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# Anion Channels in Osteoarthritic Chondrocytes

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## 1. Introduction

Osteoarthritis (OA) is the most common form of arthritis and represents a global health problem. OA is estimated to affect 40% of the population over 70 years of age and is a major cause of pain and physical disability (Lawrence, 2008). This is a condition that predominantly involves hip, knee, spine, foot and hands. Several risk factors have been associated with the initiation and progression of OA, increasing age, sex, obesity, occupational loading, malalignment, articular trauma and crystal deposition.

OA is a chronic degenerative joint disorder characterized primarily by destruction of articular cartilage, formation of reparative fibrocartilage and subchondral bone remodelling. However, not only the cartilage and bone are affected, also the synovium and the joint-stabilizing structures such as ligaments and meniscus (Baker‐LePain, 2010). Apparently, all the tissues of the joint respond to mechanical stress with the consequent loss of function and clinical deterioration.

The application of mechanical forces under physiological conditions is a preponderant factor in cartilage homeostasis. It is now well know, that environmental factors, such as compressive and tensile forces, load and shear stress have a significant influence on the chondrocyte metabolism. Also, conditions that alter the load distribution on the articular surface can induce the development of OA (Roos, 2005).

This degradative process of the cartilage in OA is a consequence of an imbalance between anabolism and catabolism of chondrocytes. Generally, chondrocytes respond with increased expression of inflammatory mediators and matrix-degrading proteinases (Kurz, 2005).

Other effect observed in chondrocytes under mechanical stimulation is the change in membrane and osmotic potential (Wright, 1992, Bush, 2001). In OA, chondrocytes undergo depolarization instead of hyperpolarization (Millward-Sadler, 2000), and the decrease of the osmotic potential has been associated with loss of volume control in early stages of OA (Stockwell, 1991, Bush, 2003). However, the sequence of mechanobiological events necessary for the maintenance of extracellular matrix (ECM) homeostasis and its involvement in the pathogenesis of OA is still poorly understood.

## 2. Articular cartilage structure

Articular cartilage is a specialized connective tissue that contains a single cell type, the chondrocytes, embedded in an ECM which is composed of water and macromolecules. Collagens, proteoglycans and noncollagenous proteins are the main components of matrix. The chondrocytes are highly differentiated cells and constitute 1% of the total cartilage volume (Stockwell, 1967). These cells are responsible of the production and organization of ECM. Cartilage is divided into four horizontal zones: superficial, transitional o middle, radial o deep, and calcified zones. Each of these layers has specific morphological and functional characteristics related to the metabolic activity.

In the superficial zone, chondrocytes are flattened and oriented parallel to the surface. This layer consists of a low proportion of proteoglycans, thin collagen fibers and higher water content (Weiss, 1968). Functionally, this zone is responsible of the highest resistance to compressive forces during joint movement.

The transitional or middle zone consist of rounded chondrocytes, a network of collagen fibers arranged radially and an increased proteoglycan content.

In the deep zone, the chondrocytes are grouped in perpendicular columns to the articular surface. This layer contains the highest proportion of aggrecan and long collagen fibers, approximately of 55 μm across (Minns, 1977).

The calcified zone links and anchors the articular cartilage to subchondral bone through collagen fibers arranged perpendicularly. The hypertrophic chondrocytes are scarce and located in uncalcified lacunae.

Also, the matrix is subdivided into the pericellular, territorial and interterritorial regions which are arranged around the chondrocytes. The pericellular matrix is composed for sulfated proteoglycans and glycoproteins. They provide protection to chondrocytes when exposed to chondrocyte load and maintain water homeostasis. Together, the chondrocyte and pericellular matrix constitute the chondron (Poole, 1997). Adjacent to this region, the territorial matrix contains a dense meshwork of collagen fibers that provide mechanical protection to the chondrocytes. The concentration of proteoglycans rich in chondroitin sulfate is higher in this region. In the interterritorial region predominates proteoglycans rich in keratan sulfate and the collagen fibers of largest diameter (Stockwell, 1990).

