CEP Clin Exp Pediatr Vol. 67, No. 11, 553-559, 2024
https://doi.org/10.3345/cep.2023.00346

Review article

Growth plate closure and therapeutic interventions

Ja Hyang Cho, MD,PhD[1,*], Hae Woon Jung, MD,PhD[2,*], Kye Shik Shim, MD,PhD[1]

[1]Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Kyung Hee University Hospital, Seoul, Korea; [2]Department of Pediatrics, Kyung Hee University Hospital, Kyung Hee University College of Medicine, Seoul, Korea

Height gains result from longitudinal bone growth, which is largely dependent on chondrocyte differentiation and proliferation within the growth plates of long bones. The growth plate, that is, the epiphyseal plate, is divided into resting, proliferative, and hypertrophic zones according to chondrocyte characteristics. The differentiation potential of progenitor cells in the resting zone, continuous capacity for chondrocyte differentiation and proliferation within the proliferative zone, timely replacement by osteocytes, and calcification in the hypertrophic zone are the 3 main factors controlling longitudinal bone growth. Upon adequate longitudinal bone growth, growth plate senescence limits human body height. During growth plate senescence, progenitor cells within the resting zone are depleted, proliferative chondrocyte numbers decrease, and hypertrophic chondrocyte number and size decrease. After senescence, hypertrophic chondrocytes are replaced by osteocytes, the extracellular matrix is calcified and vascularized, the growth plate is closed, and longitudinal bone growth is complete. To date, gonadotropin-releasing hormone analogs, aromatase inhibitors, C-type natriuretic peptide analogs, and fibroblast growth factor receptor 3 inhibitors have been studied or used as therapeutic interventions to delay growth plate closure. Complex networks of cellular, genetic, paracrine, and endocrine signals are involved in growth plate closure. However, the detailed mechanisms of this process remain unclear. Further elucidation of these mechanisms will enable the development of new therapeutic modalities for the treatment of short stature, precocious puberty, and skeletal dysplasia.

Key words: Growth plate, Closure, Therapy

Key message

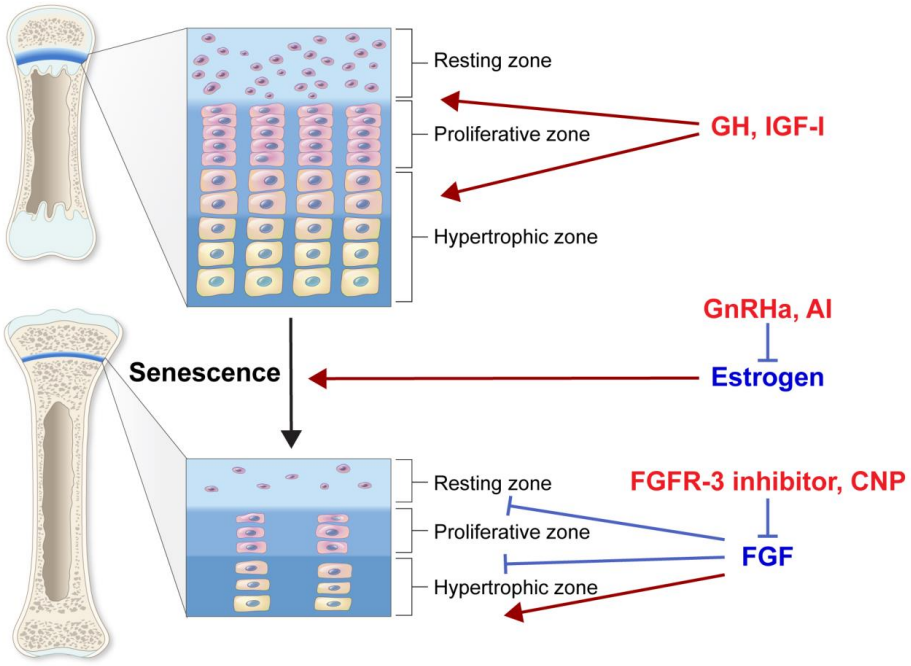
Height gains result from longitudinal bone growth. Upon adequate growth, growth plate closure limits longitudinal bone growth. To date, gonadotropin-releasing hormone analogs, aromatase inhibitors, C-type natriuretic peptide analogs, and fibroblast growth factor receptor 3 inhibitors have been studied or used as therapeutic interventions to delay growth plate closure and increase human height. The development of more effective therapeutic modalities for short stature, precocious puberty, and skeletal dysplasia is anticipated.

