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Ion Channels and Bone Homeostasis Imbalance

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ABSTRACT

To sustain the bone weight, there is a delicate balance between the osteoblast bone formation and osteoclast bone resorption known as bone homeostasis. The imbalance of bone homeostasis will induce bone disorder, such as osteoporosis and osteopetrosis. Numerous studies have shown that ion channels play critical roles in maintaining the bone homeostasis. Dysfunction of ion channels accompanied with disorder of the osteoblast bone formation and osteoclast bone resorption. In the present paper, the authors discussed the physiological roles of bone homeostasis on human body and summarized the ion channels expressing on the membrane of osteoblasts and osteoclasts. Finally, the limitations of the prior art and the prospects in this field were discussed.

Abbreviations: ENaC: Epithelial Sodium Channels; ALP: Alkaline Phosphatase; cGMP: Cyclic guanosine monophosphate; CLC: Chloride Channels; CLIC: Chloride Intracellular Channel; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; KCC: Potassium Chloride Cotransporter

Introduction

The human bone environment undergoes remodeling through bone formation and bone resorption throughout life to maintain bone homeostasis [1], which means bone resorption of osteoclasts is always accompanied with bone formation of osteoblasts [2]. The tight balance between bone formation and bone resorption regulates bone development and bone homeostasis. When the balance between bone formation and bone resorption is disrupted, it may lead to pathological conditions such as osteoporosis and osteopetrosis, whose characteristic may respectively be low bone mass and high bone mass, resulting in increased bone fragility and increased risk of fracture. As transmembrane proteins on cell membrane, ion channels are the basic excitatory units on the tissue cell membrane and participate in the process of transmitting electrical signals, which can be regarded as an excitable protein molecule reacts to specific stimuli. Depending on the permeability of the ions, the ion channels can be classified according to specific ions.

Sodium Ion Channels

Sodium ions widely exist in extracellular fluids and are the most abundant cations in human body, which are most closely related to liquid osmotic pressure. The voltage-gated sodium ion channel is a highly glycosylated complex consisting of an alpha subunit and two beta subunits. When the membrane potential is maintained at the resting membrane potential, the channel is closed, when the membrane depolarization potential is above the threshold, channel opened. The voltage-gated sodium ion channel is opened by depolarization, which allows sodium ions to flow in, causing membrane depolarization and inducing action potential [3]. It has been reported that there are two sodium channels in osteoblasts, namely voltage-sensitive sodium channels (Nav) and epithelial sodium channels (ENaC). In 1994, Killick R first discovered the ENaC channel expresses on cartilage and osteoblasts, plays a critical role in perceptual acidosis, maintenance of sodium homeostasis and transduction of mechanical stimulation. As a novel non-voltage-dependent sodium channel, ENaC is a member of the ENaC/degenerin family and transports sodium ions to critical pathways in epithelial cells, vascular endothelial cells and other tissues, which can be inhibited by amiloride. At the molecular level, ENaC consists of three homologous subunits, α, β, and γ [4]. Wherein each subunit consists of two transmembrane helices and one extracellular loop, and has a similar secondary structure, through a large extracellular

domain, which linked to the two membrane spanning domains (TM1 and TM2), and short intracellular N- and C- terminal composition [5,6]. The crystal structure and site-directed mutagenesis of ENaC indicate that ENaC has a central ion channel located on the central axis of symmetry of the three subunits [7].

