 J Life Sci, 1(1): 9-14 (2009)

Current Trends in Human Bone Development and Growth

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KEYWORDS Bone Development. Growth. Pathology Management. Research Advancements

ABSTRACT Bone as a dynamic osseous tissue had long attracted much attention from researchers who are particularly interested in the studies of its development, growth pathologies and managements. This write-up highlights some of the recent works on this tissue from literature search on the subject in contemporary books, journals, and internet to up-date information on researches and advancements focused on this aspect of bone studies. The unending research interests in any tissue such as bones continually unveil more and yet hitherto, unknown facts; thus enhancing better understanding of its nature, with subsequent improvement in the knowledge and management of bone growth and pathologies.

INTRODUCTION

Bones are rigid organs that form part of the endoskeleton of vertebrates. Bones function to move, support and protect the body, produce red and white blood cells and store minerals. Bones come in a variety of shapes and have a complex internal and external structure, allowing them to be lightweight yet strong and hard, while fulfilling their many other functions. (Cromie 1999; Adebisi 2005, 2008)

This primary bone or osseous tissue is a relatively hard and composite material, formed mostly of calcium phosphate in the chemical arrangement termed calcium hydroxyl-apatite - this is the osseous tissue that gives bones their rigidity. It has relatively high compressive strength but poor tensile strength, meaning it resists pushing forces well, but not pulling forces. While bone is essentially brittle, it does have a significant degree of elasticity contributed chiefly by collagen. All bones consist of living cells embedded in the mineralized organic matrix that makes up the osseous tissue. Bone is not a uniformly solid material, but rather has some spaces between its hard elements. The hard outer layer of bones is composed of compact bone tissue, so-called due to its minimal gaps and spaces. This tissue gives bones their smooth, white, and solid appearance, and accounts for 80% of the total bone mass of an adult skeleton. Compact bone may also be referred to as dense bone or cortical bone. Filling the interior of the organ is the trabecular bone tissue, an open cell porous network also called cancellous or spongy bone, which comprised of a network of rod- and plate-like elements that make the overall organ lighter and allowing room for blood vessels and marrow. Trabecular bone accounts for the remaining 20% of total bone mass, but has nearly ten times the surface area of compact bone. The exterior of bones - except where they interact with other bones through joints - is covered by the periosteum, which has an external fibrous layer, and an internal osteogenic layer. The periosteum is richly supplied with blood, lymph and nerve vessels, attaching to the bone itself through Sharpey's fibres (Marieb 1998; Adebisi 2002; Franceshi 2005).

RECENT DISCOVERIES IN BONE DEVELOPMENT

Of recent, researchers had been fascinated in their discoveries of some factors affecting bone development and growth which are hitherto unknown. For instance, babies born too early (premature babies) are often cared for in a fashion that minimizes physical activity in order to reduce stress and stress-related complications. However, lack of physical activity might lead to poor bone development and growth, as seen in bed-ridden children and adults. It is believed that physical activity programs - moving and pressing all joints on all limbs for several minutes a day - may promote bone development and growth in premature babies. However, a review paper found that physical activity might have a small benefit on bone development and growth over a short term and concluded that, physical activity programs cannot be recommended as a standard procedure for premature babies (Schulzke et al.

2008). Contrary view had however, been expressed from reports on ectopic bone formation (EBF) which is frequently found in various tissues and affects the prognosis of diseases accompanied by EBF; although the mechanism of EBF remains unclear, several local factors that influence the progression of EBF had been proposed since it has been observed that mechanical stress play a vital role in this phenomenon. (Ken-Ichi Furukawa 2006)

Workers at the University of Otago in Christchurch have broken new scientific ground with discoveries regarding a previously little understood heart hormone, showing how it is crucial for bone development and growth after birth. Professor Espiner and colleagues have shown for the first time that CNP, the heart hormone C- type Natriuretic Peptide which had puzzled medical scientists since its discovery in 1990, previously thought to regulate blood flow to tissues, also acts as a vital signal for skeletal growth at crucial stages in foetal and childhood development. They reported that measurements of the CNP hormone clearly correlate with growth rates in humans; when it is high, growth rates and skeletal development are intense and rapid and when it is lower, growth rates are reduced. (Espiner and Prickett 2008)

