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The role of aryl hydrocarbon receptor in bone remodeling

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ABSTRACT

Bone remodeling is a persistent process for maintaining skeletal system homeostasis, and it depends on the dynamic equilibrium between bone-forming osteoblasts and bone-resorbing osteoclasts. Aryl hydrocarbon receptor (Ahr), a ligand-activated transcription factor, plays a pivotal role in regulating skeletal system. In order to better understand the role of Ahr in bone remodeling, we focused on bone remodeling characteristic, and the effects of Ahr on bone formation and differentiation, which suggest that Ahr is a critical control factor in the process of bone remodeling. Moreover, we discussed the impacts of Ahr on several signaling pathways related to bone remodeling, hoping to provide a theoretical basis to improve bone remodeling.

Contents

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1. Introduction

The skeleton is a dynamic tissue that undergoes constant bone removal and regeneration. The appropriate course of bone remodeling determines skeleton development and regeneration (Niedzwiedzki and Filipowska, 2015). Bone remodeling occurs throughout a person's entire life, and the accurate control of the process is crucial for maintaining skeletal system homeostasis, which is closely related to bone-resorbing osteoclasts and bone-forming osteoblasts. Bone remodeling is regulated by various factors including endogenous factors as well as exogenous factors, such as nutrients and environmental pollutants.

Aryl hydrocarbon receptor (Ahr) is known as a receptor for environmental contaminants and a mediator of chemical toxicity within the last three decades. Ahr is a ligand-activated transcription factor, and belongs to the Per-Arnt-Sim superfamily of proteins. It exists in the cell of vertebrates and invertebrates. In cytosol, Ahr combined with several proteins (Hsp90, ARA9, p23 et al.) in an inactive form (Stevens et al., 2009). Upon binding to its ligand, the conformation of Ahr is changed and exposed nuclear transcription locus, which enable Ahr translocation into nucleus, where it heterodimerizes with the aromatic hydrocarbon receptor nuclear transfer protein (ARNT). Within nucleus, the Ahr/ARNT heterodimer could activate the promoter, a xenobiotic response elements (XRE) sequence, to promote gene transcription and cause all sorts of biological effects, such as toxicity, immune response, biological evolution, bone remodeling and so on.

Recent studies demonstrated that the Ahr has gained more attention in the immune system and bone remodeling effects (Monteleone et al., 2013; Nakahama et al., 2011; Veldhoen et al., 2008; Yu et al., 2014a). Despite of increasing information on Ahr, an extensive analysis is still needed to clarify the significance of Ahr in bone remodeling. Hence, in this review, we discuss the roles of Ahr in bone remodeling and its related signal pathway, thereby hope to provide further possibility as a target.

2. Bone remodeling

2.1. Physiological bone remodeling

Bone remodeling is a persistent process, and it depends on the dynamic equilibrium between formation and resorption, which mostly be regulated by osteoblast and osteoclast. Osteoblast comes from marrow mesenchymal stem cell, which produces lots of extracellular matrix protein to regulate bone formation and bone remodeling. In addition, osteoblast can also regulate the differentiation of osteoclast by producing cytokines and/or direct contact. Osteoclast from multi-core macrophages (Teitelbaum, 2000), not only plays a role in bone resorption, but also participates in regulating osteoblast differentiation and bone formation (Hwang et al., 2016). Osteoclast promotes bone matrix absorption, and makes it release the transforming growth factor (TGF-beta) and insulin-like growth factors (IGFs), which can regulate the activity of osteoblast (Tang et al., 2009). The type of membrane bound ephrinB2 ligand expressed by osteoclast could bind with EphB4 receptor, which is on the surface of osteoblast, and then enhance differentiation capacity of osteoblast and inhibit the osteoclast differentiation (Martin et al., 2010). Myocardial nutritional protein, which is a kind of soluble factor secreted by osteoclast, can promote Runx2 gene expression of osteoblast and bone formation (Walker et al., 2008). Furthermore, The type of I collagen and all kinds of proteins, which synthesised and secreted by mature osteoblast, such as osteocalcin, osteopontin, osteoprotegerin, the nuclear factor kappa B ligand (RANKL) receptor activation factors and bone sialoprotein, could regulate bone remodeling, bone mineral deposition and bone cell activity. Osteoblast could regulate autocrine and/or paracrine of bone cells by secreting IGF, IL-6 and IL-1, and it could also regulate osteoclast differentiation by producing the macrophage colony stimulating factor (M-CSF), RANKL and osteoprotegerin. M-CSF increases the number of osteoclast precursor cells and improve their survivability (De Vries et al., 2015). RANKL combines with receptor activator of nuclear factor kappa B (RANK) on the surface of osteoclast's precursor, and then promote osteoclast differentiation (Xiong et al., 2015). In order to maintain the balance between osteoblast and osteoclast, the OPG secreted by osteoblast inhibits osteoclast differentiation by preventing RANKL-RANK signaling activation (Boyce, 2013; Martin and Sims, 2015).

