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Review

Role and mechanisms of the NF-κB signaling pathway in various developmental processes

Peiqi Liu [a], Yue Li [a], Weilin Wang [a], Yuzuo Bai [a], Huimin Jia [a], Zhengwei Yuan [b,*], Zhonghua Yang [a,*]

[a] Department of Pediatric Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China
[b] Key Laboratory of Health Ministry for Congenital Malformation, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China

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ABSTRACT

Since the discovery of the nuclear factor kappa B (NF-κB) transcription factor 36 years ago, many studies have linked the NF-κB signaling pathway to pathological and physiological processes, such as inflammation, immune response, and tumorigenesis. However, as the NF-κB signaling pathway is evolutionarily conserved from flies to humans, an increasing number of studies have focused on the impact of NF-κB signaling on developmental processes. While our understanding of the mechanisms underlying NF-κB signaling involved in tissue and organ development is limited, the numerous studies conducted in recent years have provided preliminary insights into these molecular mechanisms. In this review, we summarize the latest information on the molecular mechanisms behind NF-κB signaling involved in tissue and organ development, highlighting the role and significance of the NF-κB signaling pathway in developmental processes. This review elucidates the fact that the development of nearly all tissues is associated with NF-κB signaling, either directly or indirectly.

1. Introduction

Members of the nuclear factor kappa B (NF-κB) signaling pathway include NF-κB dimers, regulators of inhibitor of kappa B (IκB), IκB kinase (IKK) complexes, and their interactors. In mammals, the NF-κB monomer family is composed of five members: RelA/p65, RelB, c-Rel, and the precursors of p50 and p52 (p105 and p100) [1,2]. These NF-κB factors can form homodimers or heterodimers in the active state, except for RelB, which only forms heterodimers [1]. Activated NF-κB dimers can translocate into the nucleus and drive the transcription of numerous target genes by binding to a recognition site within the promoters of the target genes [3]. In the canonical pathway, NF-κB dimers are inactivated by IκB complexes in the cytoplasm [3,4]. The interaction between upstream signaling molecules and receptors activates IKK complexes, which are composed of IKKα/IKK1, IKKβ/IKK2, and the scaffold protein NEMO (IKKγ) [1,2]. Activated IKK complexes directly phosphorylate IκBs, and then phosphorylated IκBs are degraded by the ubiquitin-proteasome pathway [4,5]. Ultimately, released NF-κB dimers can translocate into the nucleus. In contrast to the canonical pathway, the non-canonical NF-κB pathway depends on the phosphorylation and proteolytic processing of p100. Activated NF-κB-inducing kinase (NIK) leads to the phosphorylation and activation of IKKα [2,6], which results in the phosphorylation and hydrolysis of p100 into the p52 subunit. Next, p52-RelB translocates into the nucleus to regulate transcription [1,2,6]. The NF-κB signaling pathway can be activated by the recognition of endogenous or exogenous stimuli by receptors, including tumor necrosis factor (TNF) receptors, toll-like receptors (TLRs), T cell receptors (TCRs), and interleukin receptors (ILRs), which typically activate the canonical NF-κB pathway and its downstream transcription factors (RelA-p50) [6,7]. In contrast, ligation of TNF superfamily receptor 12 A (Fn14/TWEAK receptor), lymphotoxin β receptor (LTβR), B cell activating factor receptor (BAFF-R) [8], receptor activator of NF-κB (RANK), CD40 [8], and CD27 typically activate the non-canonical NF-κB pathway [9].

Numerous studies have uncovered diverse functions and mechanisms associated with the NF-κB signaling pathway since its discovery nearly four decades ago, as well as its impact on the occurrence and progression of diseases, such as inflammatory disease [10], autoimmune disease [11,12], and cancer [13,14]. NF-κB signaling is involved in human genetic diseases [7], wherein *IKBKG* and *NFKBIA* mutations could affect the developmental process and immunity [12,15,16]. Furthermore, Rel domain-containing proteins of the NF-κB family are evolutionarily

* Correspondence to: 36 Sanhao Street, Heping District, Shenyang, Liaoning 110004, China.
E-mail addresses: yuanzw@sj-hospital.org (Z. Yuan), yangzh@sj-hosptial.org (Z. Yang).

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conserved among Kingdom Animalia [17,18]. NF-κB signaling pathways (both classical and non-classical) have been linked to numerous cellular and tissue formation processes, including proliferation [19,20], differentiation [20,21], apoptosis [19,20], survival [19,22], necrosis [23,24], and development [19,25]. Accumulating research have demonstrated that aside from its classical effect, the NF-κB signaling pathway also has a profound impact on embryonic development, including the development of different organs and systems [17,26–28]. However, the role of NF-κB signaling on tissue and organ development has not been thoroughly clarified. Although some reviews have discussed the role of the NF-κB signaling pathway in secondary lymphoid organ development (2003) [29], hemopoiesis (2009) [30], chondrogenesis (2019) [31], stem cells (2016, 2021) [17,18] and T cells development (2022) [32], there is no systematic review of whole organism development in vertebrates. Here, we performed a systematic review on the role and mechanisms of the NF-κB signaling pathway in the development of different types of systems and their affiliated organs, and focused on summarizing recent advances in this field. In this review, we searched related literature by applying keywords related to NF-κB and embryonic development (Supplementary Material) to comprehensively review the role of the NF-κB signaling pathway in embryonic development.

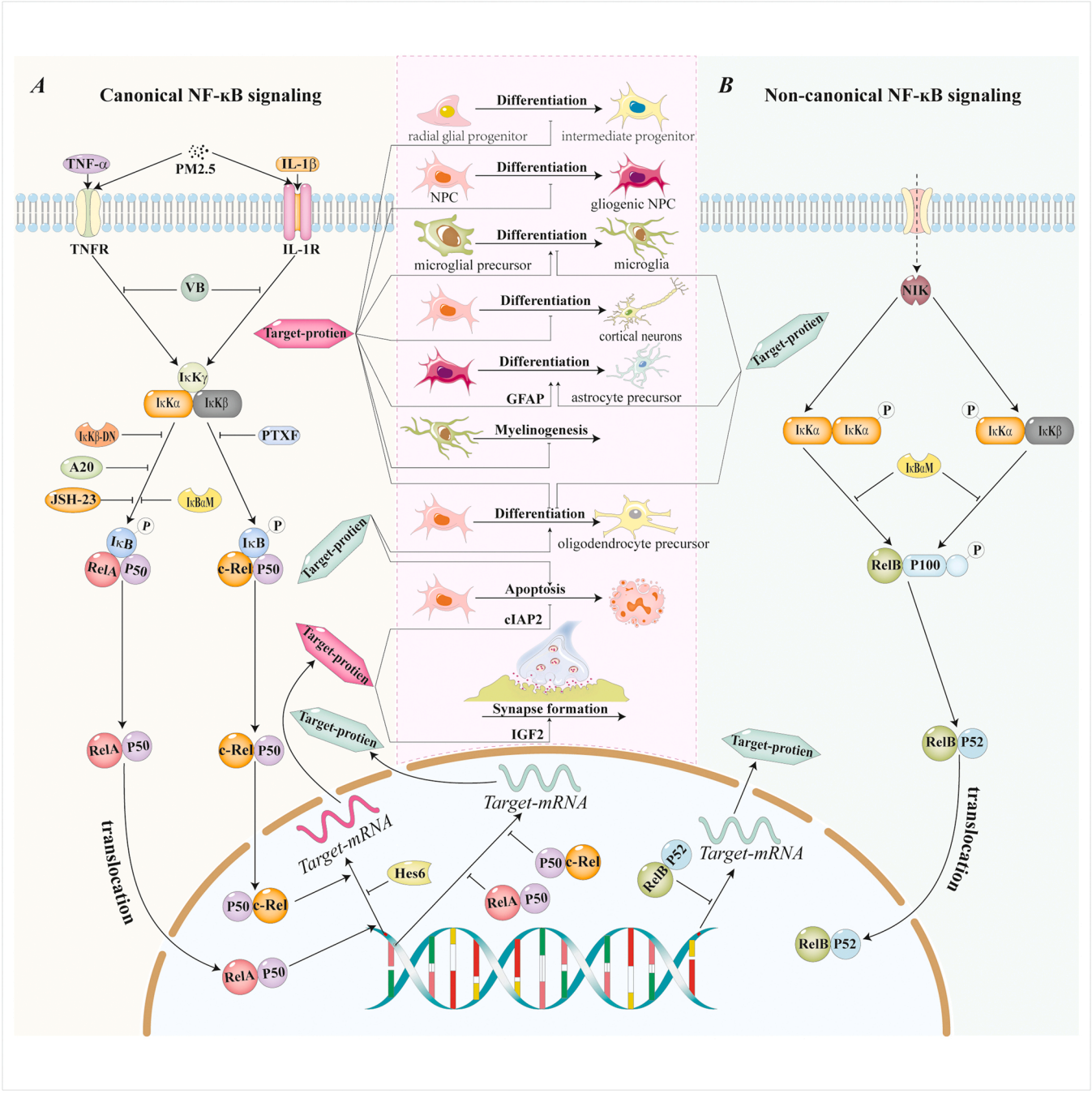

Fig. 1. Schematic depiction of the process of nervous system development mediated by NF-κB signaling pathway. *A* The process of canonical NF-κB signaling mediating nervous system development. *B* The role of non-canonical NF-κB signaling in nervous system development. Here and in succeeding figures, abbreviations are as follows: NPC, neural progenitor cell; VB, vitamin B; TNF-a, tumor necrosis factor-a; TNFR, TNF receptor; IKKβ-DN, dominant-negative IKKβ; IκBαM, mutated IκBα; PTXF, pentoxifylline; PM, particulate matter; A20, a ubiquitin editing enzyme; JSH-23, 4-Methyl-N^1-(3-phenylpropyl) benzene-1,2-diamine; GFAP, glial fibrillary acidic protein; cIAP2, cellular inhibitor of apoptosis 2; IGF2, insulin-like growth factor 2.

2. Relationship between NF-κB and nervous system development

2.1. Neural cell development

NF-κB is considered a key regulator of neural development. The canonical NF-κB pathway is involved in progenitor maintenance by upregulation of cIAP-2 (Fig. 1*A*) [33,34]. In a study using neocortical neural progenitor cells obtained from dissociated dorsal telencephalic cortices of CD1 mouse embryos, NF-κB signaling controls the timing of the neurogenic-to-gliogenic transition during the neurogenic phase. Blockade of the canonical NF-κB pathway with dominant-negative IKKβ and mutated IκBα lead to the formation of redundant gliogenic progenitors, and premature glial cell differentiation [35]. Another study using embryonic murine neural stem cells obtained a similar result wherein blockage of the NF-κB pathway via RelA inhibitor JSH-23 (Fig. 1*A*) obstructs neural progenitor cells to differentiate into astrocytic progenitor cells via excessive apoptosis, and NF-κB pathway activation via the extrinsic inflammation activator, TNF, inhibits neural progenitor cell differentiation into astrocytes [36]. RGP-selective transcripts, including NF-κB transcriptional effectors RelA, p50, and TBL1, are strongly linked to the NF-κB signaling pathway, and the NF-κB (RelA/p50) signaling pathway activated by TNF receptor 1 (TNFR1) in the developing neocortex is fundamental to maintain the neural stem cell identity of radial glial progenitors (RGPs) and disturb the genesis of intermediate progenitors, which are derived from RGPs (Fig. 1*A*) [37]. Methot et al. have shown that NF-κB signaling is downregulated during murine oligodendrogenesis [35], and a similar study on neuronal differentiation using human neural crest-derived stem cells found that c-Rel inhibition led to a significant increase in apoptosis, while the surviving cells switched their fate and differentiated into oligodendrocytes (Fig. 1*A*) [38]. Furthermore, Notch signaling is closely correlated to the NF-κB pathway to maintain neural progenitor cell identity [33,36,37]. A study using human embryonic kidney 293 cells (HEK-293) and primary neural progenitor cells revealed that hairy/enhancer-of-split transcription factor 6 (HES-6) could physically and functionally combine with RelA-containing NF-κB complexes and promote the differentiation and migration of neural progenitor cells, and RelA could antagonize the transcriptional repression effect of HES-6 on HES-1 in a dose-dependent manner, causing Notch signaling deficiency on progenitor maintenance [39]. NF-κB is not only associated with neural cell fate and apoptosis but also related to metabolism, autophagy, and cell cycle arrest in human embryonic neurogenesis. Results have shown that RelA correlated with oxidative phosphorylation, ATP synthases, ubiquinol-cytochrome c reductases, and NADH dehydrogenase categories in the context of neural differentiation [40]. Electrophoretic mobility shift assay (EMSA) identified that NF-κB dimer (RelA/p50) regulated the expression of protein tyrosine phosphatase non-receptor type 11 (PTPN11, also known as SHP-2), whose abnormal expression is related to delayed myelination and poor motor development in preterm infants, by binding with one variation of the PTPN11 promoter (g.–317 C>T) [41]. Blocking of the NF-κB pathway alleviated reactive gliosis and inflammation in white matter injury development, which is correlated with neuro-developmental deficits [42,43]. Prenatal ethanol exposure is an environmental stressor causing disturbed microglia activation and inflammation in fetal mice by increasing inflammatory signatures (IL-1β, IFN-γ, IL-6, CCL9, CXCR2) and promoting the nuclear translocation and more importantly, the phosphorylation of the p105 subunit, which can be reused by glutathione (GSH) in EOC13.31 cells [43]. It has been suggested that atmospheric particulate matter (PM) exposure, a leading environmental risk factor during pregnancy, could affect the developing nervous system [44,45]. RNA sequencing of microglia exposed to PM demonstrated that delays in microglia-derived myelinogenesis were positively associated with the p50 and NF-κB signaling pathways [44]. Furthermore, vitamin B supplementation during pregnancy alleviates PM2.5-induced hippocampal neuro-developmental inflammation and synaptic dysfunction in mice offspring by inhibiting NF- κB signaling and its upstream activation molecules, such as TNF-α and IL-1β (Fig. 1*A*) [45]. In addition, the amniotic fluid NF-κB concentration in pregnant women may be associated with the pathogenesis of fetal down syndrome, which is mainly associated with impaired brain development [46].

