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THE ROLE OF UNDER-INVESTIGATED CONNEXINS IN MUSCULO-SKELETAL TISSUE: A BRIEF REVIEW WITH EMPHASIS ON BONE TISSUE

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Abstract

Connexins (Cxs) are a family of transmembrane proteins that form gap junctions and hemi-channels, which mediate cell-cell communication between neighboring cells and the respective extracellular milieu in different tissues. Most tissues and cell types throughout the body express one or more Cx proteins, highlighting its importance in regulating cell growth, differentiation, adhesion, migration, cell death and others. Moreover, Cx can propagate intracellular signals through its C-terminus domain, and thus function beyond a mere channel. Cx43 is the most highly expressed and most well studied Cx in bone and musculoskeletal tissues, although Cx40, Cx45, Cx46 and more recently, the Cx37 have been described in bone tissue, along with Cx26, Cx32 and Cx39 in other musculoskeletal tissues. Here, we discuss the basic structure of gap junctions and the role of the Cxs in musculoskeletal tissue, with special focus on Cx37.

Keywords: connexins, bone, Cx37, bone cells, gap junction.

Resumen

EL PAPEL DE LAS ESCASAMENTE INVESTIGADAS CONEXINAS EN EL TEJIDO MÚSCULO-ESQUELÉTICO: UNA BREVE REVISIÓN CON ÉNFASIS EN EL TEJIDO ÓSEO

Las conexinas (Cxs) son una familia de proteínas transmembrana que forman uniones en hendidura y hemicanales encargados de mediar la comunicación entre células vecinas y el respectivo medio extracelular en diferentes tejidos. La mayoría de los tejidos y células expresan una o más proteínas conexina, jugando un papel importante en la regulación de la proliferación celular, diferenciación, adhesión, migración y muerte celular, entre otras funciones. Además de actuar como un canal, las conexinas pueden propagar señales intracelulares a través del dominio C-terminal. La Cx43 es la conexina mas expresada y mejor estudiada en el tejido óseo y el músculo, aunque las Cx40, Cx45, Cx46, y mas recientemente Cx37, son también detectadas en el hueso.

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A su vez la expresión de la Cx26, Cx32 y Cx39 ha sido observada en otros tejidos músculo-esqueléticos. En este manuscrito describimos la estructura básica de las uniones tipo gap y el papel que las Cxs, y en especial la Cx37, tienen en tejidos músculo-esqueléticos.
Palabras clave: conexinas, hueso, Cx37, células óseas, uniones en hendidura.

Basic structure and functions of gap junctions

The plasma membrane has a variety of specialized structures that are responsible for functions at the cellular and molecular level. Among these different types of membrane specializations are the gap junctions, also known as *nexus* junctions, which are a cluster of membrane channels that provide a conduit for the passage of ions, such as Ca^{2+}, H^{+}, Na^{+}, K^{+} and Cl^{-} and other small molecules (up to ~1.5 nm in diameter) from the cytoplasm of one cell to another.[1,2] As a result, this type of specialization plays an important role in mediating communication between different tissues and cells. For example, in the heart, a conduction system is formed through gap junction connections, which allow for the propagation of electrical impulses.[3]

Findings of the last decade have revealed that gap junctions are encoded by the gene family, known as connexins (Cxs). Cxs are grouped into five subgroups (α, β, γ, δ, or ε) in relation to their sequence and cytoplasmic loop length and are named based on their predicted molecular weight (for example, Cx43 and Cx37 are ~43 and 37kDa in size, respectively).[4]

Gap junction channels are formed through the linkage of two connexon on the plasma membrane surface of adjacent cells, which are composed of six transmembrane proteins. These channels allow for direct cell-cell communication, since the two connexon evenly align and are closely associated, with only a narrow gap of 2-4 nm separating them (Figure 1A). Currently, more than 21 different Cx proteins have been identified, but only a few have been extensively studied.[1] A complex interaction among several types of Cxs and between connexons provides a variable array of possible combinations, which modifies the affinity of the channel to certain ions (Figure 1B).

Depending on the ion concentration, the pH or extracellular signals, the connexon may be open or closed, thus regulating the activity of these molecules (Figure 1C).[5] However, the mechanisms that regulate channel opening and closure are still unclear.