Glycosphingolipids are thought to play important roles in the development and function of several tissues, although the function of glycolipids in osteoclastogenesis has not been clearly demonstrated. It has been reported that D-threo-1-phenyl-2-decanoylamino-3-morpholino-1- propanol (D-PDMP), a glucosylceramide synthase inhibitor, completely inhibited osteoclastogenesis induced by macrophage-colony stimulating factor (M-CSF) and receptor activator of NF-êB ligand (RANKL). Following treatment with D-PDMP, nearly all glycosphingolipid expression was dramatically reduced on the surface of bone marrow cells, which suggests that glycosphingolipids are necessary for osteoclastogenesis. To determine which kinds of glycolipids are important for osteoclastogenesis, several types of purified glycolipids were added to D-PDMP treated bone marrow cells, as the precursor of osteoclasts is known to express glucosylceramide (GlcCer) and lactosylceramide (LacCer). Following treatment with RANKL, ganglioside GM3 and GM1 were increased in the treated bone marrow cells, whereas other types were not detected using thin layer chromatography analysis (Fukomoto et al. 2006).

Moreover, UT Southwestern Medical Center at Dallas had discovered a protein that controls an early and significant step in the exquisitely timed process of bone formation. Eric Olson, chairman of molecular biology and colleagues have shown the protein HDAC4 to be essential for proper bone development. This finding may have widespread implications for understanding and preventing osteoporosis or other bone disorders. According to Olson, 'this was a very unexpected discovery, we were studying the role of the HDAC4 gene in the control of heart growth when we created genetically modified mice lacking the HDAC4 gene; we found that they had excess bone and died because their cartilage was converted into bone' (Midura 2007). HDAC4 belongs to a family of enzymes that inactivate genes. Unlike other members of this family which are found in numerous tissues, HDAC4 is expressed in only a few tissues, including bone. Olson and colleagues studied mice lacking the HDAC4 gene. At birth these animals had malformed skulls and spines and as they grow older (Midura 2007). Backtracking through the bone-formation process, they discovered that the defect was in the earliest steps, where the cartilage foundation was being laid and filled with minerals. Before the foundation was complete, minerals were being deposited too soon, allowing bone to harden before it was ready. Biochemical tests revealed that HDAC4 controls the early timing of osteogenesis by preventing the final step - bone-hardening - from occurring. In a related report from Griffith's Genomics Research Centre, it had been demonstrated that the Runx2 gene was a master regulator that controlled the development of osteoblasts (Morrison 2006).

By specifically blocking Runx2 protein, which controls the genes for bone hardening, HDAC4 allows the foundation and minerals to be properly laid before hardening can occur. It is believed that calcium, which is required for healthy bones, may signal the release of HDAC4 from Runx2 to initiate the bone-hardening program. The discovery that bone formation is controlled by HDAC4, an enzyme, raises possibilities for designing drugs to control this process in the settings of bone diseases, such as osteoporosis; in fact, HDAC inhibitors are currently being used for the treatment of certain cancers. It will be interesting to investigate whether these inhibitors influence the process of bone formation (Netter 2007).

Moreover, it appears that collagen 18 and

endostatin help regulate bone formation by controlling growth of blood vessels. However, further studies into how collagen 18/endostatin might aid the development of drugs to treat osteoporosis, correct some inherited bone disorders, and even build replacement bones are anticipated. (Roach and Shearer 1989)

In the mid 1960s, Urist first reported the induction of bone formation at an extra - skeletal site by the implantation of DBM. This sentinel discovery ignited a fury of research activity that has led to a vastly superior understanding of the step-by-step process of bone formation, including the role of osteo-inductive factors. The cellular and biochemical cascade involved in the DBM bone induction model have been well documented and many parallels to common clinical settings of bone induction (including fracture healing and bone graft incorporation) have been drawn. (Midura 2007)

Few years ago, Olsen and collaborators in the United States, Europe and Japan discovered a gene called CBFA1 which they described as necessary for forming a complete skeleton. According to them, this gene is essential for bone to form in the embryo, without it there is not a single bone-producing cell in the body. In the womb, most bones begin as rubbery cartilage by means not well understood. Cartilage cells start to swell as an embryo develops. The cartilage then breaks down and blood vessels start to sprout at its surface. As these blood vessels grow inward, bone cells and bone marrow replaced the cartilage and if one of two CBFA1 genes that infants inherit from their mother and father is mutated or not working properly, birth defects can occur. These include a soft spot in the top of the skull due to bone that never hardens and improperly developed collar bones which allow people to bend their shoulders across their chests. It was the study of such patients that led to the discovery of CBFA1 and its crucial role in bone formation. (Roach 1987)