2.2. Synapse and neural tube development

The RelA: p50 dimer is the most abundant NF-κB dimer in the mammalian brain and occurs in the neuronal cell body and dendritic cytoplasm in mammalian CNS synapses [6]. NF-κB drives the transcription of a wide range of target genes in neurons, such as genes regulating synaptogenesis and synaptic maturation, and cytoskeletal anchor genes [47]. Accumulating research has indicated that in the nervous system, the NF-κB signaling pathway plays different roles in different developmental phases, showing its time specificity [48–50]. A constitutively-active IKK signaling complex was observed in the axon initial segment (AIS), and further analysis using PC12 cells showed that RelA transcriptionally activated the AIS marker ankyrin-G, which could affect neuronal polarity and axonal plasticity [47,51]. Furthermore, the formation of dendritic spines in developing hippocampal neurons requires a continuous pool of activated NF-κB, as high NF-κB transcriptional activity levels are indispensable for normal dendritic spine density, spine maturity, and corresponding synaptic currents in both *in vitro* and *in vivo* hippocampal pyramidal cells [6,52]. Similarly, another study using hippocampal neurons of pregnant SD rats has shown that ubiquitin editing enzyme A20 reduced dendritic spines by suppressing NF-κB activation (Fig. 1*A*) [53]. A study using lund human mesencephalic (LUHMES) cells in neuro-developmental disorders caused by maternal infection during pregnancy showed that an inflammatory cytokine mixture can activate RelA, induce apoptosis, and reduce synapses [54]. Conversely, dexmedetomidine targets microglial NADPH oxidase 2 (NOX2) to inhibit perinatal hypoxia-induced oxidative stress and neuroinflammation and restores damaged synapses by reducing RelA and the upstream activation molecules of the NF-κB pathway, such as TNF-α and IL-1β (Fig. 1*A*) [55]. The average dendritic spine density, spine maturity, and corresponding synaptic currents in both *in vitro* and *in vivo* hippocampal pyramidal cells require high levels of NF-κB transcriptional activity, as determined by the degree of activated excitatory glutamatergic synapses in the rapid development phase of the spine and synapses [52,56]. Furthermore, NF-κB signaling is critical to synapse formation and spine maturation through its involvement in the insulin-like growth factor/insulin-like growth factor 2 receptor (IGF2/IGF2R)–mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) signaling axis in the adult brain (Fig. 1*A*) [56]. Moreover, normal neural tube development requires moderate regulation of the NF-κB signaling pathway; NF-κB deficiency or overexpression could give rise to neural tube dysplasia. Genes in the NF-κB signaling pathway, including *Bcl-10, IKKα, IKKβ,* and *TRAF6,* are involved in abnormal neural tube development in the embryonic stages in mice. Li et al. have discovered that knockouts of both *IKKα* and *IKKβ* could induce neural tube defects (NTDs), whereas the single knockout of IKKα and IKKβ, respectively, did not induce NTDs [49]. Furthermore, valproic acid (VPA) exposure can cause visible neural tube malformations on day 10 of embryonic development and alters RelA, p50, IκB, and IKK protein levels in mouse embryos [57–59]. Using an embryo-derived P19 cell line, Lamparter et al. revealed the potential mechanism of VPA-initiated teratogenesis; VPA increased NF-κB transcriptional activity while decreasing DNA binding with RelA/p50 [58]. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of the GSE4182 dataset from the Gene Expression Omnibus database comparing human amniocytes from patients with spina bifida and healthy controls indicated that the NF-κB signaling pathway (has04064) may play vital roles in the pathogenesis of spina bifida [60]. Moreover, the genome-wide DNA methylation analysis of human spinal cords with

NTDs shows that abnormal methylation and expression of tripartite motif containing 4 (TRIM4) might participate in the etiology of NTDs by regulating NF-κB signaling pathway activation [61]. Quercetin-3-glucoside (Q3G) reduced maternal diabetes-induced NTDs by inhibiting RelA expression and augmenting IκBα levels, which suppresses p65 nuclear translocation [62]. Furthermore, studies on clinical samples confirmed that the NF-κB signaling pathway is closely related to NTDs. Folic acid supplementation during pregnancy could significantly alleviate lipopolysaccharide (LPS)-induced NTDs through attenuating LPS-induced expression of myeloid differentiation factor 88 (MyD88) and inhibiting NF-κB signaling activation in placentas [63]. Although the canonical NF-κB pathway and its subunit RelA has been observed to regulate embryonic neural cell development, the detailed mechanisms of NF-κB signaling pathway-mediated nervous system development still require further research.

3. Functions of NF-κB in the development of the cardiovascular system

3.1. Heart development

As the lethality of congenital heart defect during embryonic development, studies linking the NF-κB signaling pathway to heart development remain limited. Kraut et al. reported that the constitutive activation of IKKβ (and subsequent NF-κB activation) during embryonic heart development of transgenic mice leads to defects in compact zone formation and thinner, disorganized myofibers by activating JAK/STAT/p21 to decrease cell proliferation [64]. Zhao et al. discovered that L-carnitine impacts the iNOS/NO and NF-κB pathways by regulating RelA translocation to relieve perfluorooctanoic acid-induced developmental cardiotoxicity in ED19 chicken embryo hearts with a thinner

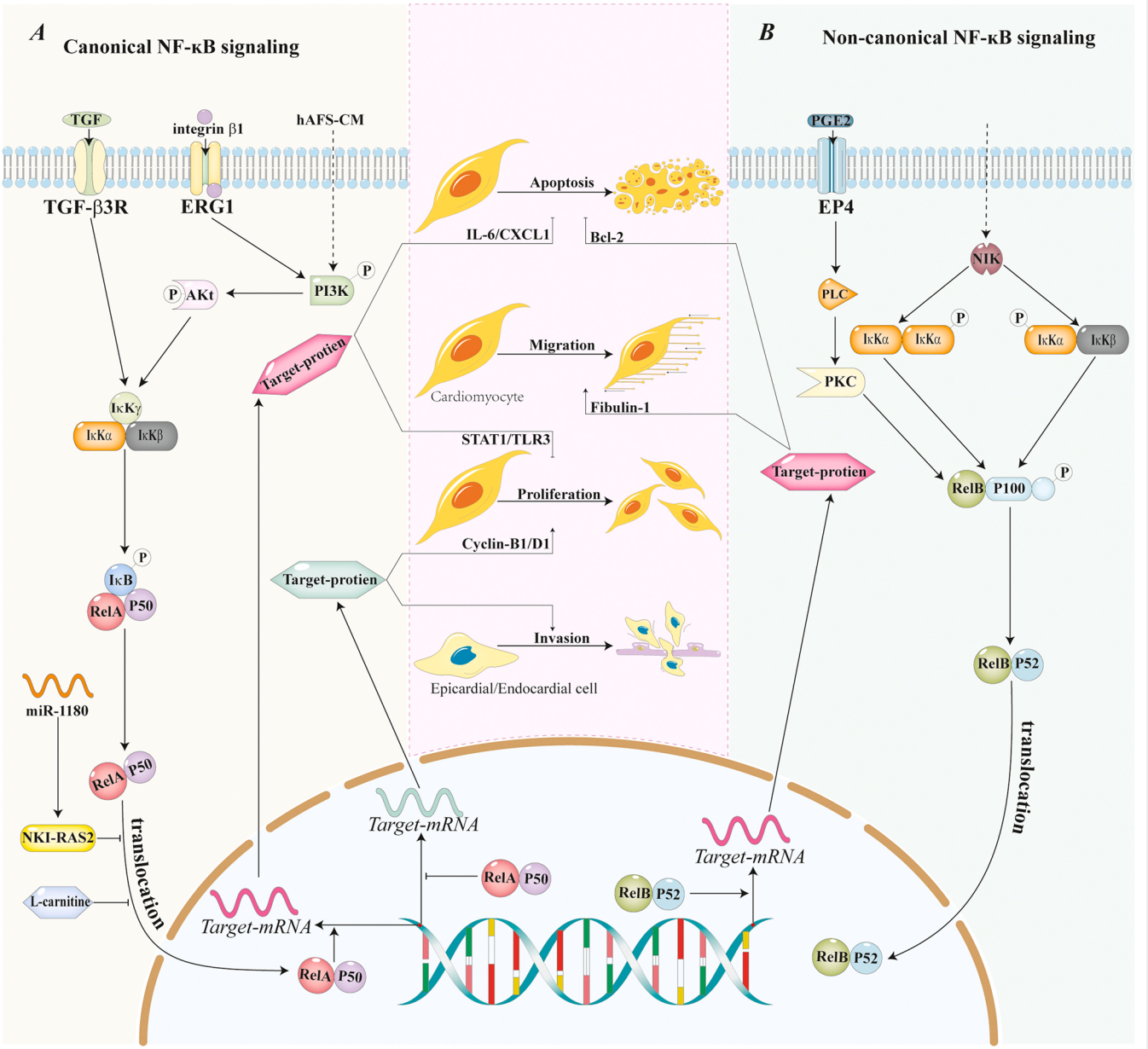

Fig. 2. Schematic depiction of the process of heart development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in heart development. ***B*** The role of non-canonical NF-κB signaling in heart development. Abbreviations are as follows: TGF, transforming growth factor; ERG1, encoded by the Kcnh2 gene, also known as hERG; hAFS-CM, secretome of human amniotic fluid-derived stem cell; PI3K, phosphoinositide-3-kinase; AKt, protein kinase B; NKI-RAS2, NF-κB inhibitor interacting RAS-like 2; PGE2, EP4, prostaglandin E receptor 4; PLC, phospholipase C; PKC, protein kinase C; CXCL1, C-X-C motif chemokine ligand 1; STAT1, signal transducer and activator of transcription 1; TLR3, toll-like receptor 3.

right ventricular wall and chicken hatchlings with left ventricle hypertrophy and abnormal cardiac function [65,66]. Another study suggested that increased NF-κB activity was indispensable for TGFβR3-mediated epicardial and endocardial cell invasion, facilitating the development of coronary vessels and heart valves during cardiac development; however, the detailed downstream mechanisms of NF-κB were not reported (Fig. 2*A*) [67]. Lazzarini et al. revealed that the secretome of human amniotic fluid-derived stem cells (hAFS-CM) could inhibit anthracycline doxorubicin (Dox)-induced senescence and apoptosis of mouse neonatal ventricular cardiomyocytes by activating PI3K/Akt signaling and promoting nuclear translocation of NF-κB (Fig. 2*A*) [68]. Ding et al. suggested that miR-1180 regulates the NF-κB pathway by inhibiting the expression of NF-κB inhibitor interacting RAS-like 2 (NKI-RAS2) to promote the proliferation of ventricular cardiomyocytes (NRVMs) in neonatal rats (Fig. 2*A*) [69]. Recently, Wang et al. reported that ERG1 (encoded by the *Kcnh2* gene, also known as hERG) mediates the differentiation of rat embryonic stem cells (rESCs) into cardiomyocytes, via the phosphorylation of IKKβ for activation of the canonical NF-κB signaling pathway to promote Bcl-2 expression [70,71]. However, it remains unclear whether the non-canonical NF-κB pathway was activated during heart development. In addition, using a Fibulin-1-deficient mice model and human ductus arteriosus (DA) tissues, Ito et al. confirmed that prostaglandin E receptor 4 (EP4) increased the expression of Fibulin-1 by activating the phospholipase C (PLC)/protein kinase (PKC)/NF-κB (RelB) signaling pathway, which could promote the migration of directional smooth muscle cells (SMCs) to endothelial cells (ECs) and contribute to the anatomical closure of the DA during heart development (Fig. 2*B*) [72].