The composition and quantity of Cxs expressed on the cellular membrane is different in each cell type and might vary over time. Further, while Cxs are expressed in several tissues and cells, they are not expressed in the red blood cells, spermatozoids or differentiated skeletal muscles of adult vertebrates.[6]

The half-life of the intercellular gap junctions is only a couple of hours, upon which they then either fuse with the lysosome or are directed to the proteosomal pathway for degradation. However, even after internalization some Cxs can be recycled back to the membrane.[7]

In addition to the role of Cxs in facilitating the exchange of molecules through the formation of gap junctions; Cxs can also initiate and propagate biochemical signals through their different structural domains. Thus, functioning not only as a channel, but also as a scaffold, facilitating intracellular signaling (Figure 2).[8] For example, opening of Cx43 hemichannels confers, at least in part, the anti-apoptotic effect mediated by bone antiresorptive bisphosphonates, mechanical stimulation and parathyroid hormone in osteoblastic cells.[9] Furthermore, opening of these hemichannels in osteocytes allow the passage of prostaglandin E_2 (PGE_2), an important extracellular mediator for bone anabolism.[10]

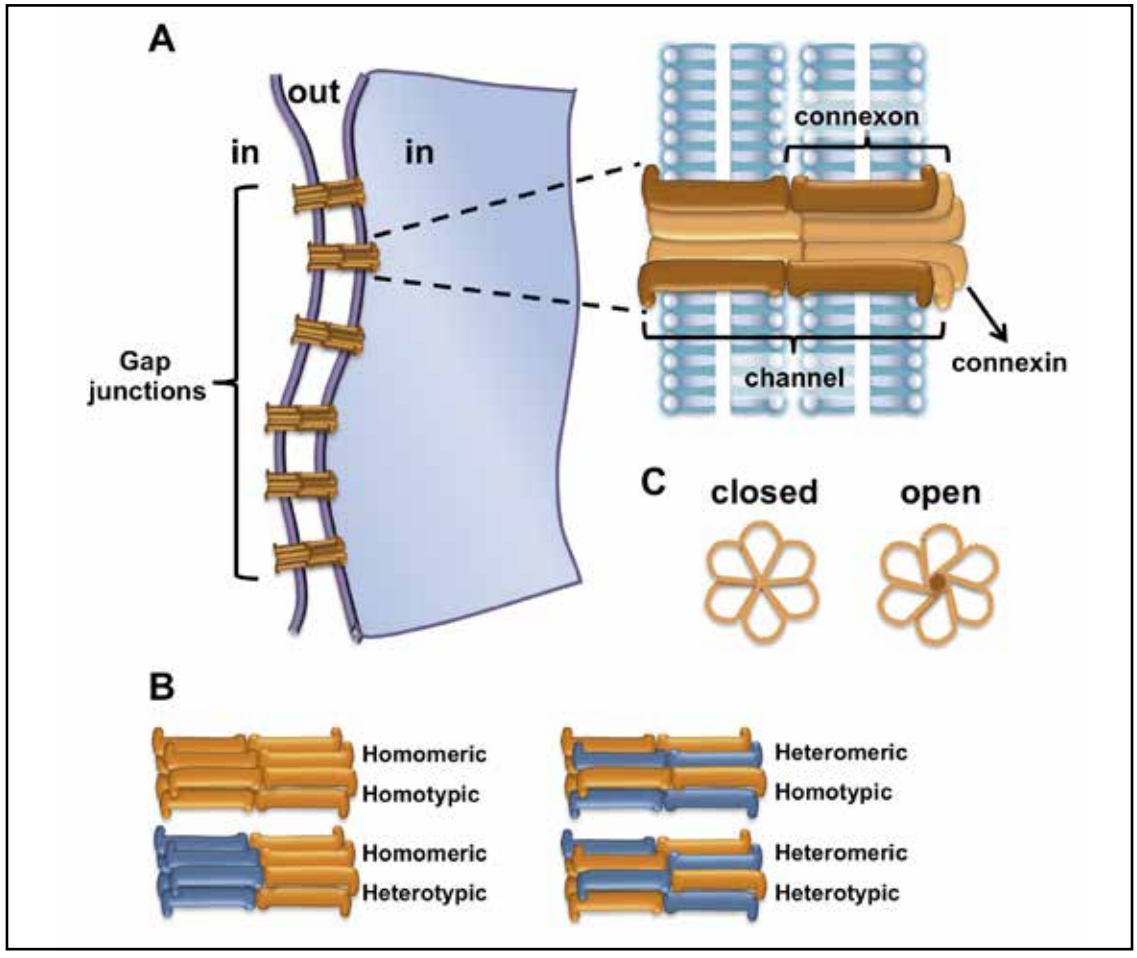

Figure 1. Schematic illustration of the gap junction structure and the complexity of the interaction between different subunits of connexins and connexons. A. Membranes of two neighboring cells forming a gap junction composed of a cluster of gap junction channels along the membrane, leaving a 2-4 nm gap. In detail, 6 connexins forming one connexon and establishing association with other connexon to form a channel. **B.