The biochemical properties of cartilage are dependent of the integrity of the matrix. In the ECM of mature mammalian articular cartilage, the collagen represents 50-60% dry weight. The network consists of collagen IX (1%), collagen XI (3%) and collagen II (≥90%) (Eyre, 1987). Type II collagen, a fibrillar protein, is composed of three identical α-1 chains in form triple helix and constitutes the basic structure of cartilage. Type XI collagen is probably copolymerized and type IX collagen is covalently linked to the type II collagen fibrils (Mendler, 1989). Among other types of collagen found in cartilage, type X collagen is described in the calcified zone (Gannon, 1991), type VI collagen promotes the chondrocyte-matrix attachment (Wu, 1987) and type III collagen is copolymerized and linked to collagen II (Wu, 1996). Generally, these collagen fibers provided to the cartilage the tensile stiffness and strength.

The second largest component of the ECM are the proteoglycans, which constitute 5 to 10% of the tissue wet weight. These are molecules consisting of glycosaminglycans (GAGs) chains bound to a protein core. Also, the aggrecan are composed of proteoglycan aggregates in association with hyaluronic acid (HA) and link protein (Hardingham, 1974). The keratan sulfate and chondroitin sulfate are the main types of GAGs. The anionic groups of aggrecan

attract cations such as $Na^+$, this allows an osmotic imbalance and the accumulation of fluid in the ECM, which is critical for the biomechanical properties of cartilage. Collagen fibrils interact with aggrecan monomers in the keratan sulfate-rich regions (Hedlund, 1999). Other proteoglycans include decorin, biglycan, lumican and fibromodulin, consisting of small leucine-rich repeat. They bind to fibrillar collagen via its core protein regulating the fibril diameter and fibril-fibril interaction in the ECM.
In addition, there are nocollagenous proteins such as fibronectin and tenascin favoring chondrocyte-matrix interaction.

## 3. Chondrocytes mechanotransduction

The articular cartilage is continuously exposed to mechanical stress which significantly affects the response of chondrocytes to their environment (Grodzinsky, 2000). Under conditions of continuous compression, the chondrocytes undergo changes in potential membrane (Wright, 1992), matrix water content, ion concentrations and pH (Mobasheri, 1998; Mow, 1999). The process of converting physical forces into biochemical signals and the subsequent transduction into cellular responses is referred to as mechanotransduction (Huang, 2004).
Miscellaneous "mechanoreceptors" including ion channels and cell adhesion molecules, such as integrins have been described in chondrocytes. Thus far, α1β1 integrin, a receptor for collagen, α5β1 integrin, a receptor for fibronectin and αVβ5 integrin, a receptor for vitronectin have been implicated in the regulation of chondrocyte behaviour (Ostergaard, 1998; Loeser, 1995). Voltage-gated $Na^+$ and $K^+$ channels (Sugimoto, 1996), epithelial sodium channels (ENaC) (Mobasheri, 1999) and N-/L-type voltage-gated $Ca^{2+}$ channels (Wang, 2000) have been considered as potential mechanosensitive ion channels.

### 3.1 Membrane potential

The negative resting membrane potential (RMP) in most cells, is the result from activity of $K^+$ (Wilson, 2004) and $Cl^-$ channels (ClC) (Tsuga, 2002; Funabashi, 2010). In chondrocytes, the RMP ranging from -10.6 mV to -46 mV (Wright, 1992; Clark, 2010; Lewis 2011), and those values are determined by the influx and efflux of cations and anions in the cell membrane. Consequently, the stability of the ECM is linked to the ionic changes and the RMP in chondrocytes. Several studies related the use of ionic blockers such as lidocaine and verapamil, showed a decrease in the synthesis of GAGs (Wu, 2000; Mouw, 2007), inhibition of chondrocytes proliferation (Wohlrab, 2002) and induction of apoptosis (Wohlrab, 2005). The permeability of ion channels is regulated by chondrocyte channelome (Barret-Jolley, 2010).
The ion channels so far identified in chondrocytes are summarized in Table 1.
The membrane potential in articular chondrocytes is primarily related to the $Cl^-$ conductance greater than $K^+$ conductance (Tsuga, 2002; Funabashi, 2010). More recently, it was showed the involvement of TRPV5 (gadolinium-sensitive cation channels) in the relatively positive RMP of the chondrocytes. Furthermore, has been suggested that the positive membrane potential is due to TRVP5 higher than that generated by potassium ions, which would allow efflux of potassium ions into the cell limiting the increase in cell volume in situations of reduced osmolarity (Lewis, 2011).