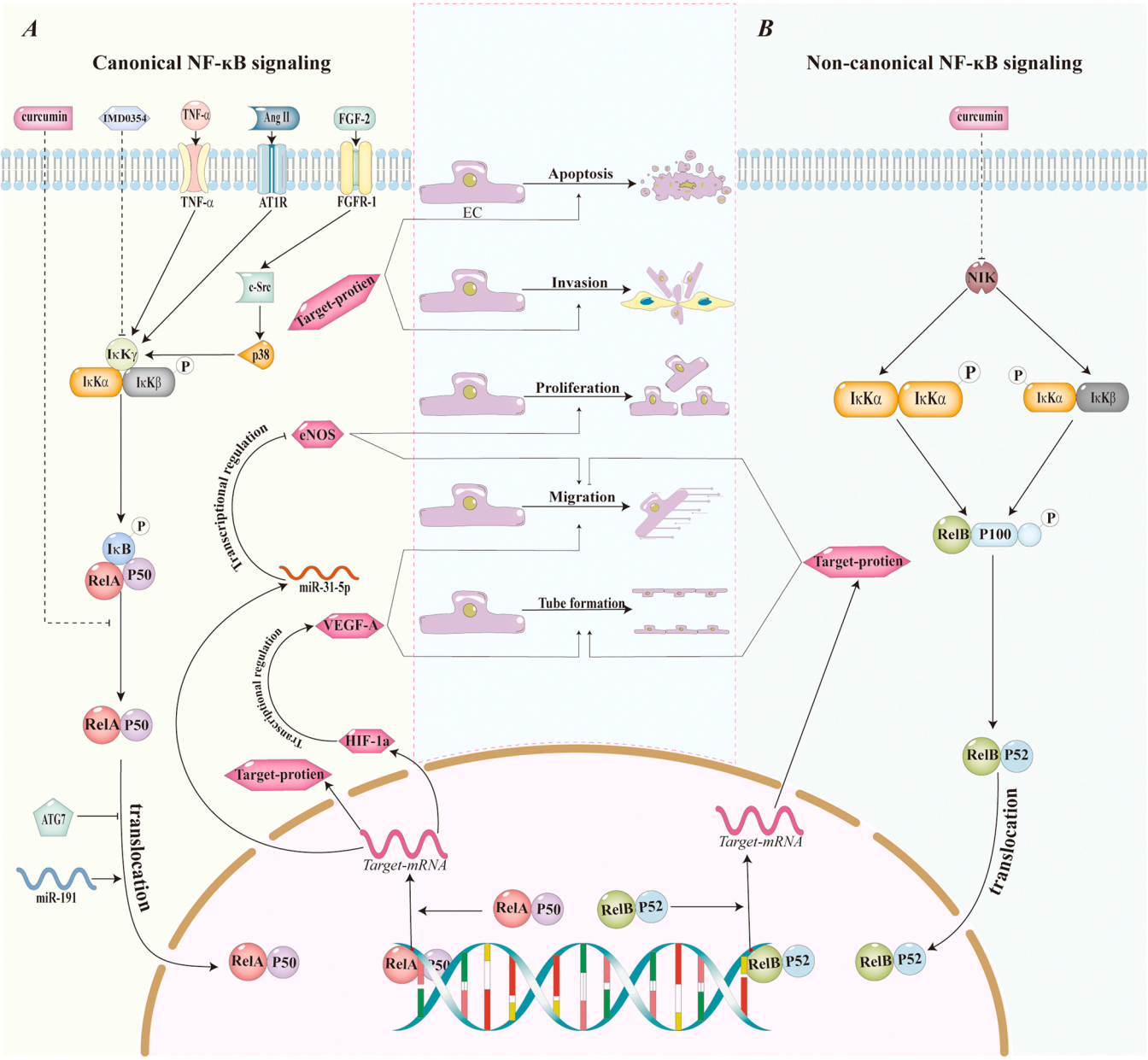

Fig. 3. Schematic depiction of the process of angiogenesis mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in angiogenesis. ***B*** The role of non-canonical NF-κB signaling in angiogenesis. Abbreviations are as follows: IMD0354, a IKKβ inhibitor; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; FGF-2, fibroblast growth factor-2; ATG7, autophagy related 7; HIF-1α, hypoxia induced factor-1α; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase.

3.2. Angiogenesis

NF-κB signaling coordinates angiogenesis by regulating the expression of angiogenic factors, such as bone morphogenetic protein (BMP)− 2, cell cycle regulator p53, matrix metalloproteinase (MMP)− 1/9, endothelial nitric oxide synthase (eNOS), tissue inhibitor of metalloproteinase (TIMP)− 1, vascular endothelial growth inhibitor, vascular endothelial growth factor (VEGF), and interleukin (IL)− 8 [73,74]. The proliferation and migration of ECs are essential to angiogenesis. Autophagy-related 7 (ATG7), an autophagy-related protein that is homologous to ubiquitin-activating enzyme E1, regulates pro-angiogenic IL-6 production [75] to promote the migration of brain ECs during angiogenesis by modulating the nuclear translocation of NF-κB in brain ECs [76]. Additionally, Gu et al. reported that miR-191-dependent activation of the NF-κB signaling pathway results in the upregulation of p65 mRNA and enhancement of p65 nuclear translocation, which upregulates p21 mRNA and arrests human dermal microvascular ECs in the S phase to inhibit their proliferation and downregulate the expression of MMP-1 [73]. A recent study has revealed that low concentrations of angiotensin II (Ang II) activate the NF-κB signaling pathway via AT1R (angiotensin II type 1 receptor), and p65 subsequently activates transcription of *angiogenic factor with G-patch and FHA domains 1* (*AGGF1*) during angiogenesis (Fig. 3*A*) [77]. Thus, one of the critical functions of the NF-κB signaling pathway is regulating the expression of genes that may affect angiogenesis. Moreover, Nagaraju et al. revealed that curcumin analogs had an antiangiogenic effect in pancreatic cancer cell lines (MIA PaCa-2 and PANC-1) by blocking NF-κB signaling pathway activation to decrease the expression of hypoxia-induced factor-1α (HIF-1α), VEGF (Fig. 3*A*) [78]. Moreover, curcumin analogs have been shown to inhibit the NIK complex [79]; thus, both canonical and non-canonical NF-κB signaling may be involved in angiogenesis. In human umbilical vein endothelial cells (HUVECs) and developing zebrafish embryos, IKKβ inhibitor (IMD0354) reduced the expression of VEGF-A and HIF-1α by suppressing the phosphorylation of IκBα to block the activation of canonical NF-κB signaling, thereby impairing EC migration and vasculogenesis (Fig. 3*A*) [80]. Tzeng et al. reported that fibroblast growth factor 2 (FGF-2) mediates the upregulation of VEGF via the c-Src/p38/NF-κB signaling pathway to promote angiogenesis in the human chondrosarcoma cell line (Fig. 3*A*) [81]. As the combination of VEGF and VEGFR induces activation of downstream signaling pathways, including focal adhesion kinase (FAK)/paxillin to mediate migration, PIP2 (phosphatidylinositol 4,5-bisphosphate) to mediate vasopermeability, RAS/mitogen-activated protein kinase (MAPK) to mediate EC proliferation, and phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) to mediate EC survival [82], it must be the downstream mechanism of NF-κB/VEGF/VEGFR signaling pathway-mediated angiogenesis. In addition, NF-κB signaling suppressed the proliferation and migration of ECs and tube formation in angiogenesis by promoting the biogenesis of miR-31–5p, which induced post-transcriptional silencing of eNOS mRNA in HUVECs and an *ex vivo* cultured model of human placental arterial vessels [83]. Ma et al. identified that HUVEC apoptosis was induced via the transduction of the rAAV2 vector to efficiently express anginex (rAAV2–anginex), while inhibiting the proliferation, migration, and invasion of HUVECs by activating NF-κB signaling and JNK phosphorylation [84].

4. Relationship between NF-κB and respiratory system development

In previous research on the bronchopulmonary dysplasia (BPD) mechanism, blockage of NF-κB/RelA impaired pulmonary endothelial cell survival and altered VEGF receptor-2 in the neonatal pulmonary vasculature [85]. In addition, Takahashi et al. have shown that the cell-permeable peptide SN50 inhibits compensatory lung growth in a C57BL/6 J mice model with left pneumonectomy by suppressing NF-κB/RelA expression in type 2 alveolar epithelial cells [86]. Furthermore, several studies have demonstrated that constitutively-active NF-κB is required for pulmonary angiogenesis and alveolar formation, which contributes to the development of BPD [85,87]. Liu et al. reported that the binding of transforming growth factor-β-inducible protein (TGFβI) to αvβ3 integrin stimulates endothelial cell proliferation and migration, and that TGFβI interacts with extracellular matrix proteins to promote NF-κB activation and lung endothelial cell migration (Fig. 4*A*) [87]. NF-κB/RelA-mediated angiogenesis during alveolar formation [87,88] contrasts with the results from studies demonstrating that activation of NF-κB suppressed angiogenesis in ECs [73,89,90]. This indicates that NF-κB/RelA may play different roles in different organs or tissues, indicating its spatial specificity. In addition to their NF-κB/RelA-related functions, IKKα and IKKβ have independent impacts on pulmonary angiogenesis. A study on pulmonary angiogenesis showed that although IKKα silencing induced mild impairments in angiogenic function, IKKβ silencing induced more severe angiogenic defects and decreased vascular cell adhesion [91]. Moreover, IKKβ silencing impairs the proliferation and survival of pulmonary ECs, while IKKβ expression negatively impacts pulmonary endothelial cell adhesion and migration by downregulating vascular cell adhesion molecule (VCAM) expression [88,91]. However, since *VCAM* is only one of the genes targeted by IKKβ to mediate angiogenesis in pulmonary ECs [88,91], the roles of additional targets and their interactions require systematic characterization. In serum-starving human embryo lung diploid fibroblasts, water-soluble fullerene inhibits autophagy and the genotoxic effect of oxidative stress, and reduces apoptosis, all of which are correlated with high NF-κB activity [92]. Furthermore, in chick embryos, Long et al. identified that NF-κB signaling activated by injection of LPS into the air chamber at the blunt end of the eggs could interfere with the differentiation of pulmonary epithelial cells (Fig. 4*A*) [93]. Another study utilizing embryonic Twist2-IKKbca mice, a developing mice model constitutively expressing an inhibitor of NF-κB kinase subunit b (IKKβca) mutant, to test the role of the NF-κB pathway specifically in the lung mesenchyme, found increased expression of the inflammatory chemokine-encoding gene *CCl-2* and vascular marker *platelet endothelial cell adhesion molecule 1* (*PECAM-1*); suggesting that IKKβ activation is important for vascular development of the lung mesenchyme [94].

5. Functions of NF-κB related to the immune system and hematopoietic development

5.1. Immune cells

Aberrant function of NF-κB signaling can disturb normal developmental processes and/or host immune defenses. Orange et al. detailed that gene mutations, such as *TNFRSF11A* (encoding RANK), *TNFRSF11B* (encoding osteoprotegrin), *CARD15* (encoding Nod2), *SQSTM1* (encoding p62), *CIAS* (encoding cryopyrin), *IKBKG* (encoding NEMO), *NFKBIA* (encoding IκBα), *IRAK4*, and *CASP12* (encoding caspase 12), resulted in immunodeficiencies by inducing the inappropriate activation of NF-κB signaling, as well as the gene mutations, such as *ED1*, *EDAR*, *EDARADD*, *CYLD*, *VHL* (encoding pVHL), *FLT4* (encoding VEGFR-3), *IKBKG*, and *NFKBIA*, led to immunodeficiencies by affecting NF-κB activation or inhibition [12]. The NF-κB signaling pathway is involved in the different developmental stages of immune cells [7], such as positive selection during peripheral B-lymphocyte development [95], commitment to a follicular or marginal zone B cell fate [96], survival and differentiation of developing lymphocytes [97], and the functional divergence of the different helper T cell subsets [98]. Subsequently, Almaden et al. confirmed that peripheral B cell maturation in the spleen was regulated by both the canonical and non-canonical NF-κB pathways via activated c-Rel and RelB, respectively, and compound deletion of c-Rel and RelB blocked B cell development in a mice model [99]. However, Paun et al. recently revealed that constitutive activation of