Physiological bone remodeling is regulated accurately by various factors, such as hormones, cytokines and other proteins. Hormones togethered with metabolism of nutrients can affect the function of osteoblast and osteoclast. They could promote bone progenitor cells to convert into osteoblast under the role of dentin matrix protein 1 (DMP1). Interestingly, cytokines could make osteoblast convert into osteoclast. In order to maintain the balance between osteoblast and osteoclast and ensure bone metabolism healthy, osteoclast could also convert into osteoblast with the effect of H_2O_2, superoxide anion, and so on.

Bone remodeling cycle includes four stages: activation, absorption, reversal and formation (Neve et al., 2011). During the activation phase, bone marrow mononuclear macrophage develops into multinucleated cells to activate osteoclast, and then entered absorption stage, which results in bone loss. After that, the process of reverse phase: osteoclast apoptosis, osteoblast precursor cell proliferation and differentiation into mature osteoblast, which migrate to the location of apoptotic osteoclast, and then a new mineralized bone matrix is formed.

2.2. Pathological bone remodeling

The regulation imbalance of bone remodeling can lead to human bone disease (Takayanagi, 2007). It is necessary to keep the balance between bone formation and bone resorption for maintaining skeleton integrity (Zaidi, 2007). When bone absorption rate is more than formation rate, it will result in bone loss, and the pathological bone remodeling will be caused. The large numbers of the osteoclast, which exist in joints pannus, bone and subchondral bone joints, are the main reason that causes the imbalance between bone absorption and bone formation. The imbalance will bring about a mass of pathological bone injury diseases (Sucur et al., 2014), including rheumatoid arthritis (RA), osteoporosis and so on (Kowada et al., 2011; Liu et al., 2015b). These diseases decrease the patient's quality of life (Liu et al., 2015a) and produce financial huge cost for healthcare systems (Leboime et al., 2010).

The expression of RANKL is increased in joint synovial cell of collagen-induced arthritis (Romas et al., 2000). RANKL, as a characteristic of osteoclast differentiation factor and osteoprotegerin ligand, can promote osteoclast differentiation (Xu et al., 2016). Colony stimulating factor (M-CSF) and RANKL are necessary factors for osteoclast formation, and they can prompt multinucleation former fusion osteoclast and former osteoclast survival (Kreja et al., 2007). Therefore, inhibiting osteoclast by regulating osteoclast precursors activated factor is to be as a potential method for the treatment of RA (Li et al., 2004).

Osteoblast also plays an important role in RA bone injury (Walsh and Gravallese, 2010). Recent researches showed that the loss of bone resulted from abnormal osteoblast appeared earlier in RA patients' and the differentiation and function of osteoblast were disorder in the location of bone erosion (Baum and Gravallese, 2014). New bone mineralization is reduced in inflammatory arthritis bone tissue, which suggests that inflammation can affect

the activity of osteoblast (Walsh et al., 2009). Osteoblast could also regulate osteoclast formation by secreting RANKL and M–CSF (Asagiri and Takayanagi, 2007; Teitelbaum, 2000). In order to further study the immune regulation of RA bone destruction, bone immune, a new research field, was established. Bone immune focuses on the interaction between skeletal system and immune system at molecular level.