Introduction

Longitudinal bone growth results from chondrogenesis at the growth plate and endochondral ossification.[1-5] Chondrocyte hypertrophy, differentiation, and proliferation as well as extracellular matrix secretion continue during growth plate maturation.[6] Once adequate growth plate maturation is achieved, unknown signals cause growth plate senescence and closure. At that time, progenitor cells within the resting zone become depleted, proliferative chondrocyte numbers decrease, and hypertrophic chondrocyte numbers and size decrease. Subsequently, hypertrophic chondrocytes are replaced by osteocytes, the extracellular matrix becomes calcified and vascularized, and longitudinal bone growth ends.[7]

Although the detailed mechanisms of these processes remain unclear, many pathways associated with genetic, intracellular, extracellular, autocrine, paracrine, and endocrine factors are involved.[8,9] Thus, the elucidation of the mechanisms underlying growth plate maturation, senescence, and closure may provide an opportunity to develop new treatment strategies for various growth disorders. This review details evidence-based reports on the mechanisms of and therapeutic trials of treatments to delay growth plate closure.

Corresponding author: Kye Shik Shim, MD, PhD. Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Kyung Hee University College of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
*These authors contributed equally to this study as co-first authors.
✉ Email: 64sks@khu.ac.kr, https://orcid.org/0000-0002-8004-151X
Received: 14 February 2023, Revised: 19 April 2024, Accepted: 10 May 2024



Graphical abstract. Growth plate closure mechanism and therapeutic interventions used to delay its senescence to increase human height. GH, growth hormone; IGF-1, insulin-like growth factor-1; GnRHa, gonadotropin-releasing hormone analog; AI, aromatase inhibitor; FGFR-3, FGF receptor-3; CNP, C-type natriuretic peptide; FGF, fibroblast growth factor.

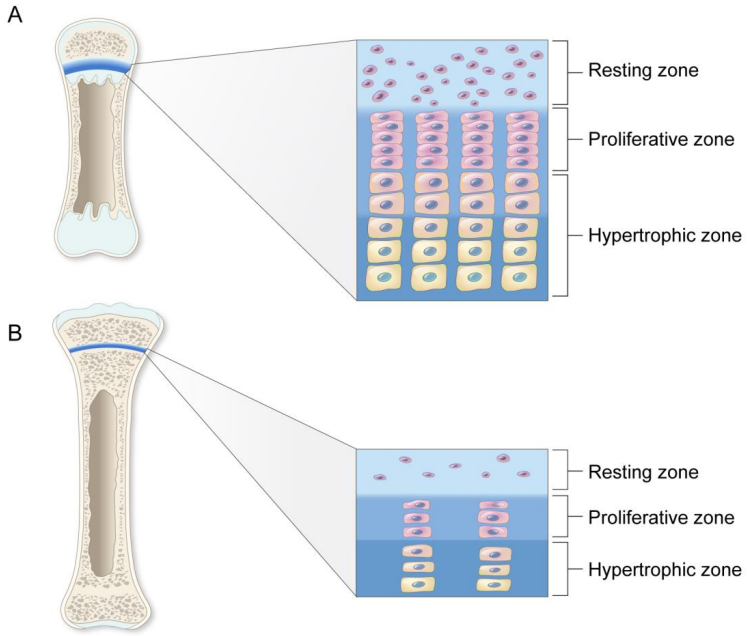


Fig. 1. Cellular patterns of chondrocyte differentiation, proliferation, and hypertrophy in a maturing (A) versus senescent (B) growth plate. Modified from Nilsson et al. Trends Endocrinol Metab 2004;15:370-4,[10] with permission of Elsevier Inc.

Growth plate structure, function, and closure

The growth plate, located between the epiphysis and metaphysis of the long bone, is divided into 3 zones according to the characteristics of the chondrocytes within each. The resting zone comprises small chondrocytes that act as progenitor cells with slow replication rates. The proliferative zone contains flat chondrocytes that line the long axis of the bone and replicate quickly. The hypertrophic zone is a layer of chondrocytes undergoing terminal differentiation that features increased thickness, surrounds a calcified matrix, and attracts factors for bone and vessel formation[1-5] (Fig. 1A).

During linear growth, growth plate thickening and maturation, chondrocyte proliferation and differentiation, extracellular matrix secretion, hypertrophic zone calcification, osteoblast invasion and differentiation, and blood vessel formation processes repeat continuously.[4-9] However, at the end of puberty, these processes cease and longitudinal bone growth is completed via the growth plate senescence and closure processes[8,9] (Fig. 1B).

