaling in neurite growth and neuronal survival. Rev Neurosci 2010;21:299-313

[15] Gutierrez H, Davies AM. Regulation of neural process growth, elaboration and structural plasticity by NF-kappaB. Trends Neurosci 2011;34:316-325

[16] Chen LF, Greene WC. Shaping the nuclear action of NF-kappaB. Nat Rev Mol Cell Biol 2004;5:392-401

[17] Viatour P, Merville MP, Bours V, et al. Phosphorylation of NF-kappaB and IkappaB proteins: implications in cancer and inflammation. Trends Biochem Sci 2005;30:43-52

[18] Sun SC. The noncanonical NF-kappaB pathway. Immunol Rev 2012;246:125-140

[19] Razani B, Reichardt AD, Cheng G. Non-canonical NF-kappaB signaling activation and regulation: principles and perspectives. Immunol Rev 2011;244:44-54

[20] Kaltschmidt B, Kaltschmidt C. NF-kappaB in the nervous system. Cold Spring Harb Perspect Biol 2009;1:a001271

[21] Imielski Y, Schwamborn JC, Luningschror P, et al. Regrowing the adult brain: NF-kappaB controls functional circuit formation and tissue homeostasis in the dentate gyrus. PLoS One 2012;7:e30838

[22] Mattson MP, Meffert MK. Roles for NF-kappaB in nerve cell survival, plasticity, and disease. Cell Death Differ 2006;13:852-860

[23] Camandola S, Mattson MP. NF-kappa B as a therapeutic target in neurodegenerative diseases. Expert Opin Ther Targets 2007;11:123-132

[24] Fridmacher V, Kaltschmidt B, Goudeau B, et al. Forebrain-specific neuronal inhibition of nuclear factor-kappaB activity leads to loss of neuroprotection. J Neurosci 2003;23:9403-9408
[25] Boersma MC, Dresselhaus EC, De Biase LM, et al. A requirement for nuclear factor-kappaB in developmental and plasticity-associated synaptogenesis. J Neurosci 2011;31:5414-5425

[26] Sanchez-Ponce D, Tapia M, Munoz A, et al. New role of IKK alpha/beta phosphorylated I kappa B alpha in axon outgrowth and axon initial segment development. Mol Cell Neurosci 2008;37:832-844

[27] Schultz C, Konig HG, Del Turco D, et al. Coincident enrichment of phosphorylated IkappaBalpha, activated IKK, and phosphorylated p65 in the axon initial segment of neurons. Mol Cell Neurosci 2006;33:68-80

[28] Politi C, Del Turco D, Sie JM, et al. Accumulation of phosphorylated I kappaB alpha and activated IKK in nodes of Ranvier. Neuropathol Appl Neurobiol 2008;34:357-365

[29] Denis-Donini S, Caprini A, Frassoni C, et al. Members of the NF-kappaB family expressed in zones of active neurogenesis in the postnatal and adult mouse brain. Brain Res Dev Brain Res 2005;154:81-89

[30] Rolls A, Shechter R, London A, et al. Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol 2007;9:1081-1088

[31] Widera D, Kaus A, Kaltschmidt C, et al. Neural stem cells, inflammation and NF-kappaB: basic principle of maintenance and repair or origin of brain tumours? J Cell Mol Med 2008;12:459-470

[32] Zhang Y, Liu J, Yao S, et al. Nuclear factor kappa B signaling initiates early differentiation of neural stem cells. Stem Cells 2012;30:510-524

[33] Meneghini V, Francese MT, Carraro L, et al. A novel role for the Receptor for Advanced Glycation End-products in neural progenitor cells derived from adult Sub-Ventricular Zone. Mol Cell Neurosci 2010;45:139-150

[34] Young KM, Bartlett PF, Coulson EJ. Neural progenitor number is regulated by nuclear factor-kappaB p65 and p50 subunit-dependent proliferation rather than cell survival. J Neurosci Res 2006;83:39-49

[35] Zhu C, Liu Z, Gui L, et al. Mutated IkappaBalpha represses proliferation of immortalized neural progenitor cells and prevents their apoptosis after oxygen-glucose deprivation. Brain Res 2008;1244:24-31

[36] Wu JP, Kuo JS, Liu YL, et al. Tumor necrosis factor-alpha modulates the proliferation of neural progenitors in the subventricular/ventricular zone of adult rat brain. Neurosci Lett 2000;292:203-206

[37] Widera D, Mikenberg I, Elvers M, et al. Tumor necrosis factor alpha triggers proliferation of adult neural stem cells via IKK/NF-kappaB signaling. BMC Neurosci 2006;7:64
[38] Rubio-Araiz A, Arevalo-Martin A, Gomez-Torres O, et al. The endocannabinoid system modulates a transient TNF pathway that induces neural stem cell proliferation. Mol Cell Neurosci 2008;38:374-380

