Growth plate, a cartilaginous tissue located at both ends of a growing long bone, is responsible for bone lengthening, acquisition of spongy or trabecular structure and accrual of trabecular bone mass during development. Growth plate function is critically important not only for healthy bone growth/attainment of peak height, but also for attainment of peak bone mass for delaying ageing-related osteoporosis onset and reducing fracture risks in adult life. Thus, understanding the regulation of growth plate function and developing targeting treatments for bone growth defects have been an active focus of investigation in the last two decades.

This critical bone growth function occurs through a highly complex process, ‘endochondral ossification’, which involves proliferation, hypertrophy, cartilage matrix synthesis and apoptosis of the growth plate chondrocytes resulting in the production of a calcified cartilage template, which is subsequently invaded by blood vessels and replaced by spongy or trabecular bone at the adjacent bone region. Due to these multiple cellular processes and dynamic biochemical changes, there are a range of endocrine factors (such as hormones and insulin-like growth factor 1 (IGF1)) and locally produced paracrine molecules (such as parathyroid hormone-related peptide (PTHrP), Indian hedgehog (IHH), bone morphogenetic proteins (BMPs), wingless/integrated proteins (Wnts), fibroblast growth factors (FGFs), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-\(\beta\)) that regulate this highly complex bone formation process as well as in controlling the variable rates of bone growth at different developmental stages. Growth plate dysregulation/dysfunction is now known to cause many bone developmental and growth disorders, including those from genetic mutations (particularly chondrodysplasia), chronic inflammatory disorders, glucocorticoid therapy and/or cancer chemotherapy (growth retardation and low bone mass), and trauma injuries (limb length discrepancy and angulation). This thematic special issue presents four reviews summarising recent advances and proposing new perspectives on molecular control of growth plate function, pathophysiology of these bone growth defects and potential treatment strategies.

Lui et al. (2014) discuss new advances in growth plate regulatory mechanisms as revealed through systematic microarray examination of gene expression in different zones of rodent growth plate, genome-wide association studies identifying genes involved in regulating human linear growth potential and conformational mouse targeting-ablation studies. They also review recent evidence for a potential BMP signalling gradient (highest in the hypertrophic zone) which may be responsible for chondrocyte-progressive chondrogenic differentiation. They summarise recent studies on the functions of C-type natriuretic peptide in promoting growth plate chondrogenesis by potentially counteracting the growth-inhibitory signalling of FGF/FGF receptor (FGFR). They then highlight some recent work that established suppressor of cytokine signalling (SOCS) as a key negative regulator of local growth hormone action in the growth plate. Furthermore, they point out that further studies are required to elucidate interactions between the endocrine factors and the local paracrine signals in regulating growth plate and to investigate mechanisms for the age-related decline in growth plate function and closure.

Dysfunctional FGF signalling is known to cause skeletal developmental disorders. Xie et al. (2014) summarise the patterns of expression of FGFs and FGFRs in the growth plate, the FGF/FGFR signalling pathway and the interplay of its downstream signalling molecules/pathways with other
molecules controlling bone development and homeostasis. Based on clues from human genetic skeletal syndromes and mouse genetic models, they also clarify the roles of FGFs/FGFRs in skeleton development and dwarfism syndromes largely associated with FGFR3 gain-of-function mutations. Furthermore, they review potential therapeutic treatments to alleviate the skeleton phenotypes resulting from FGF/FGFR signalling dysfunction, particularly the FGFR3 or downstream signalling-targeting interventions. Moreover, they propose the need to further elucidate the spatio-temporal expression and function of individual members of FGFs/FGFRs in development and in skeletal diseases, and the need to further develop effective targeting treatments.

Children with inflammatory diseases usually display some growth retardation. Sederquist et al. (2014) summarise the current knowledge on contributing factors that are related to disease itself and negatively impact on longitudinal bone growth, including malnutrition (which impairs bone growth), high-dose chronic use of glucocorticoids (which suppress bone growth) and elevated serum levels of inflammatory cytokines (which can systemically downregulate production of growth hormone and IGF1). They also review recent studies on the local action of inflammatory cytokines in the growth plate where they decrease chondrocyte proliferation and hypertrophy while increasing apoptosis. Furthermore, they review some experimental and clinical studies, which demonstrate bone growth improvements by targeting inhibition of these cytokines. They point out that, while the currently available cytokine-targeting biologics could be used to reduce growth retardation in children with chronic inflammation, further work is needed to develop more effective specific cytokine inhibitors.

Trauma injuries to the growth plate often cause growth plate dysfunction and bone growth defects due to bone repair to the injury site. Chung & Xian (2014) review the phases of the growth plate repair response and the function of signalling molecules found to be implicated by animal studies. These signalling molecules include: tumour necrosis factor alpha (TNFα), which is produced in the initial inflammatory phase and influences subsequent mesenchymal infiltration and bone cell differentiation; platelet-derived growth factor (PDGF), which acts as a chemotactic agent promoting infiltration/proliferation of mesenchymal progenitors; VEGF, which functions as a key angiogenic factor in the vascularisation of the injured growth plate; BMP and Wnt/β-catenin signalling pathways, which are found to be upregulated during the osteogenesis-response phase; and Wnt/β-catenin signalling, whose pharmacological blockage inhibits the undesirable bony repair. Chung & Xian point out that, while these findings represent some advances in understanding growth plate bony repair, future studies will be needed to further investigate the underlying pathobiology. Chung & Xian also point out that studies will be needed to explore whether these signalling molecules could potentially be explored to develop or enhance progenitor cell-based therapies for growth plate regeneration.

In summary, knowledge on the control of growth plate function and related bone growth disorders has been rapidly accruing. This thematic issue provides a recent knowledge update and new perspectives on the molecular control of growth plate function and the pathophysiology of growth plate dysfunction-related bone growth defects resulting from genetic mutations, chronic inflammation, glucocorticoid usage or growth plate injury. The featured articles also discuss potential treatments, the targets currently being investigated, and avenues for future exploration to prevent or treat these bone growth defects.

Declaration of interest
The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

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