1. Resting zone

Progenitor cells within the resting zone can continuously differentiate and proliferate into chondrocytes during growth plate maturation but lose this capacity during growth plate senescence.[10-12] Therefore, postnatal skeletal growth appears to be driven by the epiphyseal stem cell niche.[13-15]

There are 2 hypotheses regarding programmed senescence of the growth plate: cell counting and a biological timing mechanism.[10,12] In a growth plate transplantation experiment, the growth rate of the transplanted growth plate was dependent on donor animal, but not recipient animal, age. This experiment showed the finite proliferative capacity of the growth plate similar to the cell-counting mechanism.[16] In addition, in a murine study, loss of telomerase activity had no major effects on skeletal growth, indicating that telomere shortening is not the primary mechanism limiting chondrocyte proliferation.[17] However, *in vitro* studies have shown that epigenetic changes in the methylation of genomic DNA may limit chondrocyte replication.[18] The cellular programmed factors related to these theories have yet to be clearly elucidated.

Several transcription factors are considered involved in progenitor cell differentiation (Table 1). The conversion of progenitor cells in the mesenchymal condensation into the chondrocyte lineage is controlled by SRY-Box transcription factor 9 (SOX9) expression. The subsequent chondrocyte differentiation is influenced by SOX9, SOX5, and SOX6.[19]

Bone morphogenic protein (BMP) is a paracrine factor that promotes progenitor cell differentiation into proliferative chondrocytes.[20]

2. Proliferative zone

Chondrocytes continue to proliferate and differentiate into prehypertrophic and hypertrophic chondrocytes before growth plate senescence under the influence of complex interactions among paracrine, endocrine, and transcription factors[1-6] (Fig. 2).

BMP is a paracrine signal that promotes progressive differentiation from the resting state through proliferation

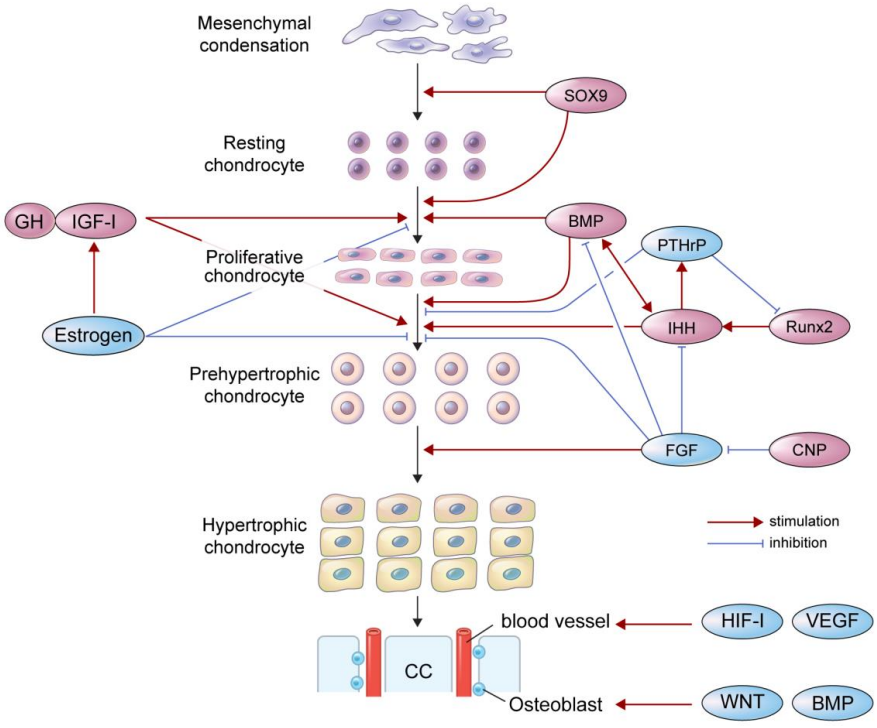


Fig. 2. Molecular networks involved in chondrocyte differentiation, proliferation, and hypertrophy. SOX9, SRY-box transcription factor 9; BMP, bone morphogenic protein; PTHrP, parathyroid hormone-related peptide; IHH, Indian hedgehog; Runx2, runt-related transcription factor 2; FGF, fibroblast growth factor; CNP, C-type natriuretic peptide; HIF-1, hypoxia-inducible factor-1; VEGF, vascular endothelial growth factor; WNT, Wingless-type mouse mammary tumor virus integration site signaling; CC, calcified cartilage. Modified from Ağırdil et al. EFORT Open Rev 2020;5:498-507 with permission.[5]