[39] Denis-Donini S, Dellarole A, Crociara P, et al. Impaired adult neurogenesis associated with short-term memory defects in NF-kappaB p50-deficient mice. J Neurosci 2008;28:3911-3919

[40] Bernardino L, Agasse F, Silva B, et al. Tumor necrosis factor-alpha modulates survival, proliferation, and neuronal differentiation in neonatal subventricular zone cell cultures. Stem Cells 2008;26:2361-2371

[41] Lou SJ, Gu P, Xu H, et al. [Effect of tumor necrosis factor-alpha on differentiation of mesencephalic neural stem cells and proliferation of oligodendrocytes in the rat]. Sheng Li Xue Bao 2003;55:183-186

[42] Scholzke MN, Rottinger A, Murikinati S, et al. TWEAK regulates proliferation and differentiation of adult neural progenitor cells. Mol Cell Neurosci 2011;46:325-332

[43] Encinas JM, Sierra A. Neural stem cell deforestation as the main force driving the age-related decline in adult hippocampal neurogenesis. Behav Brain Res 2012;227:433-439

[44] Villeda SA, Luo J, Mosher KI, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 2011;477:90-94

[45] Koo JW, Russo SJ, Ferguson D, et al. Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc Natl Acad Sci U S A 2010;107:2669-2674

[46] Calado DP, Zhang B, Srinivasan L, et al. Constitutivecanonical NF-kappaB activation cooperates with disruption of BLIMP1 in the pathogenesis of activated B cell-like diffuse large cell lymphoma. Cancer Cell 2010;18:580-589

[47] Vlantis K, Wullaert A, Sasaki Y, et al. Constitutive IKK2 activation in intestinal epithelial cells induces intestinal tumors in mice. J Clin Invest 2011;121:2781-2793

[48] Shi Y, Sun G, Zhao C, et al. Neural stem cell self-renewal. Crit Rev Oncol Hematol 2008;65:43-53

[49] Bertrand N, Castro DS, Guillemot F. Proneural genes and the specification of neural cell types. Nat Rev Neurosci 2002;3:517-530

[50] Shaker T, Dennis D, Kurra Sch D, et al. Neurog1 and Neurog2 coordinately regulate development of the olfactory system. Neural Dev 2012;7:28

[51] Castro DS, Guillemot F. Old and new functions of proneural factors revealed by the genome-wide characterization of their transcriptional targets. Cell Cycle 2011;10:4026-4031
[52] Cau E, Gradwohl G, Casarosa S, et al. Hes genes regulate sequential stages of neurogenesis in the olfactory epithelium. Development 2000;127:2323-2332

[53] Kageyama R, Ohtsuka T, Kobayashi T. Roles of Hes genes in neural development. Dev Growth Differ 2008;50 Suppl 1:S97-103

[54] Wang R, Liu K, Chen L, et al. Neural fate decisions mediated by trans-activation and cis-inhibition in Notch signaling. Bioinformatics 2011;27:3158-3165

[55] Vilas-Boas F, Henrique D. HES6-1 and HES6-2 function through different mechanisms during neuronal differentiation. PLoS One 2010;5:e15459

[56] Fior R, Henrique D. A novel hes5/ hes6 circuitry of negative regulation controls Notch activity during neurogenesis. Dev Biol 2005;281:318-333

[57] Bonini SA, Ferrari-Toninelli G, Uberti D, et al. Nuclear factor kappaB-dependent neurite remodeling is mediated by Notch pathway. J Neurosci 2011;31:11697-11705

[58] Ang HL, Tergaonkar V. Notch and NFkappaB signaling pathways: Do they collaborate in normal vertebrate brain development and function? Bioessays 2007;29:1039-1047

[59] Fujita K, Yasui S, Shinohara T, et al. Interaction between NF-kappaB signaling and Notch signaling in gliogenesis of mouse mesencephalic neural crest cells. Mech Dev 2011;128:496-509

[60] Schwamborn JC, Berezikov E, Knoblich JA. The TRIM-NHL protein TRIM32 activates microRNAs and prevents self-renewal in mouse neural progenitors. Cell 2009;136:913-925

[61] Hillje AL, Worlitzer MM, Palm T, et al. Neural stem cells maintain their stemness through protein kinase C zeta-mediated inhibition of TRIM32. Stem Cells 2011;29:1437-1447

[62] Sato T, Okumura F, Kano S, et al. TRIM32 promotes neural differentiation through retinoic acid receptor-mediated transcription. J Cell Sci 2011;124:3492-3502

[63] Beg AA, Sha WC, Bronson RT, et al. Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-kappa B. Nature 1995;376:167-170