3. Ahr affects bone formation and differentiation

Toxicological studies had shown that Ahr ligand can inhibit osteoblast differentiation (Korkalainen et al., 2009; Monnouchi et al., 2016). The expression peak of Ahr appears before osteocalcin and after alkaline phosphatase in osteoblast. Activated Ahr by TCDD restrains bone marrow-derived stem cells differentiation into osteoblast (Nguyen et al., 2013). TCDD could also result in harder bone matrix, mechanically weaker bones, thinner cortical bone, and increase trabecular bone volume fraction via Ahr pathway (Herlin et al., 2013). TCDD disrupts the bone remodeling by changing the structure of Ahr transcription activation domain, and reduces bone strength (Jamsa et al., 2001). Additionly, mice which treated with resveratrol, as an Ahr antagonist, showed increasing BMD and bone mass (Yu et al., 2014b). However, compared with wild type mice, the expression of calcitonin and alkaline phosphatase was lower in Ahr gene knockout mice (Ryan et al., 2007), which indicated that Ahr also plays an important role in the formation of osteocyte. The inconsistent studies indicate that low dose Ahr could advance bone formation and the overactive Ahr could restrict bone formation.

At present, the effect of Ahr on osteoclast has not yet been fully unified. Osteoclast specific Ahr knockout mice have increased bone mass with reduced bone resorption, illustrated that Ahr in osteoclast could promote bone loss (Yu et al., 2014b). Similarly, the antagonist of Ahr, 3, 3′- Diindolylmethane (DIM), could alleviate the collagen-induced arthritis (CIA) by reducing RANKL to blockade osteoclastogenesis (Dong et al., 2010). However, Ilvesaro J reported that the Ahr agonist (TCDD) has no effect on the formation of osteoclast (Korkalainen et al., 2009). These contradictory researches illustrate that different ligands bound with Ahr play diverse roles. The main reasons may be that the combining capacity, or the duration, or paths of different ligands are various.

4. Ahr and bone remodeling related signaling pathways

4.1. Ahr and NF-κB signaling pathway

The NF-κB family widely express various transcription factors, such as RelA (p65), RelB (p50), c-Rel and p52. The NF-κB signaling pathway includes membrane receptors, receptor related adapters, IKB kinase (IKKs), IκBs and the NF-κB dimers (P65/P50), which bind with DNA response elements to regulate gene expression. RANKL, a member of the TNF-α superfamily, can be produced in osteoblast and mesenchymal cells with the induction of hormones and other factors, such as 1, 25 $(OH)_2$ vitamin D3, parathyroid hormone, IL-1β and TNF-α. RANKL plays a pivotal role in promoting osteoclast differentiation. In osteoclast precursor cells, RANKL combines with RANK to promote osteoclast related gene expression, including tartrate resistant acid phosphatase, cathepsin K, calcitonin receptor, MMP–9, and accelerates osteoclast differentiation mature.

NF-κB signaling pathway can be regulated by Ahr (Ovrevik et al., 2014). Ahr ligand (β-NF) decreased the expression levels of the inflammatory cytokines TNF-α and IL-6 by suppressing NF-κB p65 (Hsu et al., 2015). 3-MC, a ligand of Ahr, can inhibit osteoclast formation by restraining osteoblast express RANKL (Naruse et al., 2004). Another ligand of Ahr (BaP) can reduce the formation of osteoclast by inhibiting the activity of the NF-κB (Voronov et al., 2008). However, small doses of Ahr ligand (BaP and TCDD) can not suppress RANKL expressed by osteoclast, and demonstrates that small doses of Ahr is a necessary for osteoclast to produce RANKL (Iqbal et al., 2013).

The relation between the NF-κB signal pathway and Ahr is complicated, and its mechanisms had been focused in recent researches. Firstly, Ahr binding site is close proximity or overlaps NF-κB binding site and it can bind with different subunits of NF-κB (Salisbury and Sulentic, 2015). A cross-talk between Ahr and RelB was confirmed, and Ahr together with RelB functions may be as a coordinator of inflammatory responses (Vogel and Matsumura, 2009). Ahr is positively correlated to the NF-κB subunit RelB in breast cancer (Vogel et al., 2011). Furthermore, in human mononuclear cell line, classic Ahr signaling pathways and activated protein kinase A (PKA) signaling pathways could induce RelB-Ahr dimers formation (Vogel et al., 2007). Ke et al. showed that cAMP and PKA can activate Ahr, which explained activated protein kinase A (PKA) signaling pathways could produce RelB-Ahr dimers (Oesch-Bartlomowicz et al., 2005).