Table 1. Genetic and paracrine factors controlling the growth plate function

Factor	Main functions in growth plate
Sox9	Conversion of progenitor cells into chondrocyte
Sox5,6	Differentiation of chondrocyte lineage
BMP	Differentiation of resting to proliferative to hypertrophic chondrocytes Stimulation of osteoblastogenesis
PTHrP	Slowing down chondrocyte differentiation
IHH	Differentiation of chondrocyte lineage
FGF	Inhibition of chondrocyte proliferation, stimulation of chondrocyte hypertrophy
Runx2	Stimulation of IHH Differentiation of hypertrophic chondrocyte and osteoblast
CNP	Inhibition of FGF and MAPK signaling
HIF-I	Stimulation of angiogenesis Differentiation of hypoxic chondrocyte
VEGF	Stimulation of vessel formation Stimulation of osteoclast invasion into cartilage
Wnt	Control of osteoblastogenesis

Sox, SRY-related high mobility group box genes; BMP, bone morphogenic protein; PTHrP, parathyroid hormone-related peptide; IHH, Indian hedgehog; FGF, fibroblast growth factor; Runx2, runt-related transcription factor 2; CNP, C-type natriuretic peptide; MAPK, mitogen-activated protein kinase; HIF-1, hypoxia-inducible factor-1; VEGF, vascular endothelial growth factor; Wnt, Wingless-type mouse mammary tumor virus integration site signaling.

to hypertrophic chondrocytes. BMP is involved in perichondrium, periosteum, and osteoblast development.[21-23]

Parathyroid hormone-related peptide (PTHrP), which is secreted from periarticular chondrocytes, diffuses across the growth plate cartilage to maintain chondrocyte proliferation.[24]

Indian hedgehog (IHH), secreted by prehypertrophic and hypertrophic chondrocytes, stimulates PTHrP secretion and promotes the differentiation of proliferative chondrocytes into prehypertrophic chondrocyte.[25-27]

Fibroblast growth factor (FGF) is also important for perichondria, periosteum, and osteoblast development. *In vivo* studies have indicated that FGF receptor-1 and FGF receptor-3 (FGFR-3) have growth-inhibiting effects and FGF receptor-2 has growth-promoting effects on longitudinal bone growth.[28-29] Runt-related transcription factor 2 (Runx2) is a transcription factor that is required for further chondrocyte differentiation and hypertrophy.[20]

Various endocrine factors are involved in chondrocyte proliferation and differentiation (Table 2).[30] Growth hormones (GHs) positively regulate insulin-like growth factor-1 (IGF-1) synthesis and secretion in the liver and growth plates. Longitudinal bone growth is stimulated by GH, circulating IGF-1, and locally secreted IGF-1 in the growth plate. Among them, IGF-1 produced locally from chondrocytes is especially important for chondrocyte differentiation, proliferation, and hypertrophy; moreover, it stimulates extracellular matrix production and ossification within the growth plate.[31]

Table 2. Endocrine factors control growth plate function

Factor	Main functions in growth plate
GH	Synthesis and secretion of insulin-like growth factor-I
IGF-1	Differentiation, proliferation, and hypertrophy of chondrocytes
Estrogen	Stimulation of the GH-IGF-1 axis Acceleration of growth plate senescence
Androgen	Proliferation of chondrocytes and proteoglycan synthesis Aromatization of androgens to estrogens
Thyroid hormone	Proliferation and hypertrophy of chondrocytes
Glucocorticoid	Inhibition of GH-IGF-1 axis and local secretion of IGF-1 Inhibition of chondrocyte proliferation Stimulation of apoptosis in hypertrophic chondrocytes Delay of growth plate senescence

GH, growth hormone; IGF-1, insulin-like growth factor-1.

The binding of estrogen to its receptor (estrogen receptor [ER]) stimulates the GH-IGF-1 axis, especially during the pubertal growth spurt. Both receptor subtypes (ERα and ERβ) are related with the augmentation of GH secretion and expressed in the resting, proliferative, and hypertrophic zones of the growth plate.[32-35] There is evidence that growth plate closure occurs when the proliferative capacity of progenitor cells within the resting zone becomes exhausted. Estrogen can accelerate the exhaustion of proliferative potential and advance growth plate senescence. The binding of estrogen to each ER subtype is considered related to growth plate closure. ERα appears to be the dominant mediator of estrogen actions. ERβ has some repressive functions within the long bones in mice; however, its definite roles in the long bones of humans remain unclear. Estrogen also promotes bone formation and remodeling by stimulating osteoblastogenesis and inhibiting osteoclastogenesis.[36-39]