[64] Grossmann M, Metcalf D, Merryfull J, et al. The combined absence of the transcription factors Rel and RelA leads to multiple hemopoietic cell defects. Proc Natl Acad Sci U S A 1999;96:11848-11853

[65] Alcamo E, Mizgerd JP, Horwitz BH, et al. Targeted mutation of TNF receptor I rescues the RelA-deficient mouse and reveals a critical role for NF-kappa B in leukocyte recruitment. J Immunol 2001;167:1592-1600

[66] Li Q, Estepa G, Memet S, et al. Complete lack of NF-kappaB activity in IKK1 and IKK2 double-deficient mice: additional defect in neurulation. Genes Dev 2000;14:1729-1733
[67] Mir A, Kaufman L, Noor A, et al. Identification of mutations in TRAPPC9, which encodes the NIK- and IKK-beta-binding protein, in nonsyndromic autosomal-recessive mental retardation. Am J Hum Genet 2009;85:909-915

[68] Mochida GH, Mahajnah M, Hill AD, et al. A truncating mutation of TRAPPC9 is associated with autosomal-recessive intellectual disability and postnatal microcephaly. Am J Hum Genet 2009;85:897-902

[69] Philippe O, Rio M, Carioux A, et al. Combination of linkage mapping and microarray-expression analysis identifies NF-kappaB signaling defect as a cause of autosomal-recessive mental retardation. Am J Hum Genet 2009;85:903-908

[70] Zhao M, Raingo J, Chen ZJ, et al. Cc2d1a, a C2 domain containing protein linked to nonsyndromic mental retardation, controls functional maturation of central synapses. J Neurophysiol 2011;105:1506-1515

[71] Noor A, Windpassinger C, Patel M, et al. CC2D2A, encoding a coiled-coil and C2 domain protein, causes autosomal-recessive mental retardation with retinitis pigmentosa. Am J Hum Genet 2008;82:1011-1018

[72] Ziets MN, Rennert OM. Expression profiling of autism candidate genes during human brain development implicates central immune signaling pathways. PLoS One 2011;6:e24691

[73] Naik US, Gangadharan C, Abbagani K, et al. A study of nuclear transcription factor-kappa B in childhood autism. PLoS One 2011;6:e19488

[74] Go HS, Seo JE, Kim KC, et al. Valproic acid inhibits neural progenitor cell death by activation of NF-kappaB signaling pathway and up-regulation of Bcl-XL. J Biomed Sci 2011;18:48

[75] Levine AJ, Brivanlou AH. Proposal of a model of mammalian neural induction. Dev Biol 2007;308:247-256

[76] Lenka N, Ramasamy SK. Neural induction from ES cells portrays default commitment but instructive maturation. PLoS One 2007;2:e1349

[77] Stern CD. Neural induction: 10 years on since the ‘default model’. Curr Opin Cell Biol 2006;18:692-697

[78] Mason I. Initiation to end point: the multiple roles of fibroblast growth factors in neural development. Nat Rev Neurosci 2007;8:583-596

[79] Stuhlmiller TJ, Garcia-Castro MI. Current perspectives of the signaling pathways directing neural crest induction. Cell Mol Life Sci 2012

[80] Osakada F, Takahashi M. Neural induction and patterning in Mammalian pluripotent stem cells. CNS Neurol Disord Drug Targets 2011;10:419-432

[81] de Almeida I, Rolo A, Batut J, et al. Unexpected activities of Smad7 in Xenopus mesodermal and neural induction. Mech Dev 2008;125:421-431
[82] Salewski RP, Buttigieg J, Mitchell RA, et al. The generation of definitive neural stem cells from piggyBac transposon induced pluripotent stem cells can be enhanced by induction of the NOTCH signalling pathway. Stem Cells Dev 2012

[83] Tang Y, Xie H, Chen J, et al. Activated NF-kB in bone marrow mesenchymal stem cells from SLE patients inhibits osteogenic differentiation through down-regulating Smad signaling. Stem Cells Dev 2012

[84] Yamaguchi M, Weitzmann MN, Murata T. Exogenous regucalcin stimulates osteoclastogenesis and suppresses osteoblastogenesis through NF-kappaB activation. Mol Cell Biochem 2012;359:193-203

[85] Chen G, Handel K, Roth S. The maternal NF-kappaB/dorsal gradient of Tribolium castaneum: dynamics of early dorsoventral patterning in a short-germ beetle. Development 2000;127:5145-5156

[86] DeLotto R, DeLotto Y, Steward R, et al. Nucleocytoplasmic shuttling mediates the dynamic maintenance of nuclear Dorsal levels during Drosophila embryogenesis. Development 2007;134:4233-4241

[87] Reeves GT, Stathopoulos A. Graded dorsal and differential gene regulation in the Drosophila embryo. Cold Spring Harb Perspect Biol 2009;1:a000836