** Top view of the gap junction closed and open. Schemes adapted from Biological Science, Prentice Hall; 2nd Edition (2005). **C.** Hemichannels/connexons can be formed by one (homomeric) or more types of connexins (heteromeric). Two homomeric or two heteromeric connexons for a functional gap junction are called homotypic channels whereas heterotypic channels are composed of different homomeric or heteromeric hemichannels. Scheme adapted from Kumar and Gilula (1996).[2]

Under-investigated connexins and their roles in bone metabolism

From the 21 different types of Cxs identified thus far, only a small number have been described in musculoskeletal tissue and, in particular, bone tissue.

Of these different Cxs, Cx43 was the first to be identified and is the most highly studied Cx in bone tissue. Mutations of the Cx43 gene are associated with occulodentodigital dysplasia (ODDD), a condition characterized by abnormalities that include weak enamel,

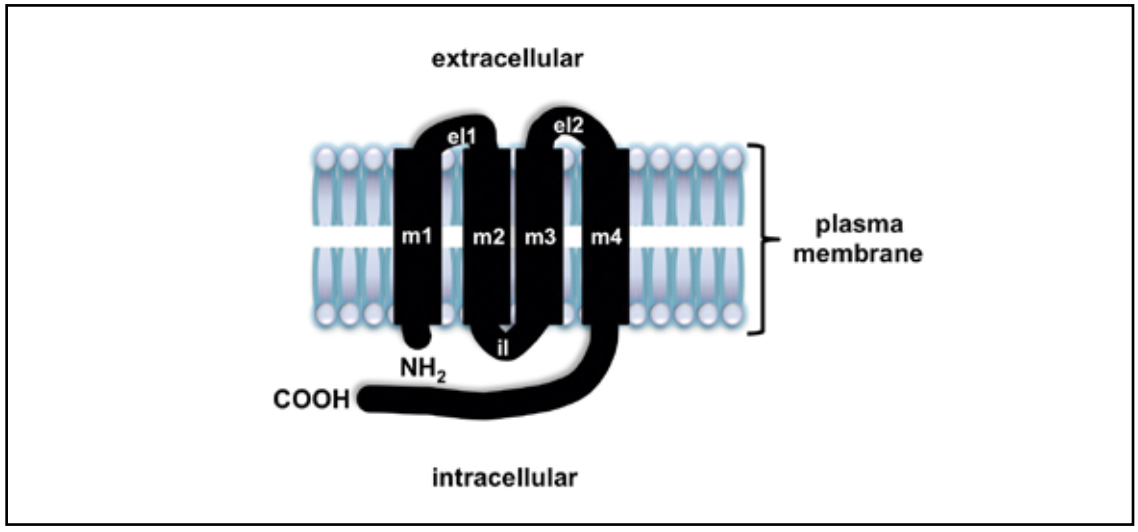

Figure 2. Schematic illustration of transmembrane domains of connexin protein. One connexin molecule originates four membrane domains (m1 to m4) with two extracellular loops (el 1 and el 2) and one intracellular (il). Also, connexin molecules have one amino (NH_2) and one carboxi (COOH) termini facing the cytoplasm. Cytoplasmic loop and COOH-terminus present variation in the sequence and length, whereas NH_2-terminus is highly conserved. Scheme adapted from Kumar and Gilula (1996).[2]

small or missing teeth, and early tooth loss and broad long bones.[11] It is estimated that approximately 1,000 people are affected worldwide; although the actual incidence is unknown since the majority of cases go undiagnosed.