Androgens with aromatized estrogen contribute to growth plate maturation and senescence through direct or indirect interactions with growth plate chondrocytes. In an organ culture study, testosterone stimulated chondrocyte proliferation with increased local IGF-1 production, while dihydrotestosterone promoted chondrocyte proliferation and proteoglycan synthesis within the growth plates. In growth plate closure, the function of androgen is attributed to the aromatization of androgen to estrogen in various peripheral tissues, including the growth plate cartilage.[40,41]

Thyroid hormones stimulate chondrocyte proliferation, hypertrophy, and growth plate maturation.[8]

Glucocorticoids inhibit longitudinal bone growth by inhibiting the GH-IGF-1 axis and chondrocyte proliferation as well as stimulating apoptosis of hypertrophic chondrocytes. It also delays growth plate senescence.[8]

3. Hypertrophic zone

1) Replacement of chondrocytes by osteocytes

Chondrocytes in the hypertrophic zone are replaced by osteocytes during growth plate maturation and senescence. To the best of our knowledge, there are 4 theories (apoptosis, autophagy, hypoxia, and transdifferentiation) regarding the mechanism of cartilage replacement in bone tissue.[11,42-46]

2) Blood vessel formation

Blood vessel formation and vascular invasion are critical for substituting avascular cartilage with vascular bone and marrow tissues. Vessel formation is mediated by hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), Runx2, FGF, BMP, transforming growth factor, IGF, and platelet-derived growth factor within the growth plate.[47-50]

3) Osteoblast differentiation and ossification

Five osteoblastic lineage differentiation steps (preosteoblasts, mature osteoblasts, osteoid osteocytes, early osteocytes, and mature osteocytes) are necessary to achieve the final development of bone tissue within the growth plate. Wingless-type mouse mammary tumor virus integration site/β-catenin signaling, Runx2, Osterix, BMP, IHH, and IGF are the required factors for differentiation.[51]

During this process, bones can deposit minerals from the extracellular matrix that are rich in type I collagen, completing ossification and growth plate closure.[52]

Therapeutic interventions for delaying growth plate closure

1. Gonadotropin-releasing hormone analog

Various preparations of gonadotropin-releasing hormone analogs (GnRHa), such as leuprolide acetate, triptorelin phosphate, and histrelin acetate, have been used as major treatment modalities for idiopathic central precocious puberty. Their effects are mediated by the desensitization of pituitary gonadotrophs occupying GnRH receptors, resulting in the suppression of gonadal sex steroid secretion and postponement of growth plate closure. The effects on adult height increase varied from 2 to 10 cm in children with precocious puberty and from 1.7 to 6.7 cm in adolescents with idiopathic short stature or growth-limiting syndromes. However, adverse effects on bone mineral density have been reported in adolescents with idiopathic short stature who do not undergo early-onset puberty.[53-56]

2. Aromatase inhibitors

Aromatase inhibitors (AIs) inhibit aromatase, which converts androgen into estrogen. Letrozole, anastrozole, and exemestane, representative selective AI, were initially used to treat breast cancer in women and gynecomastia in men. A few reports have described their positive effects on adult height after their off-label use to delay growth plate closure. However, their general use to increase height in humans is not widely accepted because of the possibility of adverse effects on bone mineral density and vertebral deformity.[57]

3. C-type natriuretic peptide analog

C-type natriuretic peptide (CNP) binds natriuretic peptide receptor-B and results in the transformation of guanosine 5 -triphosphate to cyclic guanosine monophosphate and the inhibition of mitogen-activated protein kinase (MAPK) and FGF signaling. These signaling pathways stimulate the latter steps of chondrocyte hypertrophy within the growth plate and promote growth plate closure. CNP analogs have been studied as treatment modalities in patients with achondroplasia, a disorder characterized by the activation mutation of FGFR-3, which results in earlier growth plate closure and a severely short stature. Two types of CNP analogs, a recombinant CNP analog (vosoritide) and transiently conjugated CNP (navepegritide), can inhibit MAPK and FGFR signaling and are new treatment methods for achondroplasia.[58,59]

4. FGFR-3 inhibitor

FGF binds to FGFR-3 and stimulates Ras-MAPK signaling, inhibiting chondrocyte differentiation and proliferation. FGFR3 inhibitors have been studied as treatment modalities for achondroplasia because they block the Ras-MAPK pathway and stimulate chondrocyte differentiation and proliferation. Such inhibitors include the soluble FGFR3 decoy (recifercept), anti-FGFR3 monoclonal antibody (vofatamab), and FGFR3-selective tyrosine kinase inhibitor (infigratinib).[58,60]

Conclusion

Cellular and genetic factors related to the aging of progenitor cells within the resting zone and the transdifferentiation of chondrocytes into osteocytes within the hypertrophic zone are considered important in limiting height growth; however, their exact mechanisms of action remain unclear. Many paracrine and genetic factors are also involved in chondrocyte differentiation, proliferation, and hypertrophy within the cartilage as well as vascularization and ossification in the extracellular matrix of the growth plate; however, further studies of their interaction mechanisms are needed. Among endocrine factors, estrogen and the GH-IGF-I axis are important in chondrocyte differentiation, proliferation,

and hypertrophy, but the exact mechanisms by which estrogen accelerates growth plate senescence remain unknown.