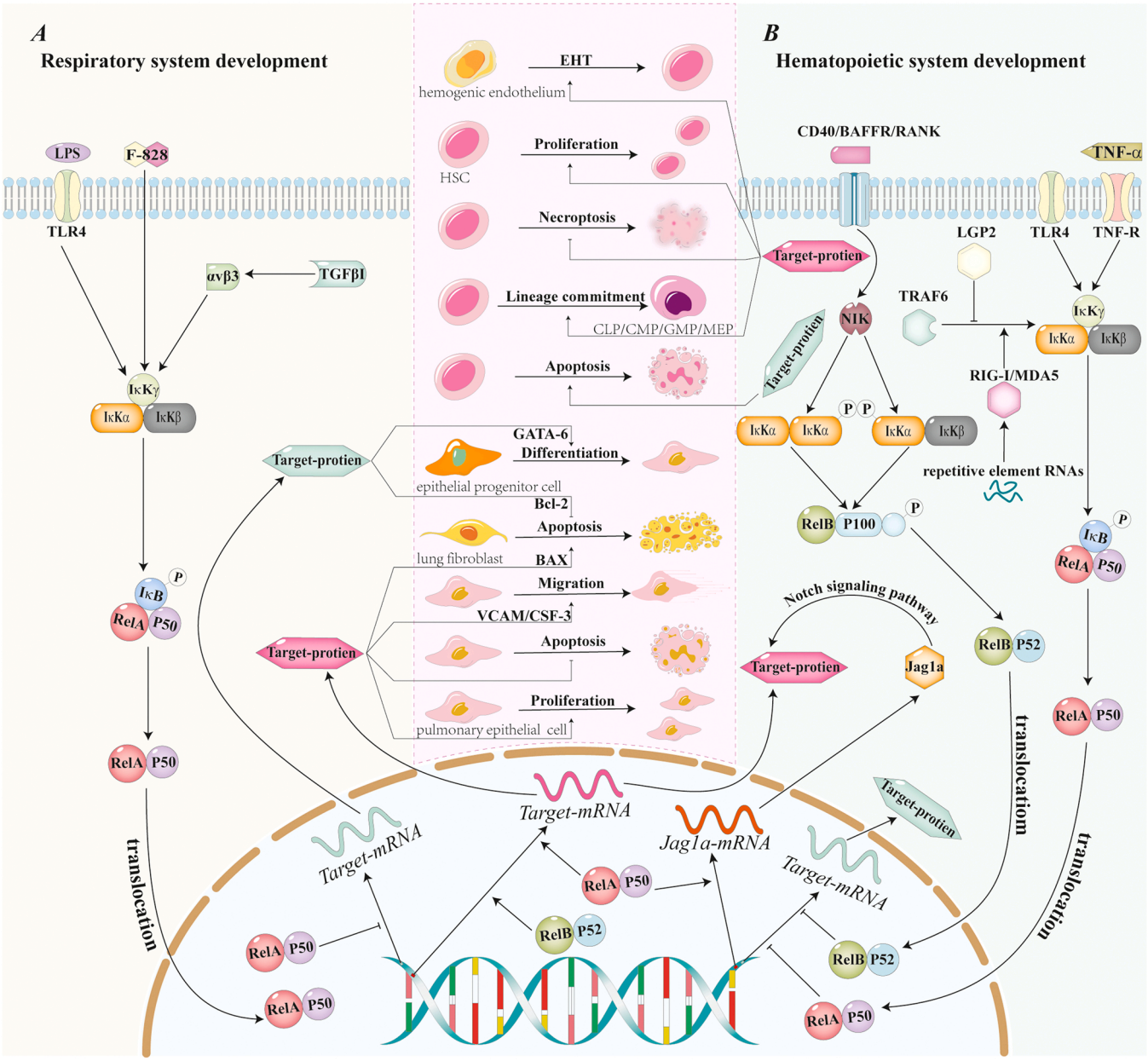

Fig. 4. Schematic depiction of the process of respiratory system and hematopoietic system development mediated by NF-κB signaling pathway. ***A*** The role of NF-κB signaling in respiratory system development. ***B*** The role of NF-κB signaling in hematopoietic system development. Abbreviations are as follows: LPS, lipopolysaccharide; F-828, water-soluble fullerene; EHT, endothelial-to-hematopoietic transition; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte/macrophage progenitor; MEP, megakaryocyte/erythrocyte progenitor; GATA-6, GATA binding protein 6; BAX, BCL2 associated X; VCAM, vascular cell adhesion molecule; CSF-3, colony stimulating factor 3; BAFFR, B cell-activating factor receptor; RANK, receptor activator of NF-κB; TRAF6, TNF receptor associated factor 6; LGP-2, laboratory of genetics and physiology 2; MDA5, melanoma differentiation-associated protein 5; RIG-I, retinoic acid inducible gene I; Jag1a, jagged canonical Notch ligand 1a.

both NF-κB signaling pathways in the bone marrow impacts the transition from pro-B to pre-B cells in early B cell development [100]. This finding is in accordance with another study that independently determined that NF-κB activation impairs early B cell development in the bone marrow by modulating B cell receptor (BCR) editing and B cell progenitor physiology [100,101]. Recently, Luo et al. reported that unlike in naïve B cells, both BCR/PI3K and CD40/NF-κB signaling were required for c-Myc expression, which is a critical mediator for germinal center B cell selection and survival [102]. Non-canonical NF-κB signaling also plays a critical regulatory role in marginal zone B cell development by cooperating with lysine-specific demethylase 1 (LSD1), a histone demethylase that regulates downstream target genes of NF-κB in the non-canonical pathway and interacts with p52 following non-canonical NF-κB activation (Fig. 5*B*) [103]. As NIK is a downstream component of B cell activating factor (BAFF)/BAFF-R-mediated non-canonical NF-κB signaling, the production of inactive B cells in response to NIK deletion during early B cell development (such as the deletion of BAFF or BAFF-R) highlights the importance of NIK in B cell development [9,104]. In addition, NIK plays a critical role in the survival of mature peripheral B cells in mice [105]. Smulski et al. reported that *BAFFR* deletion resulted in arrested development of B cells at the immature/transitional B cell stage [106]. In addition, a recent study suggested that CD40 signaling-induced non-canonical NF-κB activation facilitated the differentiation of memory B cells from germinal center B cells [107]. Furthermore, NF-κB and IL-4 signaling synergize to regulate SATB1 expression (a genome organization regulator) during Th2

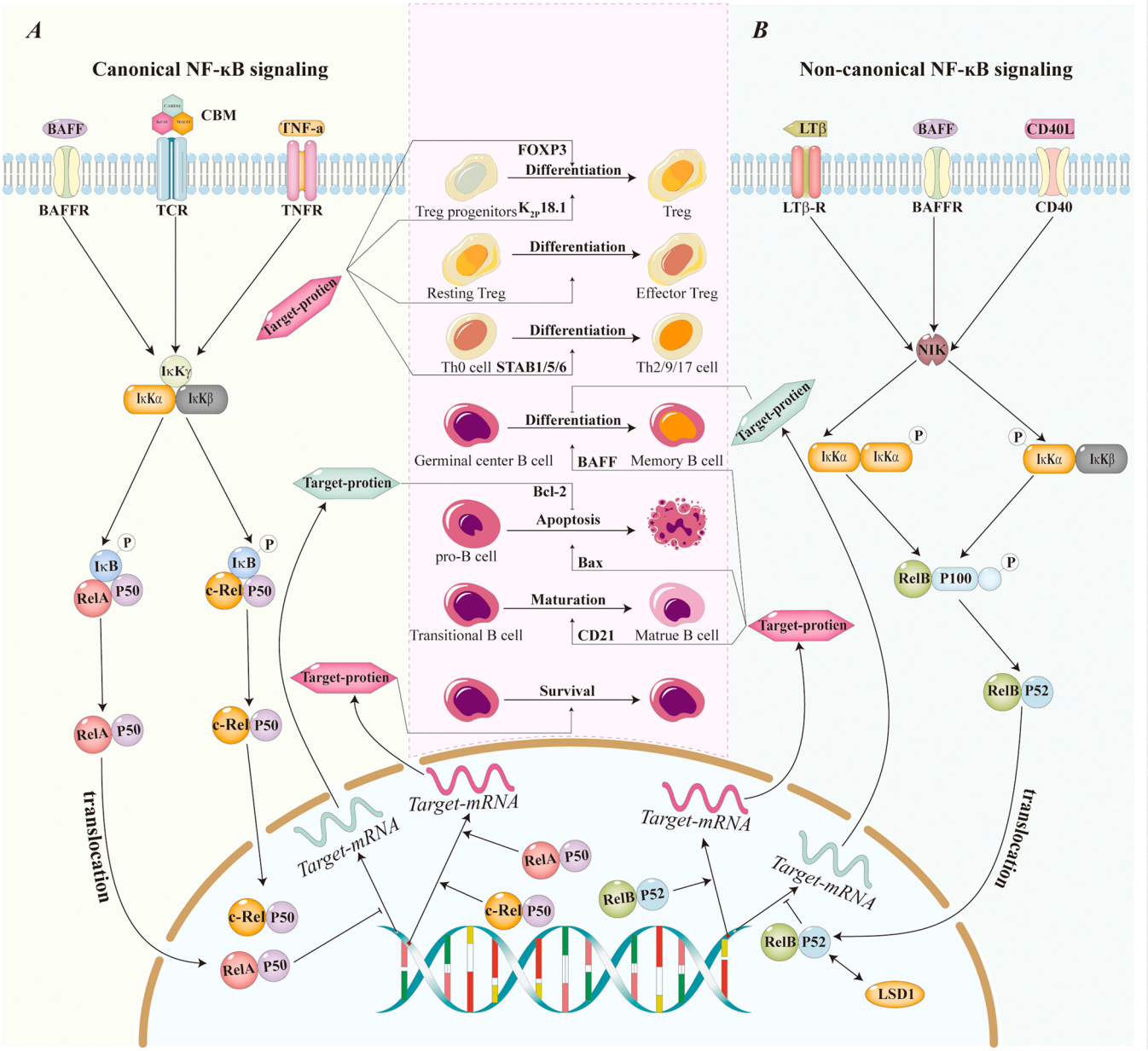

Fig. 5. Schematic depiction of the process of immune cell development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in immune cell development. ***B*** The role of non-canonical NF-κB signaling in immune cell development. Abbreviations are as follows: CBM, CARD11-Bcl10-MALT1 complex; TCR, T-cell receptor; LTβR, lymphotoxin β receptor; Treg, regulatory T cell; FOXP3, forkhead box P3; $K_{2P}18.1$, a protein encoded by the Kcnk18 gene; LSD1, lysine-specific demethylase 1.

differentiation, which impacts the expression of multiple genes involved in thymic development and the peripheral differentiation of T cells (Fig. 5*A*) [108]. Moreover, NIK regulates the differentiation of T helper type (Th1) and Th17 cells [9,109]. Recently, Jiang et al. reported that the TNFR2-STAT5 and TNFR2-NF-κB pathways were involved in the differentiation of naïve CD4 +T cells into Th9 cells [110]. TCR/NF-κB signaling could modulate regulatory T cell (Treg) development by regulating the expression of forkhead box P3 (FOXP3) (Fig. 5*A*) [111], and the deletion of $K_{2\,P}18.1$(encoded by *Kcnk18*) resulted in reduced Treg numbers in *Kcnk18*$^{-/-}$ mice, by blocking the TCR/canonical NF-κB signaling of thymic Treg progenitors to inhibit FOXP3 expression (Fig. 5*A*) [112]. Oh et al. elucidated that canonical NF-κB signaling activation by TCR played a regulatory T cell (Treg)-specific transcriptional role via the greater chromatin accessibility at Treg-enriched loci., increasing p65 binding in Treg development, in which c-Rel was critical for thymic Treg development while p65 was essential for the maintenance of Treg identity and immune tolerance [113]. Furthermore, the CARD11-Bcl10-MALT1 (CBM) complex, which controls the generation of marginal zone B and plasma cells [114], activates TCR/NF-κB signaling in Tregs to control the transformation of resting Tregs to effector Tregs (Fig. 5*A*) [114–116]. Vasanthakumar et al. suggested that tumor necrosis factor receptor superfamily (TNFRSF) signaling could activate canonical NF-κB signaling (RelA/p50) to maintain effector Treg cells in lymphoid and non-lymphoid tissues by regulating cell survival and proliferation [117]. Furthermore, it has been suggested that NF-κB activation protects developing natural killer T cells from death signals from TCR, TNFR1, or Fas in a murine model [118]. Moreover, the terminal maturation of splenic $CD4^{+}$ cDC2s (classical dendritic cells) involves Notch2 and LTβR/NF-κB signaling in the spleen [119], whereas LTβR/NF-κB signaling also regulates the development of

$CD103^{+}CD11b^{+}$ cDC2s in the small intestine [120]. Moreover, Kanaya et al. identified that the RANK/RANK ligand (RANKL)-TRAF6-triggered activation of an intrinsic NF-κB signaling pathway is essential for the differentiation and development of murine intestinal M cells located in the follicle-associated epithelium, which is responsible for the uptake of intestinal antigens [121]. Recently, Xiong et al. found that clethodim exposure plays a role in developmental immunotoxicity on macrophages and neutrophils through TLR4/NF-κB signaling pathway activation to accelerate apoptosis in transgenic zebrafish embryos [122]. Moreover, it has been suggested that spinetoram exposure, as well as the combined exposure of famoxadone-cymoxanil can induce the abnormal quantity and function of developmental neutrophils via the TLR4/NF-κB signaling pathway to upregulate the expression of apoptosis-related genes, *p53* and *Bax,* in transgenic zebrafish and transgenic zebrafish embryos [123,124]. Furthermore, recent research revealed that macrophage-derived IL-1β mediated the proliferation of myeloid progenitor cells via the NF-κB and C/EBP-β signaling pathway to fulfill emergency myelopoiesis [125]. Thus, NF-κB plays an important role in the development of immune cells.

5.2. Lymphoid organs

To date, there have been numerous reviews on the role of NF-κB signaling in lymphoid organ development. In 2002, Alcamo et al. identified RelA as a key mediator during the development of lymph nodes and Peyer's patches [126]. In 2003, Weih et al. summarized that the NF-κB pathway impacted the early development of secondary lymphoid organs and the maintenance of their structures, wherein RelB/p52 played a major role during the initiation of secondary lymphoid organ development while classical RelA/p50 was involved in