In many excitable cells, the Na+ channel is responsible for the depolarization phase of the action potential. It is now known to identify rapidly activated Na^+ conductance in chicken osteoclasts [8]. This inward current is rapidly activated at membrane potential, more positive than -30 mV (peak amplitude is 1-2ms) and then rapidly inactivated (within 5-7ms), the kinetics of ENaC is faster than other voltage-gated channels in osteoclasts. The Na^+ current can be inhibited by nanomolar concentrations of tetrodotoxin, a blocker of certain voltage-gated Na^+ channels. In chicken osteoclasts, voltage-activated Na^+ conductance at the whole cell level is relatively small compared to conductance of other channels. This low density channel and its transient activation do not allow the generation of action potentials. In other cells, Na^+ conductance plays a vital role in secretion [9] and may play a role in the regulation of cell proliferation [10]. It is conceivable that larger Na^+ conductance plays a role in the proliferation of pre-osteoclasts and that only residues remaining in differentiated chicken osteoclasts. The researchers also found that the ENaC-α were expressed in rat osteoblast-like cell line (UMR-106) and primary human osteoblasts [11] and after the ENaC gene was silenced on rat osteoblasts by siRNA technique, they found that osteogenic gene-related genes' expressions decreased (Alp, Col1); after the osteogenic estradiol added to the primary cultured rat osteoblasts and mouse osteoblasts, the expression of ENaC mRNA was increased, which proved that ENaC in osteoblasts participated in the bone formation [4]. Some scholars have also studied the effects of ferulic acid acting on rat skull proliferation and differentiation by CCK-8 and alkaline phosphatase (ALP) staining, Cyclic guanosine monophosphate (cGMP)-dependent protein kinase II (PKGII) expression was silenced by small interfering RNA (siRNA) and then mRNA expression was detected by semi-quantitative PCR. The researchers found that ferulic acid promotes proliferation, differentiation and mineralization in rat calvarial osteoblasts in vitro, via cGMP-PKGII-ENaC signaling pathway, which also enhanced expressions of osteogenic genes [12]. JL G et al. [13] also confirmed in 2017 that epithelial sodium channels can promote osteogenic differentiation through the cGmp/PKGII/ENaC signaling pathway.

In 2016, Hu Songyan found that an inhibitor of ENaC, amiloride, which reduced the number of TRAP-positive osteoclasts and inhibited the formation of osteoclasts by staining with tartrate-resistant acid phosphatase (TRAP) and bone resorption, founding the expression of the osteoclast-specific gene CK reduced, thereby demonstrating the expression on ENaC osteoclasts at the cellular level and regulating osteoclast differentiation and bone resorption, further indicating that ENaC may be involved in osteoclast function adjust [14]. Sandra J et al. [15] using immunocytochemistry and RNA sequencing found that voltage-gated sodium channel NaV channel was expressed in primary osteoblasts infant mouse skull. The carbamazepine and phenytoin, which are the NaV channel blockers, sensitive sodium currents were recorded by whole cell patch clamp recording.

Chloride Ion Channels

As the most important anions in human body, chloride ion plays an important role in the electrochemical balance between the intracellular and extracellular side. It also participates in regulating intracellular and extracellular functions through the active transport of chloride channel, which can regulate the physiological process through the change of its channel current, such as liquid secretion, cell volume regulation, transmembrane transport, excitatory conduction and intracellular acidification. It is reported that a variety of chloride channels exist in the cell membrane or organelles. Abnormal chloride channels can cause a variety of physiological diseases, such as cystic fibrosis, congenital myotonia, epilepsy, Barter syndrome, etc [16]. Chloride channels associated with bone metabolism have been reported to include chloride channels (CLC), chloride intracellular channel (CLIC), cystic fibrosis transmembrane conductance regulator (CFTR) and potassium-chloride cotransporter (KCC). Among above, CLC is a gated chloride channel. The chloride channel members in the CLC family usually play important roles in regulating electrical excitability and transepithelial cell transport. The CLC chloride channels exist both in the plasma membrane and the membrane of organelles.

As a member of the CLC family, ClC-3 chloride channel has been reported expressed in bone cells, and it may not only participate in cell proliferation and apoptosis of osteoclasts, but also promote new bone growth by osteoblasts [17]. At the same time, ClC- 3 chloride channel expressed in mouse osteoblast lineage cells and plays an important role in improving the mineralization ability of osteoblasts in vitro and promoting osteoblast differentiation [18]. By overexpressing ClC-3, the expression of osteogenic markers (Alp, Ibsp and Bglap) was also elevated, which was also contributed to the calcification ability of MC3T3-E1 cells. Knockdown ClC-3 may reversed, demonstrating ClC-3 exists in osteoblasts and contributes to osteogenic differentiation [19]. Wang H et al. proposed the expression of Clcn3, Clcn4 and Clcn5 in MC3T3-E1 cells. Wang H et al. also suggested that in the process of bone differentiation, static compression of MC3T3-E1 cells increased the expression of ClC-3 and further promoted the expression of osteogenic genes. This proves that the chloride channel ClC-3 is involved in the mechanical stimulation of MC3T3-E1 cells [20].