The complex interactions between the cellular, genetic, paracrine, and endocrine systems within the growth plates are closely related to the mechanisms of growth plate maturation, senescence, and closure. Until now, GnRHa, AIs, CNP analogs, and FGFR-3 inhibitors have been studied or used as the therapeutic modalities for delaying growth plate closure. Elucidating the detailed processes of growth plate physiology will increase our ability to explain the molecular mechanisms responsible for idiopathic short stature, central precocious puberty, and skeletal dysplasia as well as facilitate the development of more effective therapeutic modalities for these diseases.

Footnote

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID:
Ja Hyang Cho https://orcid.org/0000-0002-5562-588X
Hae Woon Jung https://orcid.org/0000-0003-0494-4626
Kye Shik Shim https://orcid.org/0000-0002-8004-151X

References

1. Maes C, Kronenberg HM. Bone development and remodeling. In: Robertson RP, editor. DeGroot's endocrinology. 8th ed. Philadelphia (PA): Elsevier Inc., 2023:869-88.
2. Maes C, Kronenberg HM. Postnatal bone growth: growth plate biology, bone formation, and remodeling. In: Glorieux FH, Pettifor JM, Jüppner H, editors. Pediatric bone. 2nd ed. San Diego (CA): Elsevier Inc., 2012:55-82.
3. Root AW. Disorders of mineral metabolism: normal homeostasis. In: Sperling MA, Majzoub JA, Menon RK, Stratakis CA, editors. Sperling pediatric endocrinology. 5th ed. Philadelphia (PA): Elsevier Inc., 2021:220-78.
4. Shim KS. Pubertal growth and epiphyseal fusion. Ann Pediatr Endocrinol Metab 2015;20:8-12.
5. A ırdil Y. The growth plate: a physiologic overview. EFORT Open Rev 2020;5:498-507.
6. Lui JC, Nilsson O, Baron J. Recent research on the growth plate: recent insights into the regulation of the growth plate. J Mol Endocrinol 2014;53:T1-9.
7. Lui JC, Jee YH, Garrison P, Iben JR, Yue S, Ad M, et al. Differential aging of growth plate cartilage underlies differences in bone length and thus helps determine skeletal proportions. PLoS Biol 2018;16:e2005263.
8. Nilsson O, Marino R, De Luca F, Phillip M, Baron J. Endocrine regulation of the growth plate. Horm Res 2005;64:157-65.
9. Eerden BC, Karperien M, Wit JM. Systemic and local regulation of the growth plate. Endocr Rev 2003;24:782-801.
10. Nilsson O, Baron J. Fundamental limits on longitudinal bone growth: growth plate senescence and epiphyseal fusion. Trends Endocrinol Metab 2004;15:370-4.
11. Emons J, Chagin AS, Sävendahl L, Karperien M, Wit JM. Mechanisms of growth plate maturation and epiphyseal fusion. Horm Res Paediatr 2011;75:383-91.
12. Kalirai H, Phillip M, Savendahl L, Wit JM. The Fifth European Growth Plate Working Group Symposium. J Pediatr Endocrinol Metab 2006;19:183-90.
13. Schrier L, Ferns SP, Barnes KM, Emons JA, Newman EI, Nilsson O, et al. Depletion of resting zone chondrocytes during growth plate senescence. J Endocrinol 2006;189:27-36.
14. Chagin AS, Newton PT. Postnatal skeletal growth is driven by the epiphyseal stem cell niche: potential implications to pediatrics. Pediatr Res 2020;87:986-90.
15. Lui JC. Home for a rest: stem cell niche of the postnatal growth plate. J Endocrinol 2020;246:R1-11.
16. Stevens DG, Boyer MI, Bowen CV. Transplantation of epiphyseal plate allografts between animals of different ages. J Pediatr Orthop 1999;19:398-403.
17. Herrera E, Samper E, Martín-Caballero J, Flores JM, Lee HW, Blasco MA. Disease states associated with telomerase deficiency appear earlier in mice with short telomeres. EMBO J 1999;18:2950-60.
18. Nilsson O, Mitchum RD, Schrier L, Ferns SP, Barnes KM, Troendle JF, et al. Growth plate senescence is associated with loss of DNA methylation. J Endocrinol 2005;186:241-9.
19. Akiyama H, Chaboissier MC, Martin JF, Schedl A, de Crombrugghe B. The transcription factor Sox9 has essential roles in successive steps of the chondrocyte differentiation pathway and is required for expression of Sox5 and Sox6. Genes Dev 2002;16:2813-28.
20. Karimian E, Chagin AS, Sävendahl L. Genetic regulation of the growth plate. Front Endocrinol (Lausanne) 2012;2:113.
21. Nilsson O, Parker EA, Hegde A, Chau M, Barnes KM, Baron J. Gradients in bone morphogenetic protein-related gene expression across the growth plate. J Endocrinol 2007;193:75-84.
22. Pizette S, Niswander L. BMPs are required at two steps of limb chondrogenesis: formation of prechondrogenic condensations and their differentiation into chondrocytes. Dev Biol 2000;219:237-49.
23. Minina E, Wenzel HM, Kreschel C, Karp S, Gaffield W, McMahon AP, et al. BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation. Development 2001;128:4523-34.
24. Hirai T, Chagin AS, Kobayashi T, Mackem S, Kronenberg HM. Parathyroid hormone/parathyroid hormone-related protein receptor signaling is required for maintenance of the growth plate in postnatal life. Proc Natl Acad Sci U S A 2011;108:191-6.
25. Karp SJ, Schipani E, St-Jacques B, Hunzelman J, Kronenberg H, McMahon AP. Indian hedgehog coordinates endochondral bone growth and morphogenesis via parathyroid hormone related-protein-dependent and -independent pathways. Development 2000;127:543-8.
26. Eerden BC, Karperien M, Gevers EF, Löwik CW, Wit JM. Expression of Indian hedgehog, parathyroid hormone-related protein, and their receptors in the postnatal growth plate of the rat: evidence for a locally acting growth restraining feedback