Whereas Cx43 and Cx45 are expressed at the surface of plasma membrane,[12] Cx46 is retained in the perinuclear compartment that is similar to the trans-Golgi compartment of osteoblastic cells.[13] However, why this Cx is retained in a specific site and what its role is in the osteoblasts is still to be investigated. Moreover, Cx45 and Cx43 are co-localized at appositional membranes and Cx45 functions as a dominant negative for Cx43 actions.[14,15] Due to changes in permeability and relative expression, these proteins can alter the expression of bone matrix proteins such as osteocalcin and bone sialoprotein. Overexpression of Cx45 decreased dye transfer and of those matrix proteins aforementioned, whereas predominance of Cx43 had the opposite effect.[16,17] Furthermore, Cx45 is involved in matrix production in the different stages of bone formation in chicken and abundantly expressed between transitions of preosteoblast to osteoblast.[18] Despite this, characterization of the bone phenotype in Cx45 global knockout did not show gross abnormalities.[17] On the other hand, this gap junction is essential for organization of blood vessels in embryos and mice with global deletion of Cx45 die between E9.5 and E10.5. However, the specific contribution of Cx45 and Cx46 in bone cells by using the Cre-loxP system has not been investigated yet.

Mice globally lacking Cx40 are viable; however, newborn mice and embryos exhibited defective axial and appendicular bone,

with abnormal rib development, lower limb malformations and delayed ossification in anklebones. This indicates the requirement of Cx40 in controlling bone development.[19]

Cx37, the last connexin reported in bone tissue, is described in a separate topic.

Cx37, the newly identified bone connexin

Mice with a global deletion of Cx37 are viable and do not display any external gross abnormalities; however, they exhibit impaired oocyte maturation and vascular endothelium architecture. Several studies provided convincing evidence that global Cx37 knockout mice lack terminally differentiated graafian follicles, resulting in female infertility due to lack of ovulation.[20-22] Since female mice are infertile, it is possible that they have altered levels of steroid hormones, especially estrogen, which could alter the bone metabolism. However, mounting evidence have shown that infertility caused by reduction in Cx37 occurs due to inability of the granulosa cells of the ovarian follicle to transport the molecules and hormones necessary for maturation, even when stimulated with gonadotropin.[20, 21]

Gene array studies demonstrated that GJA4, the gene that encodes the Cx37, is expressed in bone tissue, particularly in osteoblast and osteocytes. In addition, osteocytes exhibited 5-fold higher expression levels than osteoblasts,[23] showing that Cx37 is not restricted to vascular development and maturation of oocytes.

The direct association between bone mass and Cx37 was described by Yamada et al. (2007) and colleagues.[24] This study showed that substitution of the proline amino acid with a serine at position 1019 in the regulatory C-terminus domain of the Cx37 protein leads to misfunction of the protein. Further, patients with this polymorphism in the male Japanese population exhibited increased bone mass.[24] Interestingly, women do not reproduce the same findings, suggesting that the effect of Cx37 is gender-dependent. However, more studies are needed to address this discrepancy.

More recently, a study conducted in growing mice lacking Cx37 showed increased spinal and femoral bone mass density in males and females, although it was less pronounced in females when compared to males.[22] In addition, this study demonstrated that the cellular basis of bone gain in Cx37-deficient mice is due to impairment on osteoclast formation.[22]

Inhibition of gap junctions and hemichannels by heptanol, decreased the number of mature osteoclasts in several studies.[15,25-27] Although, due to non-specificity of its blockage, the contribution of gap junctions and hemichannels to osteoclast formation is unclear. In addition, other types of pharmacological gap-junctional blockers, such as antiarrhythmic peptides, showed a decrease in the number of TRAP-positive multinucleated osteoclasts.[28] Blocking the Cx43 gap junction, results in a lower number of TRAP-positive cells.[25] However, pharmacological blockers are not specific for each type of Cx since they inhibit groups of Cxs, thus preventing the ability to observe the contribution of each individual Cx. Despite the increases in osteoclast precursor markers CD11b, CD14, and RANK in Cx37-deficient mice, mononuclear precursor fusion is partially inhibited, which in turn leads to a reduction in the number of mature osteoclasts. Consistent with these findings, gap junctions are expressed at higher levels in the early stages of differentiation from bone marrow precursor cells when compared to mature osteoclasts.[27] Furthermore, when Cx37 is absent, mice are predisposed to atherosclerosis due to an increase in the number and recruitment of monocyte-macrophages.[29] These pieces of evidence reveal the Cx37 is involved in facilitating cell adhesion.