Furthermore, ClC-7, located in the lysosome, is critical for the function of osteoclasts, which secretes chloride ions through the wrinkle edge of osteoclasts to secrete hydrogen ions through $V\text{-}H^+$-ATPases to dissolve bone minerals in bone. Highly expressed in the sputum, ClC-7 can be inserted into the edges of the wrinkles. Lysosomal function changes in mice lacking ClC-7, which leads to

severe lysosomal storage [21]. Mice lacking Clcn7 gene presents severe osteopetrosis due to the inability of osteoclasts to secrete acid, retinal degeneration and death within 7 weeks. Clcn mutation was identified in human, and homozygous mutations resulted in osteosclerosis in malignant infants [22]. Compared with other osteosclerosis mouse models, lacking ClC-7 does not affect the generation of osteoclasts attached to bone surface. $Clcn^{-/-}$ mouse osteoclasts exhibit functional and morphological abnormalities that do not degrade bone, which is related to their ability to acidify bone and osteoclasts and then seal extracellular space. In osteoblasts, the expression of ClC-7 is expressed by wrinkles formed by fusion of vesicles containing H^+ -ATPase, and protons are secreted into the voids. Clcn7 is expressed by wrinkles formed by fusion of vesicles containing H^+-ATPase, and then protons are secreted into the voids in osteoblast. Mutations in Clcn7 have been identified in patients with malignant osteopetrosis in human infants [23]. In 2010, Stefanie Weinert et al. converted ClC-7, which produces mouse with point mutations, into an unconjugated (unc) Cl- conductor, despite maintaining lysosomal conductance and normal lysosomal pH.

$Clcn7^{-/-}$ mice show lysosomal storage diseases, however, their osteosclerosis is mild and they lack the coat color phenotype, only certain effects of ClC-7 mediated Cl^- /H^+ exchange and it can be taken over by Cl- conductance. The data show that ClC-7 may mediate Cl^-/H^+ exchange during lysosomal acidification [24]. Located in the apical membrane of epithelial cells, CFTR is a hub for transport, fluid flow and ion concentration across epithelial salts. Low bone mass and increased risk of fracture are complications of cystic fibrosis (CF), which is characterized by undecoupled bone turnover - osteoblastic bone formation damage and enhanced osteoclastic bone resorption. Intestinal malabsorption, vitamin D deficiency and inflammatory cytokines contribute to CFBD. Cftr gene knockout mice exhibited abnormal bone development and metabolism, such as reduced bone length and reduced cancellous bone volume [25]. And Le Heron L et al. [26] found that common bone deficiency disease in patients with cystic fibrosis, Cftr mRNA and protein were expressed in primary human osteoblasts.

ATP-Gated Channel

ATP is a key energy currency and a ubiquitous extracellular messenger, and it also plays an important role in bone tissue. Based on its dose and the participating purinergic receptor (P2R) subtypes, ATP can trigger many different cellular responses, including cell proliferation, differentiation, and apoptosis [27]. In the biological activities of bone tissue, ATP can be involved in bone growth, development and repair [28]. Depending on the mode of receptor transduction, P2 receptors can be divided into two families, P2X and P2Y. Among them, P2X is a family of ion receptors, which is a ligand-gated ion channel, while P2Y is a family of metabotropic receptors, belonging to G protein-coupled receptors. P2X receptor is also expressed in human and mediates a variety of functions, including muscle contraction, neuronal excitation and bone formation, with subunits of intracellular N- and C- termini, two transmembrane domains and an extracellular ligand bind to the loop, but has no crystal structure. The effect of P2X on osteoblast is mainly to regulate the release of cytokines. P2X also regulates the start of osteoblast apoptosis on osteoclast [29]. It is reported that seven different P2 receptor subtypes were expressed in osteoblasts, including P2X2, P2X5, P2X7, P2Y1, P2Y2, P2Y4 and P2Y6. In the same time, Gallagher and Buckley reported that P2Y2 was strongly expressed in human osteoblast, while P2Y1 receptors were more predominant in rat osteoblast [30].