The cellular activities in bone are tightly regulated by cytokines and hormones both in normal and pathologic states. For example, parathyroid hormones (PTH) and its somatic homolog PTHrP, control bone modeling and remodeling. A major research effort had focused on the regulation of osteoblast function by PTH. The initial approaches have been to analyze the effects of PTH on an osteoblast's ability to synthesize specific macromolecules found in bone matrix, properly assemble them in the extracellular environment, and miniralise this matrix. Using several osteoblastic models, from cell line to primary tissue, it was discovered that PTH, through the activation of protein kinase A (PKA), can dramatically effect an osteoblast's ability to produce matrix macromolecules, alter its ability to assemble these macromolecules into an extracellular matrix, regulate its mineralization of this matrix, and even change its shape by stimulating microfilament polymerization and cell spreading. Anticipated research in this area will define the molecular mechanisms operating in primary bone formation. Such research will yield increased knowledge of an osteoblast's functions in bone homeostasis. Ultimately, it will provide a better understanding of bone development and pathology, and may offer new therapies to augment bone healing and treat bone disease. (Roach 1999)

Bone continuously remodels in response to mechanical and physiological stresses, allowing vertebrates to renew bone as adults. Bone remodeling consists of the cycled synthesis and resorption of collagenous and non-collagenous extra-cellular matrix proteins, and an imbalance in this process can lead to disease states such as osteoporosis, or more rarely, osteopetrosis. There is evidence that the extra-cellular matrix glycoprotein osteonectin rich in cysteine (BM-40) may be important in bone remodeling. Osteonectin is abundant in bone and is expressed in areas of active remodeling outside the skeleton. In vitro studies indicate that osteonectin bind collagen and regulate angio-genesis, metalloproteinase expression, cell proliferation and cell-matrix interactions. In some osteopenic states such as osteogenesis imperfecta and selected animal models for bone fragility, osteonectin expression is decreased. To determine the function of ostenonectin in bone, contact x-ray, histomorphometry and Northern-Blot analysis was used to characterize the skeletal phenotype of oseteonectin-null mice. It was found that osteonectin-null mice have decreased bone formation and decreased osteoblast and osteoclast surface and number, leading to decreased bone remodeling with a negative bone balance and causing profound osteopenia. Such observation indicates that osteonectin supports bone remodeling and the maintenance of bone mass in vertebrates. (Siegfried 2007)

Treatment of ovariectomized rats with

melatonin prevents bone loss by an effect partly dependent on residual estradiol levels. Melatonin presumably acts as an autacoid in bone cells since it is present in high quantities in bone marrow, where bone cell precursors are located. Melatonin dose-dependently augments proteins that are incorporated into the bone matrix, like procollagen type I c-peptide. Osteoprotegerin, an osteoblastic protein that inhibits the differentiation of osteoclasts is also augmented by melatonin in vitro. Another possible target cell for melatonin is the osteoclast, which degrades bone partly by generating free radicals. Melatonin through its free radical scavenger and antioxidant properties may impair osteoclast activity and bone resorption. At least in one study melatonin was both inhibitory to osteoclastic and osteoblastic cells. Therefore, the documented bone-protecting effect of melatonin in ovariectomized rats can depend in part on the free radical scavenging properties of melatonin (Cardinalis 2008)

In a recent research, it had been identified that one of the main drugs used in the chemotherapy treatment, that is, methotrexate, results in the deterioration of a child's bone growth plate within just seven days of treatment commencing. Methotrexate impacts on the cells within the bone and reduces the bone's volume and thickness. Children undergoing chemotherapy with this drug are 39 percent more likely to have a bone fracture than another child. The research has also found that by including folinic acid in chemotherapy treatment, the bone growth plate is protected retaining its ability to generate new bone. It was also found that the bone retains its thickness and normal cell replication, reducing the likelihood of these survivors suffering osteoporosis (Xian 2006)

The osteoclast originates as a monocyte in the bone marrow and, given the right stimulus, becomes a mature bone resorbing cell. The Darnay laboratory has identified a critical factor, known as TRAF6, inside the cell that is required for the maturation of the osteoclast from its monocyte origin. Thus, targeting TRAF6 with a small molecule-like drug would help to prevent the unwanted bone destruction caused by bone diseases. To this end, Darnay has determined the three-dimensional structure of TRAF6 and with the support of the Lawrence Research Award,, had identified a small molecule inhibitor that blocks the function of TRAF6. By using virtual screening through molecular modeling and a high-throughput screening assay, Darnay identified a lead compound that could be a potential therapeutic drug for preventing bone destruction. (Darnay 2007)