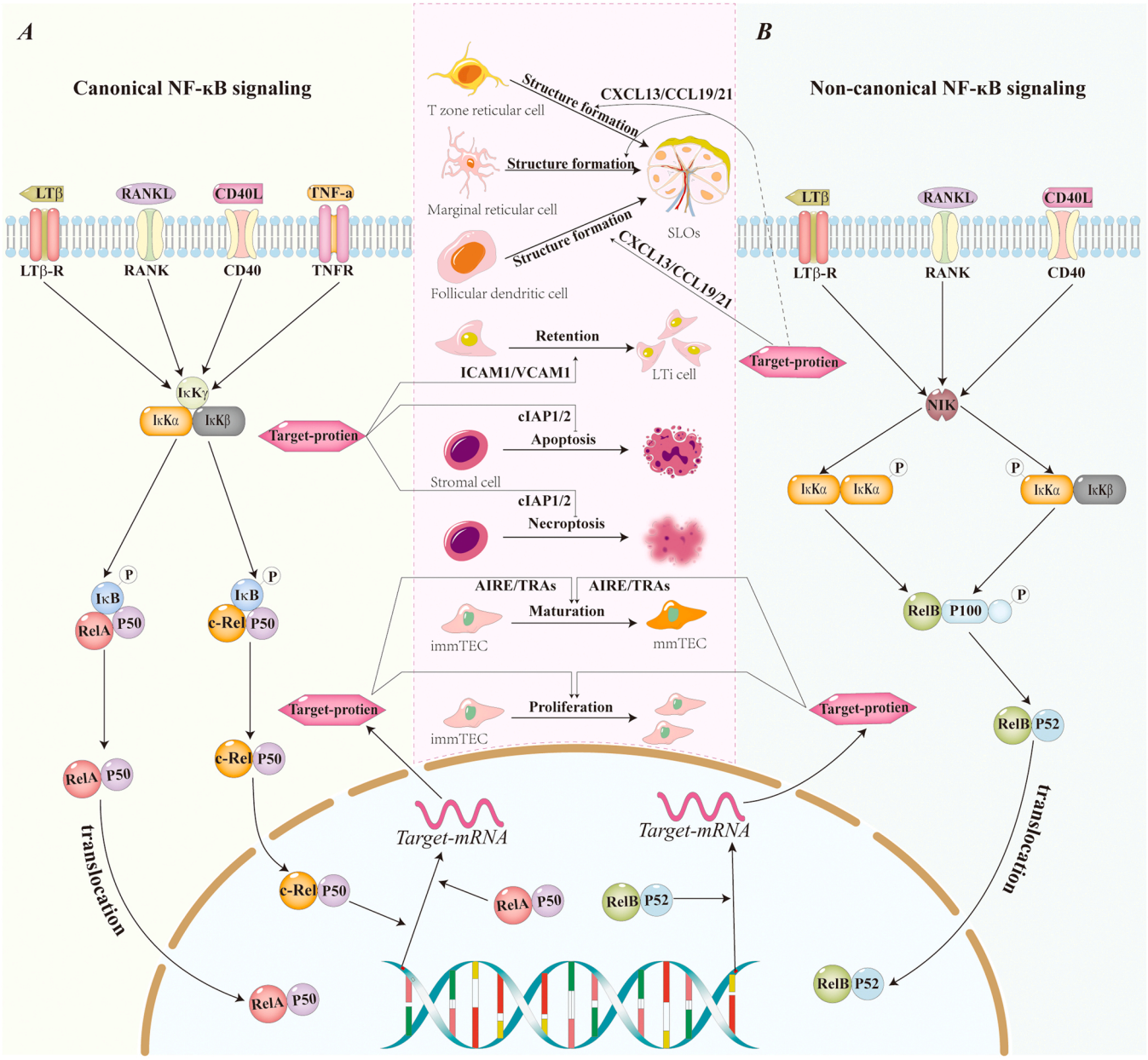

Fig. 6. Schematic depiction of the process of lymphoid organ development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in lymphoid organ development. ***B*** The role of non-canonical NF-κB signaling in lymphoid organ development. Abbreviations are as follows: CXCL13, C-X-C motif chemokine ligand 13; CCL19, C-C motif chemokine ligand 19; ICAM1, intercellular adhesion molecule 1; AIRE, autoimmune regulator; TRAs, tissue-restricted antigens; TEC, thymic epithelial cell; LTi, lymphoid tissue inducer; SLOs, secondary lymphoid organs.

later development [29]. In 2014, Sun et al. reviewed that some underlying molecules, including RANK, CD40, and LTβR, mediated the thymic medullary microenvironment and self-tolerance establishment through NF-κB signaling in the embryonic thymus and postnatal thymus [127], In 2018, Zhu et al. reported that thymic medulla and medullary thymic epithelial cell (mTEC) numbers were decreased in *Ikkα*$^{-/-}$ newborn mice; similarly, mTEC numbers distinctly decreased in *Ikkα*$^{KA/KA}$ mice owing to IKKα inactivation, which impairs LTβR-, CD40-, or RANK-mediated canonical and non-canonical NF-κB activities in mTECs (Fig. 6) [128]. Our review focused on providing a summary of the representative articles based on these reviews in recent years. For instance, TNF superfamily receptors, including CD40, LTβR, and RANK [129–132], are expressed in mTECs and function in both the canonical and non-canonical NF-κB pathways, contributing to thymic epithelial cell maturation and thymus development [129,131,133]. As mentioned in Section 5.1 *Immune cells*, Cheng et al. indicated that spinetoram and famoxadone-cymoxanil exposure can induce developmental toxicity of thymus and thymic T cells by promoting apoptosis via the transient potential receptor vanilloid 4 (TRPV4)/NF-κB(p65) signaling pathway in zebrafish embryos [123,124]. Moreover, Galindo-Villegas et al. revealed that the hyposmolality of the aquatic environment induced developmental immunity in skin keratinocytes of newly hatched zebrafish embryos via the TRPV4/TGF-β–activated kinase 1 (TAK1)/NF-κB/IL-1β signaling pathway, and the embryo skin was the first organ to mount an innate immune response [134]. Activation of the canonical NF-κB pathway in secondary lymphoid organs facilitates the differentiation of fibroblastic stromal cell subsets, including T zone reticular cells, follicular dendritic cells, and marginal reticular cells, which produce chemokines such as chemokine C-X-C motif ligand 13 and chemokine C-C motif ligand 19 and 21; their functions provide the basis for the well-organized tissue structure in secondary lymphoid organs (Fig. 6*B*) [135]. Additionally, Pflug et al. reported that NIK impacts the development of secondary lymphoid organs [9], which is in accordance with the review by Randall et al. [136]. Furthermore, Xu et al. discovered that lymph nodes failed to develop in a *RelA*$^{-/-}$*FADD*$^{-/-}$*RIP3*$^{-/-}$ mice model, wherein the embryonic lethality of RelA-deficient mice, induced by FADD-dependent apoptosis and RIP3-dependent necroptosis, was fully rescued by the combined ablation of *FADD* and *RIP3* [27]. In addition, Onder et al. revealed that lymph node (LN) development relies on the interaction of lymphoid tissue inducer cells with lymphatic endothelial cells (LECs) to activate LECs, which is mediated by the RANKL-induced non-canonical NF-κB pathway in a conditional deficiency mouse model [137]. Recently, McCorkell et al. suggested that ablation of IKKα in LECs resulted in the absence of LNs in a *Ikkα*^{Lyve1} mice model [138]; this also illustrated that the inactivation of IKKα impacted LN development. To date, numerous researchers consider that both the canonical and non-canonical NF-κB pathways are involved in the development of lymphoid organs. However, whether there is crosstalk between the canonical and non-canonical NF-κB pathways in the developmental stages, the detailed mechanisms of this crosstalk, or the mechanism by which one of these pathways plays a leading role in different developmental stages still need further elucidation.

5.3. Hematopoietic system

Activation of both the canonical and non-canonical NF-κB signaling pathways regulates the homeostasis and intrinsic functions of hematopoietic stem cells (HSCs) [139]. According to Espín-Palazón et al., the activation of TNFR2 activates NF-κB [140,141] to promote the transcription of *jag1a*, whose expression product is a ligand that activates Notch signaling during HSC development (Fig. 4*B*) [17]. Moreover, the absence of NIK decreases proliferation and promotes apoptosis, resulting in the dysregulation of the self-renewal and expansion capacities of HSCs [9]. These critical findings suggest that NF-κB signaling plays a pivotal role in HSC development. Furthermore, He et al. reported that the endothelial cell–derived TLR4–MyD88–NF-κB signaling pathway is indispensable to mediate the activation of the downstream Notch signaling pathway in order to facilitate the emergence of hematopoietic stem and progenitor cells (HSPC) through the endothelial-to-hematopoietic transition (EHT) process in zebrafish and mouse embryos (Fig. 4*B*) [142]. In addition, Lefkopoulos et al. recently suggested that the RIG-I-like receptors (RLRs) signaling pathway interacts with NF-κB signaling to regulate the emergence of HSPCs in zebrafish embryos, through TRAF6 as the signaling mediator of RLRs signaling (Fig. 4*B*) [143]. The TNF-α/NF-κB/cIAP2 pathway has been identified to promote HSC survival and myeloid differentiation by preventing necroptosis rather than apoptosis in TNFα-exposed HSCs [144]. Therefore, the NF-κB signal pathway is indispensable to hematopoietic system development.

6. Impact of NF-κB on digestive system development

6.1. Digestive gland development

Our understanding of the role of NF-κB in the morphogenesis of the digestive system remains limited because research on NF-κB signaling in the digestive tract is predominantly focused on gastrointestinal immune system regulation in the embryonic stage (see Section 5). A study on embryonic submandibular salivary gland (SMG) development illustrated that the ectodysplasin (EDA)/ectodysplasin receptor (EDAR)/NF-κB pathway had a profound impact on epithelial cell proliferation, lumina formation, and histodifferentiation in the mouse salivary gland (SMG) development process (Fig. 7*A*) [16]. Häärä et al. indicated that EDA/EDAR signaling regulates branching morphogenesis of the developing SMG via NF-κB signaling [145]. Subsequently, Suzuki et al. considered that transcription factor NF-κB mediated EDA/EDAR signaling in salivary gland development [146]. Furthermore, hypohidrotic ectodermal dysplasia-immunodeficiency (HED-ID) is a rare X-linked recessive developmental syndrome associated with *IKBKG* mutations, featuring abnormal hair, teeth, sweat gland, as well as salivary gland development; *IKBKG* encodes NEMO, the regulatory subunit of the IKK complex for the activation of the canonical NF-κB signaling pathway [15,16]. Beg et al. made the novel discovery that disruption of the *RelA* locus led to immense liver degeneration caused by hepatocyte apoptosis, which resulted in lethality at days 15–16 of embryonic development in *RelA*$^{-/-}$ mice [147]. However, TNF/RelA double-deficient mice proceeded with embryogenesis and had normal livers, which suggests that RelA could resist apoptosis to abolish TNF-mediated liver degeneration [148]. In addition, the NF-κB pathway is involved in liver regeneration after partial hepatectomy (PH). Liver regeneration was impaired with 50% mortality after PH in mice with hepatocyte-specific disruption of *NEMO* suggest that the NF-κB pathway is essential for liver regeneration [149,150]; however, another study on PH in *RelA* knockout mice presented a contrasting result, wherein normal liver regeneration still occurs in livers lacking RelA/p65 after 80% PH [150]. This indicates that further research is needed on the role of the NF-κB signaling pathway on liver development and regeneration. Large tumor suppressor kinases 1 and 2 (LATS1/2) of the Hippo pathway inhibit NF-κB signaling in pancreatic progenitors to promote cell differentiation and epithelial morphogenesis. Moreover, the deletion of LATS1/2 in murine pancreas progenitor cells stimulates the abnormally high expression of p50 and RelA and initiates pancreatic epithelial-mesenchymal transition (Fig. 7*A*) [151]. Considering these preliminary findings, the role of canonical NF-κB signaling in the embryogenesis of the digestive tract requires further clarification.

6.2. Tooth development

Yang et al. confirmed that inhibition of miR-143–3p can elevate the extent of RelA phosphorylation, as well as the expression of its target genes, such as *RANK*, and induce dental pulp stem cell (hDPSCs)

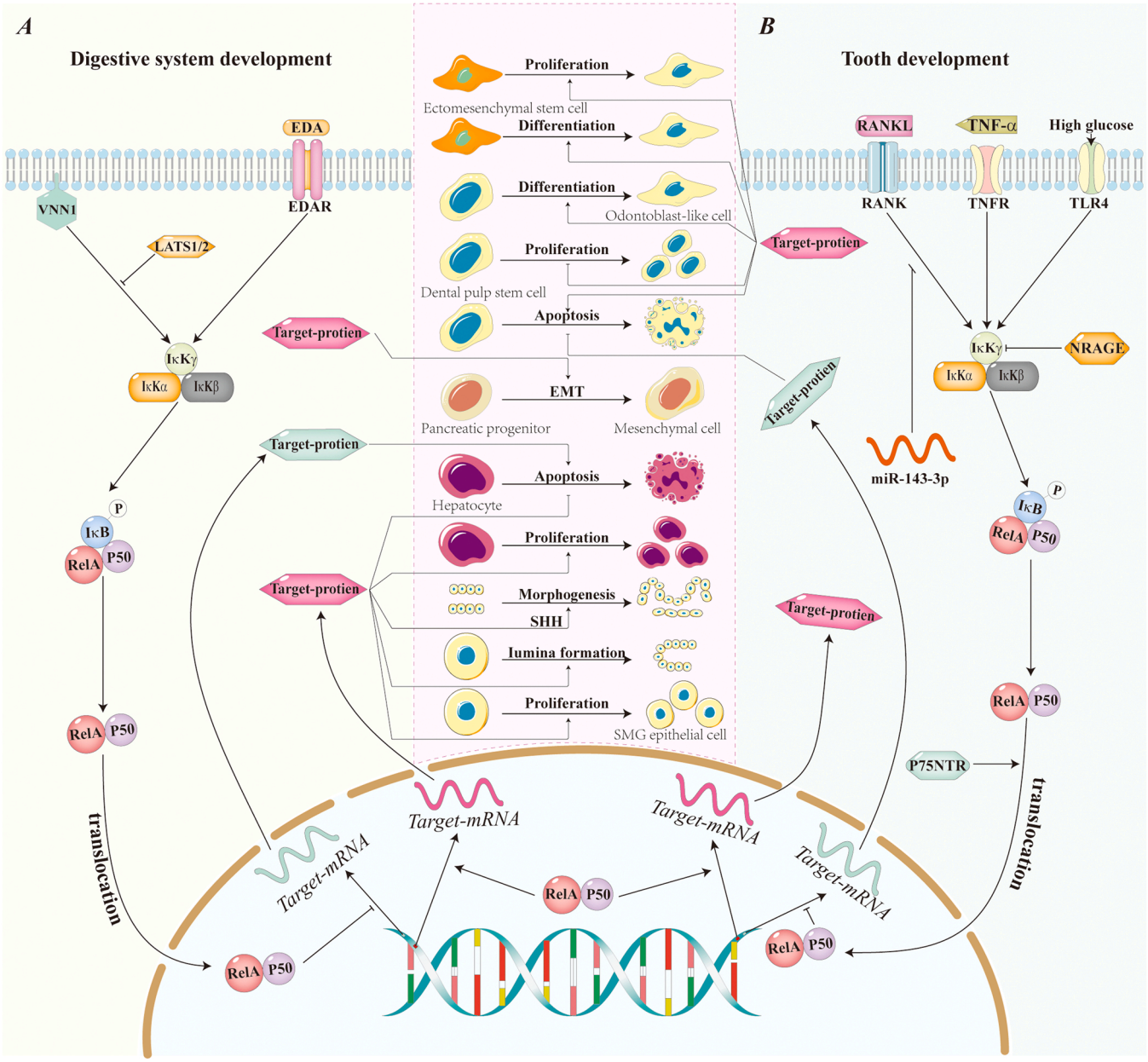

Fig. 7. Schematic depiction of the process of digestive system development and tooth development mediated by NF-κB signaling pathway. ***A*** The role of NF-κB signaling in digestive system development. ***B*** The role of NF-κB signaling in tooth development. Abbreviations are as follows: VNN1, vanin 1; EDA, ectodysplasin; LATS1, large tumor suppressor kinases 1; EMT, epithelial to mesenchymal transition; SMG, submandibular salivary gland; P75NTR, also known as NGFR (nerve growth factor receptor); NRAGE, neurotrophin receptor-mediated melanoma antigen-encoding gene.