4.2. Ahr and Wnts signaling pathways

Wnt signaling is a critical regulator of cell growth, differentiation, and death, and it has emerged as a key mechanism to regulate bone formation in mammals (Kobayashi et al., 2016; Shi et al., 2007). There are two kinds of Wnt proteins in the outside of the cell membrane: one kind (e.g., Wntl, Wnt2, Wnt3, Wnt3a, Wnt8 and Wnt8b) combines with LRP/FZD and creates synergiest activate the Wnt/β-catenin classic signaling pathways (Rulifson et al., 2000). Another kind (e.g., Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a and Wntl1) integrates Frizzled and activates heterologous trimer G protein, and it can also improve the level of intracellular calcium and other effect (Rulifson et al., 2000). Wnt protein is the initiation of classic Wnt/β-catenin pathway, and plays a vital role in the process of osteoblast proliferation and differentiation (Kobayashi et al., 2016) (Baron and Kneissel, 2013).

Recent researchs showed that the diversity of Wnt signaling pathway components was associated with bone mineral density (Riancho et al., 2011; Rivadeneira et al., 2009). Wnt3a can induce the proliferation of adult human mesenchymal stem cells and suppress osteogenic differentiation (Boland et al., 2004). Wnt3a gene knockout cause early death of embryonic and bone loss (reduced bone mineral density and the number bone trabecular) (Boland et al., 2004). Wnt5a increases ALP activity, osteocalcin and Runx2 gene expression, and induces osteogenic differentiation of human adipose stem cells (Santos et al., 2010).

Osteoblast's differentiation and function are closely connected with the activation of Wnt signaling pathways, especially canonical Wnt signaling (Baron and Kneissel, 2013). The Wnts protein, which bind with ligand receptor on the surface of the osteoblast membrane (LRP5/6 ligands Frizzleds coreceptor), stabilize and enrich β-catenin complexes in the cytoplasm. Then, the activated β-catenin enters into the nucleus and combines with the target genes related to early osteogenesis (Osteoblast transcription factor, Runx2), and participates in new bone formation. When the pathway is being suppressed, a serious shortage of osteogenesis is generated and it will bring several bone diseases, such as osteoporosis, osteoarthritis, bone tumors, inflammatory arthritis and so on (Monroe et al., 2012). R-spondins (Rspo1, 4) could regulate factors, which secreted by Wnts (such as Wnt1, 3a and 7a, 11), to insure stabilization of β-catenin (Kim et al., 2006). In C2C12 and early calvaria bone cells, Rspo1 coordinates with Wnt3a to induce osteoblast differentiation and osteoprotegerin expression (Lu et al., 2008). Some transfer membrane proteins adjust the Wnt signaling

pathway by adhesion Wnts or secretion antagonists.

There is a crosstalk between Ahr and Wnt/β-catenin. Ahr can regulate Wnt signaling pathways, which include canonical Wnt signaling and non-canonical Wnt signaling (Schneider et al., 2014; Wang et al., 2016; Wincent et al., 2015). Ahr agonist (TCDD) affects the transcription of Wnt signaling pathway proteins (rspo1), which is a classic Wnt signaling pathways' activator (Binnerts et al., 2007; Kim et al., 2006). Therefore, it is speculated that Ahr regulates the classic Wnt signaling pathways by misinduction of Rspo1 (Mathew et al., 2008). Wnt5a is a typical of the non-classical Wnt signaling pathway protein, but also it can activate the classic Wnt signaling pathways (van Amerongen et al., 2012). Prostate cancer cells given Ahr agonist (TCDD and/or BaP) can rapidly induce the expression of Wnt5a and increase LEF1 mRNA expression level (Hruba et al., 2011), which is considered as a classic Wnt signal target genes (Francis et al., 2013).