In addition to effects of Cx37 associated to its channel activity, the C-terminus tail of the Cx37 is a substrate for GSK-3β (glycogen synthase kinase 3), more specifically at the 319 amino acid position.[30] GSK-3β is involved

in Wnt/β-catenin signaling and its inhibition is responsible for stabilization of β-catenin.[31] Moreover, authentic osteocytes and bone lysates from Cx37-deficient mice and MLO-Y4 osteocytic cells silenced for Cx37 exhibited activation of Wnt/β-catenin signaling (data not published). These pieces of evidence suggest that, by a mechanism not clearly understood, Cx37 might repress the Wnt/β-catenin pathway and its absence leads to an increase in the accumulation of β-catenin and consequently contributes to high bone mass.

Although little work has been done to further understand the action of Cx37 in bone, this Cx has emerged as a potential candidate for the development of mimetic peptides, which could be used to selectively target osteoclast precursors and thus reduce bone resorption.

Connexins in other musculoskeletal tissues

Cartilage

Cartilage is an elastic connective tissue composed of collagen fibers, proteoglycans, and elastin fibers, which are produced by chondrocytes.

Studies have demonstrated the expression of various different Cxs in chondrocytes. In human primary costal and articular cartilage, chondrocytes express Cx32 and Cx46, as well as, Cx43 and Cx45, which form heterotypic channels, and modulate rapid Cx43 channel gating properties likely through Cx45 docking induced conformational changes.[32] In addition, studies examining an animal model, in which Cx29 was replaced by the LacZ reporter; found that Cx29 is expressed in chondrocytes of the intercalated discs and in the epiphysis of developing bones.[33]

Ligament

In ligaments, a fibrous avascular tissue composed of cells and extracellular matrix that connects bones or cartilage to one another, the expression of numerous Cxs has been detected. Periodontal ligament fibroblasts (PDLFs) express a variety of different Cxs, including Cx32, Cx40, Cx43, and Cx45,[34-37] which are differentially localized with Cx40/43 and Cx32/45 forming heteromeric channels. Immunohistochemical analysis observed punctuated expression of Cx40/43, suggesting these forms might exist in the membrane and primarily form gap junction channels, whereas Cx32/45 are ubiquitously expressed in all cells and are present in both the cytoplasm and the cell membrane.[34-37] Previous work has demonstrated that Cx40 and Cx45 are involved in regulating the contractile function of PDLFs, while Cx43 may be involved in regulating their secretory function.[34-37] Further, in cultured and intact human PDLFs, Cx43 was shown to be expressed only when cell-cell contact was established, whereas Cx32 was expressed in the cytoplasm regardless of whether there was cell-cell contact.[34-37] Cx43 expression and gap junction channels were also detected in medial collateral ligaments.[34-37]

Tendon

Tendons are tough bands of fibrous connective tissue, made of collagen similar to ligaments, which connect muscles to bone and are capable of withstanding tension. Cx43, Cx32 and Cx26 expression has been detected in tendons;[38] and studies have demonstrated the essential role of gap junction intercellular communication in stimulating strain induced collagen synthesis by tendocytes.[39] In addition to their expression in human tendons, Cx43 and Cx32 have also been observed in sheep,[40] equine,[41] and avian[42] tendons. These two Cxs are differentially localized and are unable to form heteromeric channels.[39] Within the cellular rows, Cx32 is expressed between tenocyte bodies, whereas Cx43 is present both between cell bodies and at the regions where the lateral and longitudinal cellular processes connect.[42] Further these two Cxs differentially modulate tenocyte collagen

secretion in response to mechanical stimulation, where Cx43 is inhibitory, while Cx32 is stimulatory.[42]