apoptosis, which promotes the differentiation of hDPSCs into odontoblast-like cells (Fig. 7*B*) [152]. High expression of neural crest stem cell marker p75NTR in the late bell stage promotes odontogenesis and mineralization by upregulating RelA in the proliferation and differentiation of ecto-mesenchymal stem cells from the first branchial arches of mice embryos [153]. Embryos from a maternal gestational diabetes rat model were used to evaluate tooth germ cell proliferation and apoptosis; high glucose treatment in dental epithelial and mesenchymal cells can activate the canonical NF-κB/RelA pathway by TLR4/MYD88/TRAF6 signaling, promote apoptosis, and suppress cell proliferation [154]. Subsequently, the neurotrophin receptor-mediated melanoma antigen-encoding gene (NRAGE) could inhibit the proliferation and promote differentiation of mouse dental pulp cells by the downregulation of NF-κB/p50 during tooth development (Fig. 7*B*) [155]. Sirtuin-6 (SIRT6) does not affect tooth development before birth, whereas delay in tooth eruption and delayed development of dental roots was observed in *Sirt6* conditional knockout neonatal mice, due to the fact that SIRT6 affects cellular mitochondrial energy metabolism in dental mesenchymal cells by activating the NF-κB/p65 signaling pathways [156]. These findings highlight the importance of NF-κB signaling in tooth development. As the canonical NF-κB signaling pathway is activated and the importance of NF-κB signaling should be highlighted in tooth development.

7. Role of NF-κB in the development of skin and skin appendages

Recent studies have demonstrated that NF-κB signaling is involved in skin immunity, inflammation, differentiation, and dysplasia during development. The prenatal skin creates a strong network of various

innate and adaptive cells to protect the fetus from perinatal infections [157,158]. Langerhans cell precursors gradually acquire the RANK, an upstream molecule of NF-κB signaling, to prolong their survival in humans [157]. Research using a zebrafish embryo model has shown that embryo skin can mount an innate immune response through the TRPV4/TAK1/NF-κB signaling pathways by sensing the osmotic stress (Fig. 8*A*) [134]. Furthermore, extracellular matrix (ECM) degradation and basement membrane (BM) defects in *integrin-β1* KO embryos, which were provoked by activating the integrin-β6/TGF-β1/Tenascin C (TNC) axis of dermal fibroblast and the TNC/TLR/NF-κB axis of dermal macrophage in embryonic development, could effectively be reversed through treatment with TGF-βR1 and NF-κB inhibitors (Fig. 8*A*) [159]. Schmidt-Ullrich et al. identified that as direct target genes of Wnt/β-catenin signal, the NF-κB (p65) activated by EDA/EDAR plays a significant role in the proliferation and down growth of hair placodes by inducing the expression of Shh and Cyclin D1 [160]. Zhao et al. transfected NF-κB and lymphoid enhancer-binding factor 1 (Lef-1) expression vectors into fibroblasts and demonstrated that NF-κB and the downstream transcription factor of β-catenin signaling (Lef-1) promote the differentiation of fibroblasts into sweat gland cells, suggesting that there is crosstalk between the EDA/EDAR/NF-κB and Wnt/β-catenin/Lef-1 signaling pathways [161]. In addition, the LIM homeobox transcription factor LHX2, which is transcriptionally activated by NF-κB/RelA in hair follicles (HF), activates TGF-β2 signaling to regulate primary HF morphogenesis [162]. Besides, in HED-ID, which is mentioned in Section 6 Impacts of NF-κB on digestive system development, dysplasia of sweat glands, hair, and teeth was provoked by impaired but not abolished NF-κB signaling induced by mutations of the *IKBKG* gene [15,

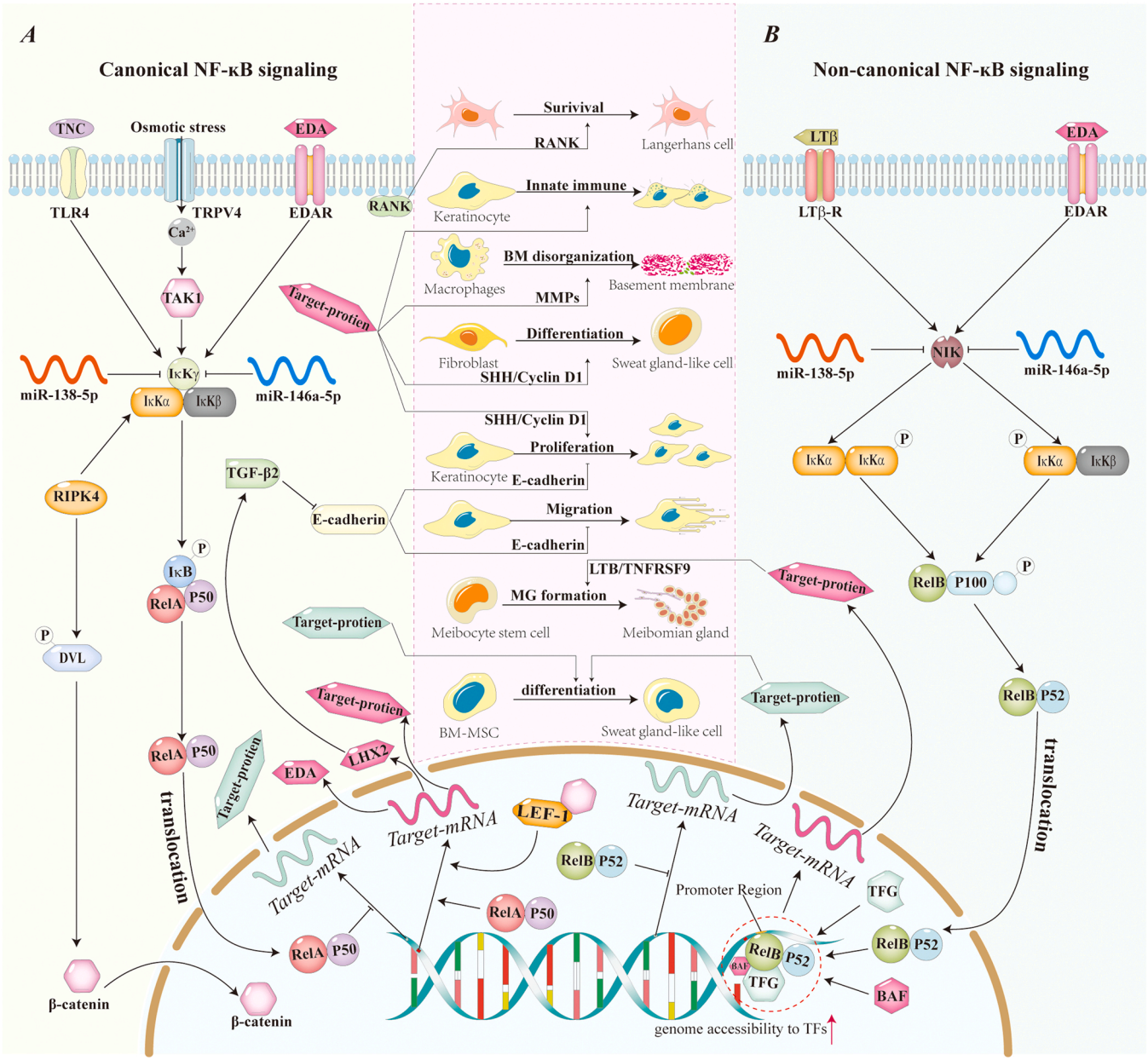

Fig. 8. Schematic depiction of the process of skin and skin appendages development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in skin and skin appendages development. ***B*** The role of non-canonical NF-κB signaling in skin and skin appendages development. Abbreviations are as follows: TNC, Tenascin C; TRPV4, transient potential receptor vanilloid 4; TAK1, TGF-β–activated kinase 1; RIPK4, receptor-interacting serine/threonine kinase 4; LHX2, LIM homeobox transcription factor 2; LEF-1, lymphoid enhancer-binding factor 1; MMP, matrix metalloproteinase; TNFRSF9, tumor necrosis factor receptor super family 9; TFG, trafficking from ER to golgi regulator; BAF, BAF45d of the NF-κB-associated SWI/SNF; DVL, dishevelled.

163]. Bartsocas-Papas syndrome (BPS), characterized by popliteal pterygia, syndactyly, ankyloblepharon, filiform bands between the jaws, cleft lip and palate, and genital malformations, is associated with receptor-interacting serine/threonine kinase 4 (RIPK4) variants, and reporter assays showed that the identified RIPK4 variant, which presented with substitution of a conserved aspartic acid to histidine in the kinase domain, disrupted the RIPK4-dependent activation of the NF-κB and Wnt/β-catenin pathways (Fig. 8*A*) [164]. Moreover, EDA/EDAR/RelA pathway is important for hair shaft bending by cooperating with SHH, BMP, and Wnt signaling [165–167], while non-canonical NF-κB signaling can be activated by lymphotoxin-β, a downstream target of EDA/EDAR/RelA pathway, to be involved in hair-phenotype determination [168]. RelB/p50, which is activated by the EDA-recruited linker protein TFG, can interact with BAF45d of the NF-κB-associated SWI/SNF (BAF) complex to initiate a signaling cascade and facilitate the transcription of *LTβ* and *TNFRSF9* in developing skin appendages (Fig. 8*B*) [167]. Downregulation of miR-138–5p activates NF-κB signaling-related critical molecules, RelA, p50, and RelB, to promote the differentiation of bone marrow-mesenchymal stem cells (BM-MSCs) into sweat gland-like cells. In contrast, upregulation of miR-146a-5p inhibits NF-κB signaling-related critical molecules, IRAK1, TRAF2, and TRAF6, to promote stem cell differentiation [169], suggesting that both canonical and non- canonical NF-κB signaling pathways are involved in this process, and that these miRNAs synergistically target NF-κB signaling pathways and its downstream factors [169]. However, additional experimental evidence is required to validate these initial observations.