It had been observed that potassium appears to counteract the bad effects of high-salt diets by preventing bones from decaying at a fast rate (Siegfried 2007). The observation provided more evidence of the importance of a balanced and proper diet, and confirmed that diets high in salt can cause bone loss. Sellmeyer recruited 60 postmenopausal women to participate in her study. For three weeks, she put them on low-salt diets only 2 grams of salt a day, less than the 6 grams, or 1.5 teaspoons recommended by federal health officials. The researcher measured two things: how much calcium the women's bodies lost through urination and how much of a protein called NTX they lost that is created when bones decay. Then, the women all went on a high-salt diet, 9 grams of salt a day for a month. That amount of salt is on the high end of what Americans typically consume. Half of the women took potassium supplements, while half took a placebo. The potassium appeared to protect the bones of the women who took it. They lost less calcium than they did on the low-salt diets, and the amount of lost protein was only slightly higher. From the results, the women who didn't take potassium on the high-salt diet suffered from higher rates of loss of potassium (33% more) and the protein (23% more). This indicates that salt consumption quickens bone decay. It appears that diet high in salt pulls calcium out of bones, but potassium limits the damage. (Siegfried 2007)

RECENT ADVANCEMENTS IN BONE RESEARCH

Researchers at Queensland University of Technology had developed biodegradable materials that carry bone growth enhancing substances to encourage bones to heal quickly with much less intervention. This was made from polymers that can be loaded with calcium phosphate compounds - known bone growth facilitators, and placed on bone defects. As the microspheres degrade the calcium, phosphate compounds are absorbed and encourage the bone to grow quickly into the area and build new bone. The microspheres, which are highly porous, range in size from 50 to 500 microns and have calcium phosphate abundantly deposited

throughout the pores, can be used in a variety of ways. They could be used to fill bone defects or cavities, to coat load bearing implants, and to make scaffolds for the regeneration of bone. The team had also integrated a dense ceramic core with a porous ceramic layer that can be used in place of metal implants for some clinical situations because it will attach to and integrate with bone and eventually degrade away. The unique core structure of the material will provide the mechanical properties needed for load-bearing bones and the outside porous layer will assist with the bone repair. (Science Daily 2006, 2007)

Titanium implants were successfully introduced by Brånemark and co-workers in 1969 for the rehabilitation of edentulous jaws. After 40 years of research and development, titanium is currently the most frequently used biomaterial in oral implantology, and titanium-based materials are often used to replace lost tissue in several parts of the body. It had also been suggested that coating dental implants with a synthetic bone material prior to implantation allows such implant to become incorporated much more successfully into the jaw, leading to smiles all round. (Science Daily 2008)

Hyaluronic hydrogels developed by Carnegie Mellon University researchers may provide a suitable scaffolding to enable bone regeneration. The hydrogels have proven to encourage the growth of pre-osteoblast cells, cells that aid the growth and development of bone. Currently, physicians are able to treat patients with damaged bone tissue, like those who have bone fractures that fail to heal, using demineralized bone matrix, a biological material obtained from cadavers. Demineralized bone matrix is rich in growth factor proteins which signal bone cells in the area to multiply and form complex bone tissue, while other proteins in the matrix regulate the activity of the growth factors. Demineralized bone matrix is in limited supply, and because it comes from a human donor, there is a risk of transmitting viruses to the recipient; however, researchers have been developing synthetic alternatives to demineralized bone matrix. They created a flexible hydrogel using biologically active and degradable hyaluronic acid. Hydrogels, which are considered to be the state-of-the-art in tissue design, are made from polymers that swell in water to form a gel-like material. They interact with growth factors much like demineralized bone matrix does, providing scaffolding for bone cells to proliferate and form new tissue. The researchers found that, in vitro, the hydrogels promoted cell proliferation, differentiation and mineralization of pre-osteoblast cells. Further research has created a hybrid hydrogel that incorporates a nanogel structure. This new hydrogel promotes the differentiation of cells, much like the hyaluronic acid gel while also releasing nanogels in a controlled and targeted manner. The researchers hope that this structure could be used to partner tissue engineering with gene therapy. (Washburn et al. 2008)

It is hence, anticipated that such researches and reports like these will eventually allow us to achieve the ultimate goal of bone tissue engineering: to reconstruct entire bones with associated joints, ligaments, or sutures. (Franceshi 2005)

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