loop after birth. J Bone Miner Res 2000;15:1045-55.
27. Kindblom JM, Nilsson O, Hurme T, Ohlsson C, Sävendahl L. Expression and localization of Indian hedgehog (Ihh) and parathyroid hormone related protein (PTHrP) in the human growth plate during pubertal development. J Endocrinol 2002;174:R1-6.
28. Minina E, Kreschel C, Naski MC, Ornitz DM, Vortkamp A. Interaction of FGF, Ihh/Pthlh, and BMP signaling integrates chondrocyte proliferation and hypertrophic differentiation. Dev Cell 2002;3:439-49.
29. Lazarus JE, Hegde A, Andrade AC, Nilsson O, Baron J. Fibroblast growth factor expression in the postnatal growth plate. Bone 2007;40:577-86.
30. Murray PG, Clayton PE. Endocrine control of growth. Am J Med Genet 2013;163:76-85.
31. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors and the skeleton. Endocr Rev 2008;29:535-59.
32. Albin A, Niklasson A, Westgren U, Norjavaara E. Estradiol and pubertal growth in girls. Horm Res Paediatr 2012;78:218-25.
33. Leung K, Johannsson G, Leong GM, Ho KY. Estrogen regulation of growth hormone action. Endocr Rev 2004;25:693-721.
34. Chagin AS, Sävendahl L. Oestrogen receptors and linear bone growth. Acta Paediatr 2007;96:1275-9.
35. Börjesson AE, Lagerquist MK, Windahl SH. The role of estrogen receptor α in the regulation of bone and growth plate cartilage. Cell Mol Life Sci 2013;70:4023-37.
36. Weise M, De-Levi S, Barnes KM, Gafni R, Abad V, Baron J. Effects of estrogen on growth plate senescence and epiphyseal fusion. Proc Natl Acad Aci USA 2001;98:6871-6.
37. Börjesson AE, Windahl SH, Karimian E, Eriksson EE, Lagerquist MK, Engdahl C, et al. The role of estrogen receptor-α and its activation function-1 for growth plate closure in female mice. Am J Physiol Endocrinol Metab 2012;302:E1381-9.
38. Börjesson AE, Lagerquist MK, Liu C, Shao R, Windahl SH, Karlsson C, et al. The role of estrogen receptor α in growth plate cartilage for longitudinal bone growth. J Bone Miner Res 2010;25:2414-24.
39. Nilsson O, Weise M, Landman EB, Meyers JL, Barnes KM, Baron J. Evidence that estrogen hastens epiphyseal fusion and cessation of longitudinal bone growth by irreversibly depleting the number of resting zone progenitor cells in female rabbits. Endocrinology 2014;155:2892-9.
40. Vanderschueren D, Laurent MR, Claessens F, Gielen E, Lagerquist MK, Vandenput L, et al. Sex steroid actions in male bone. Endocr Rev 2014;35:906-60.
41. Nilsson O, Chrysis D, Pajulo O, Boman A, Holst M, Rubinstein J, et al. Localization of estrogen receptors-alpha and -beta and androgen receptor in the human growth plate at different pubertal stages. J Endocrinol 2003;177:319-26.
42. Chrysis D, Nilsson O, Ritzen EM, Sävendahl L. Apoptosis is developmentally regulated in rat growth plate. Endocrine 2002;18:271-8.
43. Emons J, Chagin AS, Hultenby K, Zhivotovsky B, Wit JM, Karperien M, et al. Epiphyseal fusion in the human growth plate does not involve classical apoptosis. Pediatr Res 2009;66:654-9.