Shuxing et al. [31] analyzed the fitting effect of P2 receptor family in MC3T3-E1 cells by fluorescence quenching and Hill equation. Among them, the authors used a combination of Hill equations for each receptor to fit experimental data revealing that P2Y1 and P2Y7 mediate the increase in [Ca2+]i at very low and high ATP concentrations, respectively. It not only analyzes the expression of P2 receptor in osteoblasts, but also the interaction of individual P2 receptors in the overall response to extracellular ATP. Relevant data indicate that P2X3 and P2X2/receptor antagonist A-317491 (5-[(3-phenoxyphenyl) methyl-[(1S)-1,2,3,4-tetrahydronaphthalene-1-Carbamoyl] benzene-1,2,4-tricarboxylic acid] transiently attenuates bone cancer-induced pain in mice but has no effect in the later stages of the malignant process [32]. It has also been found that the P2X3 receptor is upregulated in the dorsal root ganglion function in a rat model of bone cancer [33]. It has also been reported that cancer-related bone pain is associated with osteoclast activation and Ca^{2+} imbalance [34,35].

Transient Receptor Potential Channel, TRP

It is well known that both the external Ca^{2+} and intracellular Ca^{2+} signaling are critical to bone homeostasis.

First, the normal function of bone depends on normal serum calcium levels, while bone also plays an important role in maintaining systemic calcium homeostasis. In fact, 99% of calcium in body is stored in bone, which contributes to its mechanical structural properties. Therefore, bone needs enough calcium to maintain bone integrity. What's more, intracellular Ca^{2+} is also an important second messenger in bone. Intracellular Ca^{2+} signaling in osteoblasts, osteoclasts, chondrocytes, and nerve endings has been shown to regulate many functions, including differentiation, signal transduction and mechanical transport, permeation and perception of painful stimuli. Therefore, fine-tuning of intracellular Ca^{2+} levels is critical for normal bone homeostasis, at the same time, transporters abnormalities, which are also involved in Ca^{2+} signaling, will clearly lead to diseases that also affect bone structure or function [36]. Maintenance of extracellular and intracellular Ca^{2+} homeostasis is important for bone biology and is largely dependent on Ca^{2+} channels. There are several types of Ca^{2+} channels, including

a) The ryanodine receptor (RyR) and the inositol-1,4,5-triphosphate receptor (IP3R), mediates the release of Ca^{2+} from the endoplasmic reticulum (ER).

b) Storage-operated calcium channels (SOCE), including ORAI1 and STIM1, mediates flux of extracellular Ca^{2+} into ER via ORAI1 when STIM1 detects depletion of intracellular stores,

c) Voltage-gated Ca^{2+} channels (VGCC)), allows Ca^{2+} to flow into cells for depolarization

d) A stretch-activated Ca^{2+} channel mediates Ca^{2+} influx after mechanical stimulation

e) A transient receptor potential (TRP) family for cations [37].