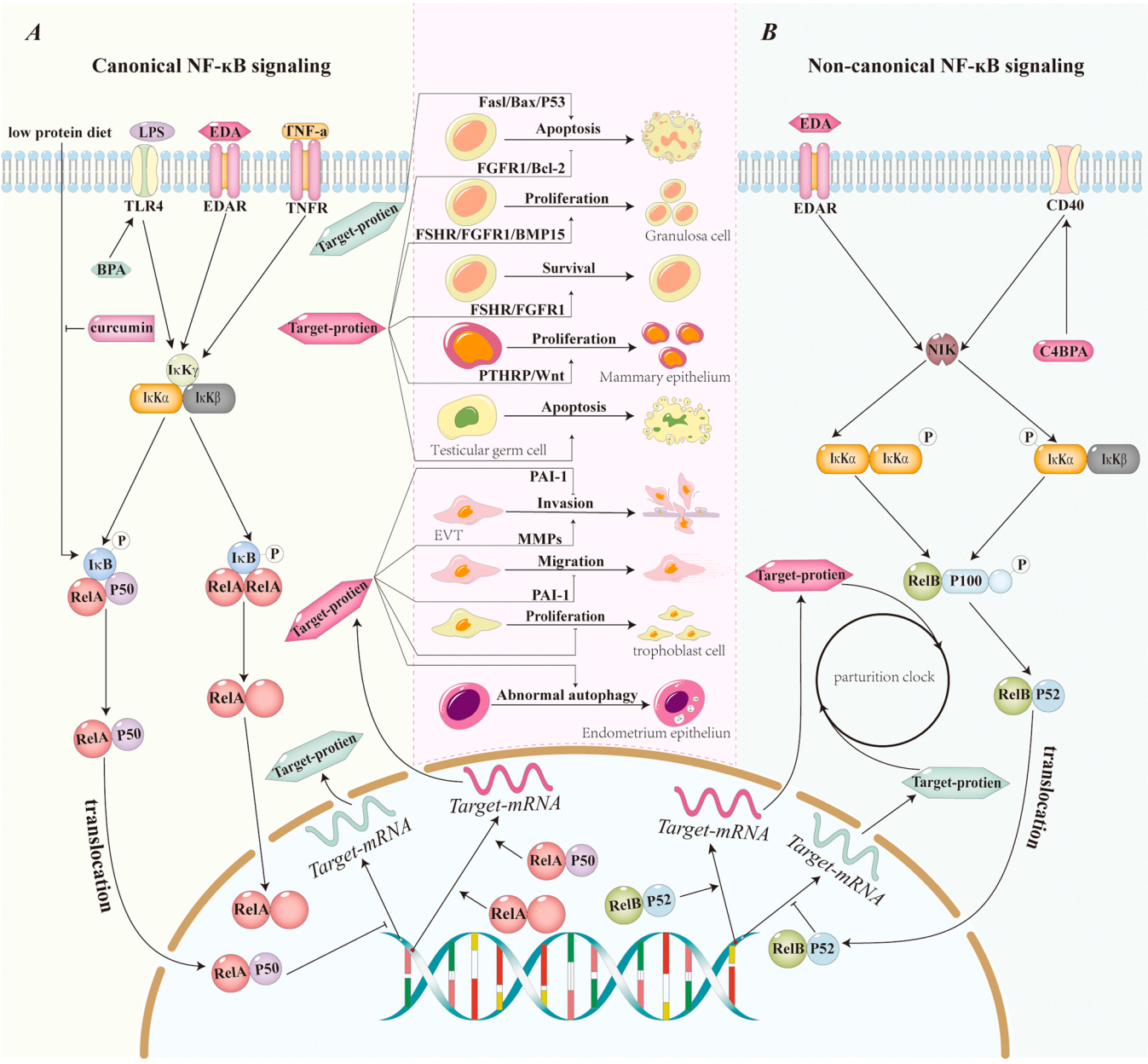

Fig. 9. Schematic depiction of the process of reproductive development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in reproductive development. ***B*** The role of non-canonical NF-κB signaling in reproductive development. Abbreviations are as follows: BPA, bisphenol A; Fasl, also known as CD95L; FGFR1, fibroblast growth factor receptor 1; FSHR, follicle-stimulating hormone receptor; PTHRP, parathyroid hormone-related protein; PAI-1, plasminogen activator inhibitor-1; EVT, extra-villous cytotrophoblast; C4BPA, C4b-binding protein A.

8. Role of NF-κB in reproductive system development

8.1. Follicular development

Only a few studies have investigated the role of the NF-κB signaling pathway in mammalian reproductive development, most of which focused on ovarian follicular and fetal appendage development. Xu et al. reported that NF-κB signaling is activated to promote granulosa cell proliferation and differentiation by upregulating follicle-stimulating hormone receptor (FSHR) expression during the transition from secondary to antral follicles in mice (Fig. 9*A*) [170]. However, NF-κB activation can inhibit granulosa cell apoptosis by downregulating FasL (CD95L) and caspase-3 expression in secondary and antral follicles [170], and the concomitant degradation of IKBα and upregulation of p65 and p50 indicates that the canonical NF-κB pathway is activated during this process. Furthermore, p65 promotes the transcription of fibroblast growth factor receptor 1 (FGFR1) (Fig. 9*A*) [171], which regulates proliferation and apoptosis to facilitate follicle development [172] and granulosa cell survival [170,171]. A study by Yuan et al. suggests that NF-κB functions as a p65 homodimer in the canonical pathway in the granulosa of porcine follicles [171]. As mentioned above, most of research about the role of NF-κB in follicular development focus on the canonical NF-κB pathway, the same goes for mammary gland and testis development.

8.2. Mammary gland development

As a ligand of the TNF family, EDA regulates the morphogenesis of several ectodermal appendages [173] including skin, tooth, or mammary bud explants [174]. EDA/NF-κB signaling plays a pivotal role in embryonic mammary gland development [174,175]. Although NF-κB signaling is not required for the formation of endogenous mammary placodes, some studies utilizing hκybrid embryos of K14-EDA mice, with transgenic overexpression of EDA, and the IκBαΔN mouse strain, wherein NF-κB is suppressed due to ubiquitous expression of a non-degradable IκBα, demonstrate that NF-κB (RelA) is required for the formation of supernumerary mammary placodes in neck region that runs along the mammary line [174,176]. Another study using the same animal model and embryonic mammary buds from embryos illustrates that overexpression of EDA caused highly increased ductal growth and branching that correlated with enhanced cell proliferation in both female and male mice through canonical NF-κB signaling and its target genes *PTHRP, Wnt10a/b* (Fig. 9*A*) [175].

8.3. Testis development

Phthalate chemical plasticizers, which maybe alter genetic targets by activating signal transduction pathways including NF-κB signaling, then damage the fetal and newborn rat testis through testicular germ cell apoptosis and neutrophil infiltration [177]. Another study using Sertoli cell lines showed that RelA/p50 could transcriptionally activate the expression of Rnf33, whose protein is involved in spermatogenesis by interacting with kinesin motor proteins to combine with the microtubule [178]. Recently, Tavignot et al. demonstrated that the lack of peptidoglycan recognition protein-LF (PGRP-LF) function can lead to increased expression of Diap1 to inhibit apoptosis by inducing abnormal activation of the NF-κB/IMD signaling pathway, which could lead to genitalia defects during drosophila development [179].

8.4. Fetal appendage development

As previously mentioned, NF-κB signaling coordinates angiogenesis by promoting the expression of pro-angiogenic factors such as VEGF. The placental growth factor (PIGF) is a member of the VEGF family of proteins [180], whose primary functions are to support angiogenesis and modulate trophoblast growth and differentiation [181]. PIGF is regulated by the NF-κB signaling pathway, as RelA can transcriptionally activate PIGF expression during hypoxia [180]. Moreover, the NF-κB signaling pathway regulates placental development by promoting extra-villous cytotrophoblast (EVT) invasion to sufficient levels while preventing over-invasion into maternal tissues [74]. Furthermore, NF-κB activation upregulates the expression of MMP-2 and MMP-9 [172] to promote epithelial to mesenchymal transition (EMT) [74], which is a significant contributor to EVT invasion [182]. However, contradictory results from another study suggest that NF-κB signaling activated by TNF-α leads to the upregulation of plasminogen activator inhibitor-1 (PAI-1) expression, which inhibits EVT migration and trophoblast invasion [183]. In addition, Qi et al. described that dietary curcumin supplementation significantly rescues the inhibition of placental growth induced by a low protein maternal diet, promotes cell proliferation in the labyrinthine layer to facilitate placental growth, and increases the blood sinusoid area of the placenta by inhibiting the NF-κB signaling pathway [184]. Meng et al. suggested that Bisphenol A (BPA) exposure leads to a thin endometrium epithelium in the offspring of female rats, which is related to the TLR-4/NF-κB signaling pathway; this could affect fertilized egg implantation in future generations (Fig. 9*A*) [185]. In recent research, Smaducin-6 was identified as a potential therapeutic candidate for congenital zika syndrome (CZS), wherein Smaducin-6 could block Pellino1-mediated ZIKV vertical transmission to the fetus, which in turn promotes neurogenesis by inhibiting the NF-κB/RelA signaling pathway in placental trophoblasts of C57BL/6 mice [186]. Furthermore, proteomics analysis revealed that C4BPA is significantly abundant in exosomes purified from fetal cord arterial blood of full-term fetuses and binds to CD40 of placental villous trophoblast to activate p100 processing to p52. These results suggest that non-canonical NF-κB signaling plays a role in the placental clock and governs the time duration of human pregnancy (Fig. 9*B*) [187]. These contradictory results indicate that NF-κB signaling plays various roles in the trophoblast lines through downstream transcription.

9. Role of NF-κB in the development of skeletal and muscular system

9.1. Chondrogenesis and endochondral ossification

Mechanisms of bone development include endochondral ossification and intramembranous ossification. Most bones are developed from endochondral ossification, which involves a chondrogenesis phase (including MSC condensation and differentiation of MSCs into chondrocytes) and a growth plate development phase (including chondrocyte proliferation, chondrocyte hypertrophy, chondrocyte apoptosis, vascular invasion, and calcification). RelA is expressed in the growth plate, mainly in the resting and hypertrophic zones, suggesting that NF-κB signaling is involved in endochondral ossification [188,189]. BMPs are essential for MSC condensation, and NF-κB signaling regulates the expression of BMP-2 (Fig. 10*A*) [189]. Furthermore, upregulation of RelA in growth plates induces chondrocyte proliferation and differentiation and inhibits apoptosis by enhancing BMP expression [31]. Additionally, BMP-2 could induce the expression of SRY-box transcription factor 9 (Sox9) via NF-κB signaling [31], and runt-related transcription factor 2 (Runx2), a target of Sox9, is an important transcription factor for the differentiation of MSCs into chondrocytes and the regulation of chondrocyte hypertrophy [189]. Some studies have suggested that insulin-like growth factor-I (IGF-I) promotes chondrocyte proliferation and differentiation by activating RelA through the PI3K/Akt pathway (Fig. 10*A*) [189,190]. The effects of growth hormone (GH) on growth plate chondrogenesis are mediated by the interaction between RelA and the STAT5b transcription factor [189,190]. These findings suggest that the canonical NF-κB signaling pathway is involved in chondrogenesis and growth plate development. However, the non-canonical NF-κB pathway also regulates chondrocyte proliferation and differentiation in the proliferative zone during endochondral

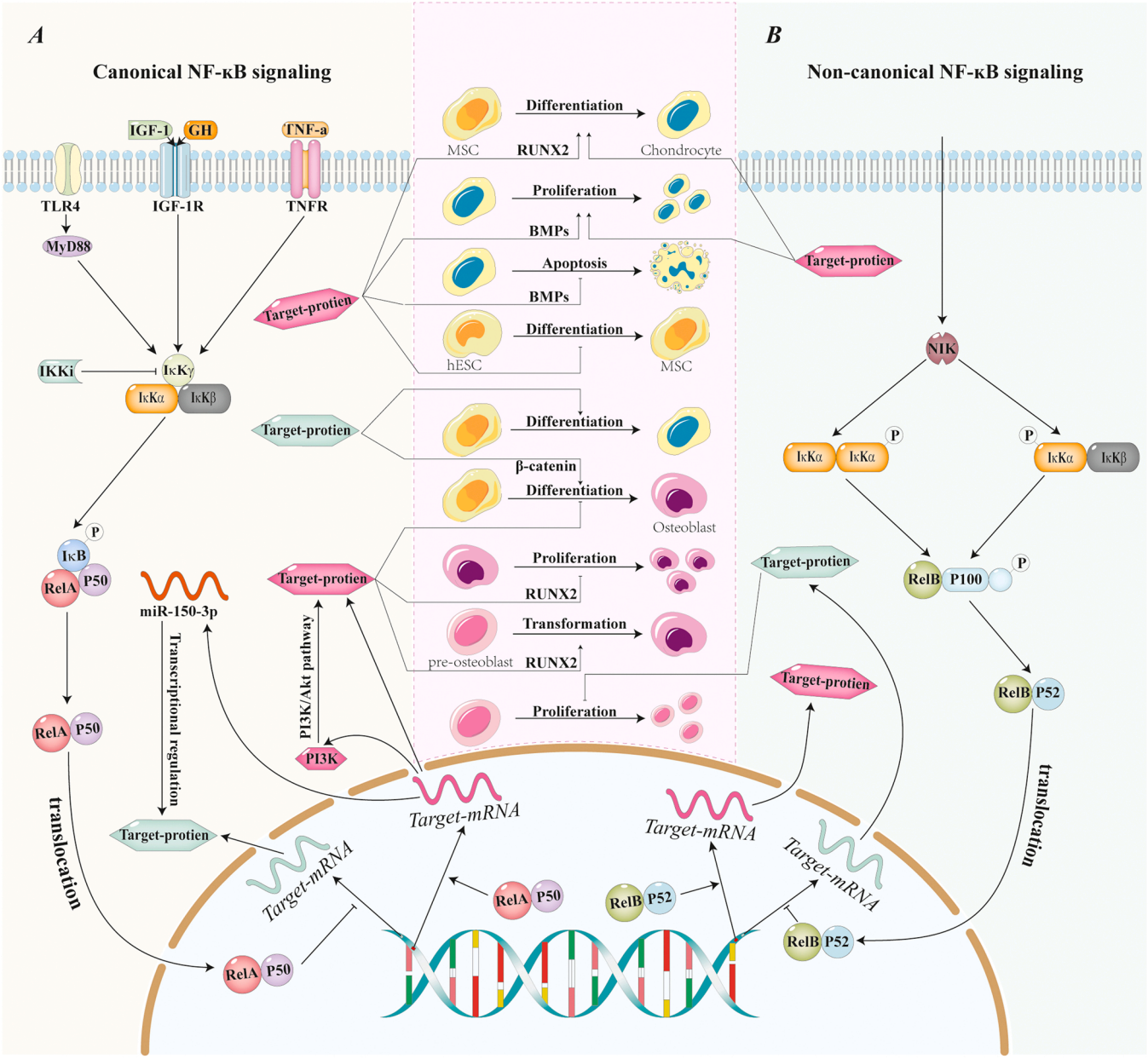

Fig. 10. Schematic representation of the process of bone development mediated by NF-κB signaling pathway. ***A*** The role of canonical NF-κB signaling in bone development. ***B*** The role of non-canonical NF-κB signaling in bone development. Abbreviations are as follows: IGF-1, insulin-like growth factor-1; GH, growth hormone; IKKi, small-molecule IKK inhibitor; RUNX2, runt-related transcription factor 2; BMP, bone morphogenetic protein; MSC, mesenchymal stem cell; ESC, embryonic stem cell.

ossification [31,191]. Moreover, the endochondral ossification of Meckel's cartilage, in which the non-canonical NF-κB (RelB/p52) pathway may act as an important regulator during Meckel's cartilage morphogenesis, has a core effect on the formation of the mandibular bone in mice [192].