Interestingly, several studies have also illustrated that the activation of Ahr can decrease Wnt5a expression. Giving an Ahr agonist (TCDD) in the process of development palate in mice, the expression of Wnt5a and LEF1 is reduced (Hu et al., 2015). In lung fiber cells, Wnt5a is also decreased with Ahr agnoist (TCDD or ITE) (Henry et al., 2010). Similarly, when pluripotent stem cells (WB-F344) is given with the Ahr agonist (PCB126), the microarray analysis shows that the expression of Wnt5a, Wnt4, Fzd1 and Fzd4 are dropped (Faust et al., 2013). Moreover, Prochazkova et al. showed that Ahr could down-regulated the expression of Wnt/β-catenin in the process of the development of liver (Prochazkova et al., 2011). Activated Ahr could also inhibit the classic Wnt signaling pathways in intestinal tissue of mice, and the Ahr in intestinal tissue is considered as a permanent inhibitor of classic Wnt signaling pathway (Kawajiri et al., 2009). The activation of classic Wnt signaling pathway could promote the formation of intestinal tumor, and it can explain the reason why Ahr knockout mice spontaneous suffers colon cancer (Najdi et al., 2011; Polakis, 2012). Although these findings suggest that activation of Ahr can reduce Wnt signaling pathways, but we do not know which or what cascade Wnt signaling is disorder, as well as the biological significance of these findings.

4.3. Ahr and MAPK signaling pathways

Mitogen-activated protein kinases (MAPKs) is an ancient serine/threonine kinase, which exists in all eukaryotes, and it plays a crucial role in cell proliferation, differentiation and survival. ERK, p38 and JNK are the main members of MAPKs family, and the activation of ERK1/2 is necessary for bone cells growth (Thompson et al., 2011). ERK, p38 and JNK could promote osteoclast differentiation (Bozec et al., 2008; Stevenson et al., 2011), and activated ERK1/2 signaling pathway is also indispensable for bone matrix and osteoblast (Rubin et al., 2002). ERK1/2 could increase eNOS and decrease RANKL (Rubin et al., 2003), and result in enhancing bone formation and reducing bone loss. Activation ERK1/2 is necessary for TGF-β to induce the differentiation of mesenchymal stem cells to osteocyte (Arita et al., 2011).

MAPKs plays an important role in the process of osteoblast's development. Recent studies demonstrate that MAPKs regulated bone formation by acting on osteoblast, which indicate MAPKs is a core conductor for bone formation (Ge et al., 2007; Greenblatt et al., 2010; Zou et al., 2011). ERK1/2 and p38 signal pathway can induce the phosphorylation and activation of Runx2, which is a mainly transcription factors for osteoblast differentiation (Ge et al., 2012). Highly active p38/MAPK enhances osteoblast differentiation and bone mass (Whitehouse et al., 2010). Moreover, when p38 gene is deleted, osteoblast differentiation is abated and bone loss is generated (Ge et al., 2012), which illustrates that p38/MAPK take part in bone development. The vitro studies have shown that p38/MAPK could regulate osteoblast specific gene expression and JNK signaling pathway can positively regulate osteoblast differentiation (Greenblatt et al., 2013; Ortuno et al., 2010). The JNK inhibitors reduce the expression level of osteoblast related gene, such as Bsp, Ocn, Atf4 and Fra1, which confirmed that osteoblast mineralization is blocked.

The Ahr is closely connected with MAPK signaling pathway. Ahr expression/activity in PTC is strictly related to a constitutive active ERK/MAPK pathway (Occhi et al., 2015). Ahr agonists (ITE and TCDD) activate MAPK signal pathway by increasing cell plasma calcium levels, which induce the expression of MMP-1 (Tsai et al., 2014). Naphthoflavone, ahr agonist, significantly activated ERK/MAPK signal pathways through the way of Ahr dependence, and it affects breast cancer resistance (Wang et al., 2014). Further, our previous research has shown that activated Ahr can significantly inhibit the proliferation and differentiation of osteoblast through enhancing ERK/MAPK phosphorylation (Yu et al., 2014a). Additionly, activated Ahr by B(a)P resulted in p38/MAPK activation along with testicular apoptosis and steroidogenic dysfunction (Banerjee et al., 2016).

5. Conclusions

Bone remodeling is a continuous process, and it relies on the dynamic equilibrium between bone-forming osteoblasts and bone-resorbing osteoclasts. Although different ligands of Ahr play inconsistent role on bone formation and differentiation, it is confirmed that Ahr play an important role in bone formation and differentiation, and it is closely in connection with the key signaling pathways related to bone remodeling. Therefore, we hypothesized that by targeting the role of Ahr, it could regulate bone remodeling and improve bone destruction. However, more researches needs accurately to clarify the mechanisms that Ahr affects bone remodeling in the future.

Conflicts of interest

The authors do not declare any conflict of interest relevant to this manuscript.

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