It has been reported that TRPV6 is necessary to ensure adequate intestinal calcium absorption during dietary calcium deprivation and thus prevent excessive reduction of bone mineralization [38]. These findings also highlight the importance of proper dietary calcium absorption in bone. The bone abnormalities during normal calcium intake indicate that TRPV6 indirectly affects bone only by participating in intestinal calcium transport. However, TRPV6 expressed in osteoblasts and osteoclasts, although the expression levels are very low [39,40], it theoretically possible directly regulated their differentiation or function. However, recent studies have convincingly demonstrated that TRPV6 does not participate in osteogenic Ca^{2+} uptake or mineralization [41]. Together, these results confirm TRPV6 lack of a direct role in bone metabolism. In conclusion, TRPV6 affects bone metabolism by promoting intestinal calcium transport and is particularly desirable during dietary calcium deficiency. On the other hand, in osteoclasts, in vitro studies have shown that TRP channels may be one of the Ca2+ entry pathways leading to Ca^{2+} oscillation [42]. It is also found that the cortical bone mass of TRPV5-/- mice reduced, which was associated with an increase in the number of osteoclasts, although bone resorption parameters are reduced [43]. These results convincingly demonstrate that TRPV5 is important for systemic calcium homeostasis by fine-tuning renal calcium reabsorption. Skeletal defects in TRPV5-/- mice may be due to abnormal external calcium balance or change in osteoclast Ca^{2+} signaling. It is worth noting that TRPV5 didn't express in osteoblasts. Moreover, in osteoclasts, TRPV5 is located at the edge of the wrinkles and may contribute to bone resorption. According to van der Eerden, in vitro differentiation of hematopoietic precursors isolated from TRPV5 null mice resulted in more and larger osteoclasts with severely impaired resorption capacity. TRPV5 and TRPV6 are known highly selective channels for calcium ions [44].

Rossi showed that TRPV1 expressed in osteoclasts in vitro and in vivo, which demonstrated that TRPV1 antagonist I-RTX inhibits human osteoclast formation in vitro [45], while TRPV1 agonist resin toxin increases osteoclast formation. Thereafter, Aymen I. Idris examined the effects of TRPV1 ion channel antagonist capsazepine on mouse osteoclast and osteoblast differentiation and osteoporosis induced by ovariectomy in vivo. They found that adding capsazepine, a pharmacological blockade of ion channels, also is a TRPV1 blocker. TRPV1 may have an inhibitory effect on osteoclastic bone resorption which can protect mice from oophorectomy-induced bone loss, meanwhile may also inhibit osteoblast activity and bone formation [46]. TRPV4 is a preferred cation channel for Ca^{2+}, originally characterized by the conversion of osmotic pressure. TRPV4-mediates Ca^{2+} signaling in response to cartilage osmotic fluctuations, which is a potential mechanism for chondrocytes. Recent studies have shown that TRPV4 signaling plays a crucial role in skeletal development, and the loss of gene coding for mouse TRPV4 leads to accelerated aging of joint degradation [47]. Christopher J O'Conor detected the effect of TRPV4 deficiency on the intrinsic ability of bone marrow stem cells (MSCs) and adipose-derived stem cells to detect the phenotype of $Trpv4^{-/-}$ mice and the function of TRPV4 at cellular level. Linkages further confirm that the lack of TRPV4-mediated signaling in the presence of obesity catabolism, biomechanics and inflammatory factors accelerates the progression of osteoarthritis in OA's high-fat diet model [48]. Transient receptor potential vanilloid channel 2 (TRPV2) was significantly expressed in RANKL-treated RAW264.7 cells (pre-osteoclasts). Calcium oscillation in pre-osteoclast RAW264.7 cells was activated by RANKL-dependent TRPV2 and activated intracellularly calcium oscillation at the same time, and then activation of osteogenesis by NFATc1 [49].

Prospective

Ion channel is one of the basic ways to exchange and transmit signals between cells, which have become the drug targets for research in biology, medicine, pharmacy, etc. A large number of research reports indicate that ion channels can also be used as research for the treatment of osteoporosis. Many scholars have demonstrated that the function of differentiation and proliferation of osteoblasts osteoclasts can be regulated by ion channels.

However, there are several problems and phenomena:

a) The ion channels existing in bone tissue are not unique and may be affected by other channels while studying.

b) In molecular biology experiments, due to in vitro cell experiments, it has been separated from the original environment and its internal environment has also changed accordingly. It has changed from the in vivo situation, and the in vitro experiment cannot accurately explain the research mechanism. But with the development of technology and thinking, these problems will eventually be solved.

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