[88] Ayyar S, Pistillo D, Calleja M, et al. NF-kappaB/Rel-mediated regulation of the neural fate in Drosophila. PLoS One 2007;2:e1178

[89] Lake BB, Ford R, Kao KR. Xrel3 is required for head development in Xenopus laevis. Development 2001;128:263-273

[90] Torchinsky A, Toder V. To die or not to die: the function of the transcription factor NF-kappaB in embryos exposed to stress. Am J Reprod Immunol 2004;51:138-143

[91] Chambers SM, Fasano CA, Papapetrou EP, et al. Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. Nat Biotechnol 2009;27:275-280

[92] Tsuji O, Miura K, Fujiyoshi K, et al. Cell therapy for spinal cord injury by neural stem/progenitor cells derived from iPS/ES cells. Neurotherapeutics 2011;8:668-676

[93] Lilienbaum A, Sage J, Memet S, et al. NF-kappa B is developmentally regulated during spermatogenesis in mice. Dev Dyn 2000;219:333-340

[94] Nishikimi A, Mukai J, Yamada M. Nuclear translocation of nuclear factor kappa B in early 1-cell mouse embryos. Biol Reprod 1999;60:1536-1541

[95] Paciolla M, Boni R, Fusco F, et al. Nuclear factor-kappaB-inhibitor alpha (NFKBIA) is a developmental marker of NF-kappaB/p65 activation during in vitro oocyte maturation and early embryogenesis. Hum Reprod 2011;26:1191-1201

[96] Dominguez I, Sanz L, Arenzana-Seisdedos F, et al. Inhibition of protein kinase C zeta subspecies blocks the activation of an NF-kappa B-like activity in Xenopus laevis oocytes. Mol Cell Biol 1993;13:1290-1295
[97] Richardson JC, Garcia Estrabot AM, Woodland HR. XrelA, a Xenopus maternal and zygotic homologue of the p65 subunit of NF-kappa B. Characterisation of transcriptional properties in the developing embryo and identification of a negative interference mutant. Mech Dev 1994;45:173-189

[98] Correa RG, Tergaonkar V, Ng JK, et al. Characterization of NF-kappa B/I kappa B proteins in zebra fish and their involvement in notochord development. Mol Cell Biol 2004;24:5257-5268

[99] Shingo T, Sorokan ST, Shimazaki T, et al. Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. J Neurosci 2001;21:9733-9743

[100] Torres J, Watt FM. Nanog maintains pluripotency of mouse embryonic stem cells by inhibiting NFkappaB and cooperating with Stat3. Nat Cell Biol 2008;10:194-201

[101] Kim YE, Kang HB, Park JA, et al. Upregulation of NF-kappaB upon differentiation of mouse embryonic stem cells. BMB Rep 2008;41:705-709

[102] Kang HB, Kim YE, Kwon HJ, et al. Enhancement of NF-kappaB expression and activity upon differentiation of human embryonic stem cell line SNUhES3. Stem Cells Dev 2007;16:615-623

[103] Yang C, Atkinson SP, Vilella F, et al. Opposing putative roles for canonical and non-canonical NFkappaB signaling on the survival, proliferation, and differentiation potential of human embryonic stem cells. Stem Cells 2010;28:1970-1980

[104] Mitsui K, Tokuzawa Y, Itoh H, et al. The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells. Cell 2003;113:631-642

[105] Guan X, Yabuuchi A, Huo H, et al. Derivation of human embryonic stem cells with NEMO deficiency. Stem Cell Res 2012;8:410-415

[106] Dutta D, Ray S, Home P, et al. Self-renewal versus lineage commitment of embryonic stem cells: protein kinase C signaling shifts the balance. Stem Cells 2011;29:618-628

[107] Luningschror P, Stocker B, Kaltschmidt B, et al. miR-290 Cluster Modulates Pluripotency by Repressing Canonical NF-kappaB Signaling. Stem Cells 2012;30:655-664

[108] Saporta MA, Grskovic M, Dimos JT. Induced pluripotent stem cells in the study of neurological diseases. Stem Cell Res Ther 2011;2:37

[109] Rajasingh J. Reprogramming of somatic cells. Prog Mol Biol Transl Sci 2012;111:51-82

[110] Kwak JH, Jung JK, Lee H. Nuclear factor-kappa B inhibitors; a patent review (2006-2010). Expert Opin Ther Pat 2011;21:1897-1910

[111] Saldanha-Araujo F, Haddad R, Malmegrim de Farias KC, et al. Mesenchymal stem cells promote the sustained expression of CD69 on activated T-lymphocytes: roles of canonical and non-canonical NF-kappaB signaling. J Cell Mol Med 2011