9.2. *Intramembranous ossification and osteogenesis*

In contrast to endochondral ossification, osteoblasts directly differentiate from MSCs through intramembranous ossification [193], whose phases include MSC condensation; osteogenic differentiation of MSCs into osteoprogenitor cells, pre-osteoblasts, and osteoblasts; osteoblast differentiation into osteocytes; maturation; and mineralization. Therefore, osteoblasts are extremely important for bone development. IKK inhibits canonical NF-κB signaling to promote the differentiation of human embryonic stem cells into MSCs with multipotential capacity to differentiate into osteoblasts or chondrocytes *in vitro* and to form bone *in vivo* [194]. miR-150–3p inhibits osteogenic differentiation of MSCs by targeting and repressing the expression of β-catenin, and TNF-α/NF-κB signaling upregulates miR-150–3p expression by acting on an NF-κB binding site in the miR-150 promoter (Fig. 10*A*) [195]. In addition, MyD88-dependent activation of NF-κB signaling suppresses osteogenic differentiation, and MyD88 expression is upregulated by methyltransferase-like 3 (METTL3) via m6A methylation of MyD88 mRNA (Fig. 10A) [196]. A recent study revealed that the deletion of RelA represses BM-MSC proliferation while promoting the osteogenic and chondrogenic differentiation of BM-MSCs [197]. Furthermore, Runx2, an osteoblastogenic transcription factor, inhibits the proliferation of mesenchymal progenitor cells (MPCs) and mature osteoblasts, mediates osteoblast differentiation, and promotes the transformation of

osteoprogenitors to osteoblasts [198,199]. Although RelB does not impact MPC maintenance and differentiation from MSCs, it negatively regulates the commitment of pre-osteoblasts, pre-osteoblast proliferation, osteoblast differentiation, and mineralization by binding to sites in the Runx2 promoter and downregulating Runx2 expression (Fig. 10*A*) [198]. Taken together, these findings suggest that NF-κB signaling plays a vital role in various stages of the intramembranous ossification process.

9.3. Limb development

Previous studies have shown that IKKα is required for limb development during embryogenesis [17]. Recently, De Luca et al. discovered that NF-κB inhibition leads to abnormal limb development and delayed bone growth by influencing GH- and IGF-1-mediated longitudinal bone growth and growth plate chondrogenesis in rodents [190,200]. However, owing to the lethality associated with NF-κB activation during embryonic development, reports describing the function of NF-κB in limb development are limited.

9.4. Skeletal muscle development

A few studies have reported the roles of NF-κB in skeletal muscle development. NF-κB inhibits myogenesis by inducing the transcription factor YY1 and Cyclin D1 as well as suppressing MyoD [201–203]. Bakkar et al. suggested that the canonical NF-κB signaling pathway negatively regulates myogenesis, while the non-canonical pathway promotes the formation of myotubes and facilitates their maintenance during myogenesis [203,204]. In addition, under physiological conditions, TNF-like weak inducer of apoptosis (TWEAK) interacts with fibroblast growth factor-inducible molecule 14 (Fn14), which activates the non-canonical NF-κB pathway via TRAF adaptors and promotes

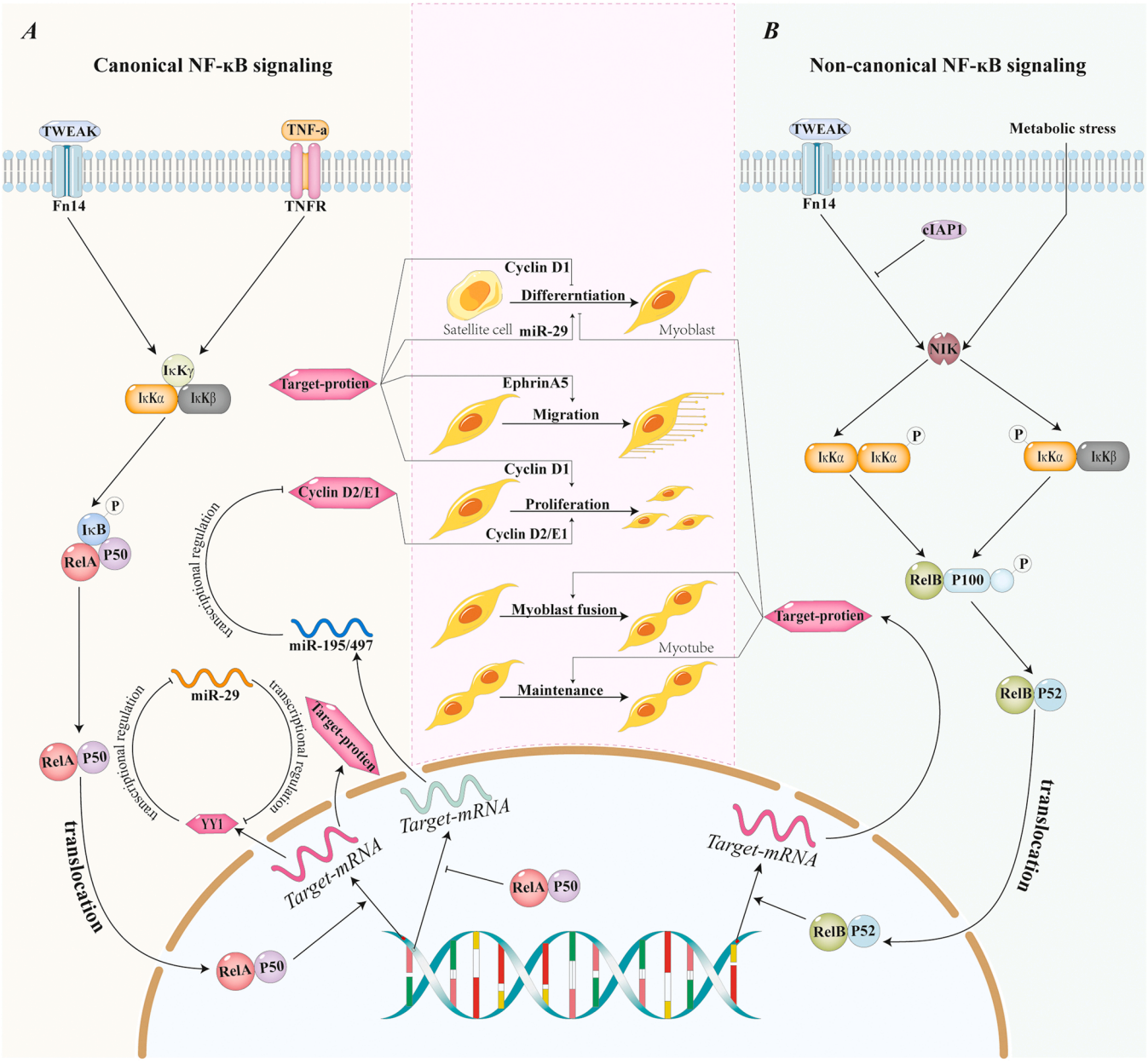

Fig. 11. Schematic depiction of the process of skeletal muscle development mediated by NF-κB signaling pathway. ***A*** The role of NF-κB signaling in skeletal muscle development. ***B*** The role of NF-κB signaling in skeletal muscle development. Abbreviations are as follows: TWEAK, TNF-like weak inducer of apoptosis; Fn14, fibroblast growth factor-inducible molecule 14.

myogenesis by increasing myoblast fusion (Fig. 11*B*) [204–206]. This interaction, however, does not activate canonical NF-κB signaling [206]. Furthermore, upregulation of miR-195 and miR-497 facilitates muscle development and myoblast differentiation, and NF-κB activation downregulates miR-195 and miR-497 expression in myoblasts and skeletal muscle (Fig. 11*A*) [207]. However, Gu et al. reported that NF-κB activation induces the expression of EphrinA5 to facilitate myoblast migration and neonatal skeletal muscle growth in $NG2^{+}$ interstitial cells (Fig. 11*A*) [208]. Reports on the function of NF-κB signaling in smooth muscle development are lacking; thus, the findings mentioned earlier may not be representative of the role played by NF-κB signaling in the development of all types of muscle.

10. Conclusions and future perspectives

Recently, numerous studies examining the novel roles of NF-κB signaling have emerged; for example, Liu et al. identified that the NIK/sine oculis homeobox (SIX) signaling axis regulates inflammatory gene expression, and then inhibits the transactivation function of RelA and RelB as a negative feedback circuit [209]. Zheng et al. discovered that genetic inactivation of RelA and MYD88 (an upstream regulator of the NF-κB complex) in human cells might facilitate the survival and chimerism of human cells in early mouse embryos, by overcoming cell competition (a supervision mechanism to ensure normal development and a barrier to interspecies chimerism) between human and mouse pluripotent stem cells (PSCs) [210]. In this review, we have summarized the emerging functions of the NF-κB signaling pathway in the regulation of tissue development. In the context of reported studies, we highlight that NF-κB signaling, either directly or indirectly, is associated with embryogenesis and developmental processes of nearly all organs and systems; In particular, RelA in canonical NF-κB signaling is profoundly implicated in these processes. Moreover, physiological homeostasis of NF-κB signaling is important for development during embryogenesis, as abnormal development is related to both the overexpression and inhibition of NF-κB signaling [17,64,147,194]. To summarize, current studies on NF-κB signaling pathways impacting developmental process remain limited, especially in the urinary and digestive system. Moreover, the role of the NF-κB signaling pathway in development is usually synergistic with other pathways. For example, NF-κB synergizes with the IGF2–IGF2R pathway to regulate synapse formation and spine maturation [56] as well as the Wnt/β-catenin/Lef-1 pathway to promote the differentiation of fibroblasts into sweat gland cells [161]. These complicated interactions are often referred to as “crosstalk” [211]. Such crosstalk occurs between the NF-κB pathway and other pathways (such as the PI3K/Akt signaling pathway [189]) but can also occur between the canonical and non-canonical NF-κB pathways. For example, RANKL mediates the activation of the canonical and non-canonical NF-κB pathways in osteoclasts [212], canonical NF-κB signaling induces RelB expression to activate non-canonical NF-κB signaling [213], and activation of the non-canonical NF-κB pathway by LTβR also could mediate the phosphorylation of p105 [214]. Furthermore, as described in this review, the aberrant activity of the NF-κB signaling pathway contributes to the abnormal development of organs and systems via a variety of cell events, such as differentiation [40,135], apoptosis [54,84], proliferation [82,87], migration [88,208], and invasion [74,183], and other cell events, such as NF-κB/GSDMD-mediated pyroptosis in mouse adipose tissue [215] and RAS-selective lethal 3 (RSL3)/NF-κB-induced ferroptosis in glioblastoma [216]. Due to its broad applications, NF-κB signaling is a potential therapeutic target for several diseases. NF-κB inhibitors are being studied for their ability to treat and prevent lung cancer [217]; celastrol is being developed as a therapeutic nanodrug for rheumatoid arthritis as it regulates the NF-κB and Notch1 pathways [218]. Similarly, targeting NF-κB signaling could also be a potential approach to treat dysplastic diseases. Moreover, vitamin B and folic acid significantly alleviates neuro-developmental disorders by inhibiting the canonical NF-κB signaling pathway [45,63]. Furthermore, tumor-related studies have noted the effectiveness of drugs targeting non-canonical NF-κB signaling pathways, which should be a focus of future research on embryonic developmental diseases [13]. In addition, pathogen-derived LPS, which is one of the distinctive microbial macromolecular ligands designated as microbial-associated molecular patterns to specifically recognize and bind the pattern recognition receptors [219], can be utilized to induce maldevelopment in embryos [63,93,219]. Neish et al. described how pathogens evolved to interfere with NF-κB signal transmission by post-translational modifications [219]; however, studies on the relationship between pathogens and NF-κB signaling during embryogenesis are limited. Thus, there are still many tasks deserving more studies before clinical application, because the role of NF-κB signaling in development is extraordinarily intricate, and the impact of NF-κB signaling on several stages of human development and disease remain uncharacterized. The activity of NF-κB signaling at the physiological level is essential to maintain normal developmental processes, while inappropriate activation or suppression beyond the need for development would result in dysplasia. Meanwhile, the diversity and functional uncertainty of cell events induced by the NF-κB signaling pathway, such as pyroptosis and ferroptosis, must be further elucidated via comprehensive studies using efficient experimental models, to lay a solid theoretical foundation for the development of novel therapeutics.

Ethical approval and consent to participate

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CRediT authorship contribution statent

Peiqi Liu: Investigation, Software, Data curation, Writing - original draft. **Yue Li:** Investigation, Software, Data curation. **Weilin Wang:** Supervision. **Yuzuo Bai:** Supervision. **Huimin Jia:** Supervision, Funding acquisition. **Zhengwei Yuan:** Funding acquisition, Funding acquisition, Conceptualization, Writing - review & editing. **Zhonghua Yang:** Funding acquisition, Conceptualization, Writing - review & editing.

Author contributions

PL prepared the manuscript and figures. WW, YB and HJ reviewed the manuscript. ZWY, ZHY and HJ obtained funding. ZHY and ZWY conceived the original idea, reviewed, and edited the manuscript. All authors have approved the final manuscript.

Submission declaration and verification

The work described has not been published previously.

Consent for publication

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The authors declare that there are no conflicts of interest.

Data Availability

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.113513.

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