44. Settembre C, Arteaga-Solis E, McKee MD, de Pablo R, Al Awqati Q, Ballabio A, et al. Proteoglycan desulfation determines the efficiency of chondrocyte autophagy and the extent of FGF signaling during endochondral ossification. Genes Dev 2008;22:2645-50.
45. Shapiro IM, Adams CS, Freeman T, Srinivas V. Fate of the hypertrophic chondrocyte: microenvironmental perspectives on apoptosis and survival in the epiphyseal growth plate. Birth Defects Res C Embryo Today 2005;75:330-9.
46. Moskalewski S, Malejczyk J. Bone formation following intrarenal transplantation of isolated murine chondrocytes: chondrocyte-bone cell transdifferentiation? Development 1989;107:473-80.
47. Stewart AJ, Houston B, Farquharson C. Elevated expression of hypoxia inducible factor-2alpha in terminally differentiating growth plate chondrocytes. J Cell Physiol 2006;206:435-40.
48. cramer T, Schipani E, Johnson RS, Swoboda B, Pfander D. Expression of VEGF isoforms by epiphyseal chondrocytes during low-oxygen tension is HIF-1 alpha dependent. Osteoarthrit Cart 2004;12:433-9.
49. Lin C, McGough R, Aswad B, Block JA, Terek R. Hypoxia induces HIF-1 alpha and VEGF expression in chondrosarcoma cells and chondrocytes. J Orthop Res 2004;22:1175-81.
50. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581-611.
51. Noble BS. The osteocyte lineage. Arch Biochem Biophys 2008;473:106-11.
52. Saltarelli MA, Quarta A, Chiarelli F. Growth plate extracellular matrix defects and short stature in children. Ann Pediatr Endocrinol Metab 2022;27:247-55.
53. Krishna KB, Fuqua JS, Rogol AD, Klein KO, Popovic J, Houk CP, et al. Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. Horm Res Paediatr 2019;91:357-72.
54. Yang EH, Jo HY, Park SJ, Yoo HW, Choi SH, Kim HY, et al. Effect of gonadotropin-releasing hormone agonist treatment on near final height in girls with central precocious puberty and early puberty. Ann Pediatr Endocrinol Metab 2023;28:49-53.
55. Cho AY, Ko SY, Lee JH, Kim EY. Effects of gonadotropin-releasing hormone agonist treatment on final adult height in boys with idiopathic central precocious puberty. Ann Pediatr Endocrinol Metab 2021;26:259-65.
56. Yanovski JA, Rose SR, Municchi G, Pescovitz OH, Hill SC, Cassorla FG, et al. Treatment with a luteinizing hormone-releasing hormone agonist in adolescents with short stature. N Engl J Med 2003;348:908-17.
57. Mauras N, Ross J, Mericq V. Management of growth disorders in puberty: GH, GnRHa, and aromatase inhibitors: a clinical review. Endocr Rev 2023;44:1-13.
58. Allen DB, Merchant N, Miller BS, Backeljauw PF. Evolution and future of growth plate therapeutics. Horm Res Paediatr 2021;94:319-32.
59. Ichiki T, Jinno A, Tsuji Y. Natriuretic peptide-based novel therapeutics: long journeys of drug developments optimized for disease states. Biology (Basel) 2022;11:859-73.
60. Kim HY, Ko JM. Clinical management and emerging therapies of FGFR3-related skeletal dysplasia in childhood. Ann Pediatr Endocrinol Metab 2022;27:90-7.

How to cite this article: Cho JH, Jung HW, Shim KS. Growth plate closure and therapeutic interventions. Clin Exp Pediatr 2024;67:553-9.