Skeletal muscle

Skeletal muscle, a striated muscle tissue that is attached to bones by tendons, is made up of myofibers, which are formed through the activation, proliferation, and differentiation of myogenic satellite cells.[43,44] During myogenesis, satellite cells proliferate into myocytes, which differentiate into myoblasts and then fuse to form myotubes. Following myotube maturation, completion of myogenesis results in a newly formed muscle myofiber.[45] All three myogenic cell types express Cx40, Cx43, and Cx45, whereas only myotubes express Cx39. Previous studies have demonstrated that in the absence of Cx43 or Cx45, differentiation is delayed both *in vitro* and *in vivo*, and removal of Cx43 leads to decreased myogenin expression, as well as, reduced cell fusion; suggesting that Cx43 plays a role in myoblast differentiation.[45-47] On the other hand, Cx39, which does not form gap junction channels and may or may not form hemichannels, is involved in the muscle differentiation process, but not in the process of myogenic differentiation.[45] Further, myogenesis is enhanced in Cx39-deficient murine embryos and Cx43 expression is increased, suggesting that Cx43 may compensate for the loss of Cx39 during myogenesis and muscle regeneration.[46] These studies demonstrate the contribution of Cx proteins in myogenesis; however, it is important to note that these studies do not distinguish between the specific roles of gap junction channels and hemichannels.[45]

Cx39, Cx43 and Cx45 are expressed in denervated skeletal muscles of rodents and the deficient expression of Cx43 and Cx45 drastically prevents muscle atrophy.[48] These three Cxs are also expressed in muscles of mdx mice, a model of Duchenne disease and the deficiency of Cx43 and Cx45 in this model completely prevents cell apoptosis in mdx mice.[49]

Conclusions

Little or nothing has been added to musculoskeletal field regarding other Cxs aside from Cx43. Despite a lack of studies that elucidate the role of Cxs in musculoskeletal tissue, Cx37 has emerged as a potential target candidate to develop new pharmacological therapies to target and inhibit its actions, which would lead to reduced bone resorption and preservation of bone mass.

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Asociación Argentina de Osteología y Metabolismo Mineral

INSTITUTO UNIVERSITARIO DEL HOSPITAL ITALIANO

Curso Superior Universitario de OSTEOLOGÍA 2017

DIAGNÓSTICO Y TRATAMIENTO DE LAS ENFERMEDADES ÓSEAS METABÓLICAS

Curso universitario anual presencial y trabajo en campus virtual

Directoras: Dra. Luisa Plantalech (HIBA) - Diana Gonzalez (AAOMM)
Coordinadora: Dra. María Diehl (HIBA-AAOMM)
Fechas de inicio y finalización: Marzo a Diciembre 2017
Carga horaria: 140 hs.

Dirigido a: Médicos internistas, de familia, ginecólogos, endocrinólogos, reumatólogos, geriatras, nefrólogos, pediatras, fisiatras, ortopedistas, especialistas en medicina del deporte, médicos veterinarios, odontólogos, bioquímicos, kinesiólogos, nutricionistas, farmacéuticos y otros profesionales de carreras afines.

INICIO MÓDULO **2 de AGOSTO 2017**

CONTENIDOS

MÓDULO I: ENFERMEDADES DEL METABOLISMO MINERAL Y ÓSEO

Metabolismo del calcio, fósforo y magnesio. Mineralización ósea. Remodelado óseo. Hipercalcemia, hiperparatirodismo, hipocalcemia e hipoparatiroidismo, hipovitaminosis D (raquitismo y osteomalacia), hiperfosfatemia (Enfermedad renal crónica). Hipofosfatemia (raquitismos). Calcificaciones ectópicas. Litiasis renal. Enfermedad de Paget. Displasias óseas. Metástasis óseas. Tumores primarios del hueso. Enfermedades óseas esclerosantes.

MÓDULO II: ENFERMEDADES ÓSEAS FRAGILIZANTES, INFILTRATIVAS Y ESCLEROSANTES.

Osteoporosis: posmenopáusica, premenopáusica, senil, secundarias, inducida por corticoides. Tratamiento de la osteoporosis: bifosfonatos, teriparatida, denosumab, estroncio, nuevas drogas. Osteogénesis Imperfecta. Necrosis ósea vascular, Edema óseo, Sudeck. Mastocitosis, Enfermedad de Gaucher. Osteoesclerosis. Osteoporosis en situaciones espaciales: SIDA, cirugía bariatrica, enfermedad intestinal, transplante de órganos.

Informes e Inscripción:
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