| Ion channels | Reference |
|---|---|
| Voltage-gated $K^+$ channels | Walsh, 1992<br>Sugimoto, 1996<br>Wilson, 2004<br>Mobasheri, 2005<br>Ponce, 2006<br>Clark, 2010 |
| Voltage-gated $Na^+$ channels | Sugimoto, 1996<br>Ramage, 2008 |
| Voltage-gated $Ca^{2+}$ channels | Shakibaei, 2003<br>Sanchez, 2004<br>Mancilla, 2007<br>Xu, 2009 |
| Voltage-activated $H^+$ channels | Sanchez, 2006 |
| $Cl^-$ channels (ClC) | Sugimoto, 1996<br>Tsuga, 2002<br>Isoya, 2009<br>Okumura, 2009<br>Funabashi, 2010<br>Perez, 2010 |
| ATP-dependent $K^+$ channels | Mobasheri, 2007 |
| $Ca^{2+}$-dependent $K^+$ channels | Grandolfo, 1992<br>Long, 1994<br>Martina, 1997<br>Mozrzymas, 1997<br>Mobasheri, 2010 |
| Transient receptor potential (TRP) channel | Sanchez, 2003<br>Phan, 2009<br>Lewis, 2010 |
| Epithelial sodium channels (ENaC) | Trujillo, 1999<br>Shakibaei, 2003<br>Lewis, 2008 |

Table 1. Ion channels described in chondrocytes

Therefore, it has been proposed that the ClCs functions in chondrocytes could be involved in setting of the membrane potential or anionic osmolyte channels (Barret-Jolley, 2010).

### 3.2 Mechanotransduction in osteoarthritic chondrocytes

*In vivo*, the extracellular environment surrounding the chondrocytes is negatively charged and provides a high osmolarity, from 480 mOsm to 55 0mOsm under load (Urban, 1993; 1994; Xu, 2010). Under physiological conditions, chondrocytes are able to regulate their volume through osmotic pressure cycles (Bush, 2001). However, in OA, the chondrocytes have decreased osmotic potential and increased water content (Stockwell, 1991). Furthermore, in osteoarthritic chondrocytes described a high recovery of the increased volume, which promotes the progression of the disease (Jones, 1999; Bush, 2005).

In this matter, in the superficial and middle zones of normal cartilage and the zone of fibrillated osteoarthritic cartilage has been demonstrated the expression of ATP-dependent $K^+$ channels (Mobasheri, 2007). Under normal conditions, mechanical stimulation produces hyperpolarization of the membrane of chondrocytes, but in OA the depolarization is induced. According to studies preformed with sodium channel blockers, this response could be due to the involvement of $Ca^{2+}$-dependent $K^+$ channels (stretch-activated channels) in the process of chondrocyte mechanotransduction (Wright, 1996).

In osteoarthritic chondrocytes has been suggested that the response of membrane depolarization is due to the autocrine / paracrine activity of soluble factors. *In vitro*, mechanical stimulation of chondrocytes at 0.33 Hz induces membrane hyperpolarization due to IL-4 (Millward-Sadler, 1999) with the consequent increase in aggrecan mRNA levels. Interestingly, in osteoarthritic condrocytes, membrane depolarization is induced by proinflammatory cytokine IL-1 (Salter, 2002). Altered mechanotransduction in OA may contribute to the response of the chondrocyte favoring ECM degradation and disease progression.

Moreover, osmotic fluctuations, in addition to the volume change in chondrocytes (Bush, 2005; Kerrigan, 2006; Lewis, 2011) involve the filamentous actin restructuring (Chao, 2006; Erickson, 2003). Similarly, the osmotic stimulation of chondrocytes increases cytosolic calcium concentrations with the consequent regulation of metabolism, cell volume, and gene expression (Liu, 2006; Hardingham, 1999). In this case, a possible candidate in the chondrocyte mechanotransduction is the transient receptor potential vanilloid 4 channel (TRPV4), a $Ca^{2+}$-permeable, nonspecific cation channel (Liedtke, 2000; Phan, 2009).

## 4. Anion channels

The anion channels are a membranal class of porin ion channel that allow the passive diffusion of negatively charged ions along their electrochemical gradient. These channels allow the flow of monovalent anions such as $I^-$, $NO_3^-$, $Br^-$, and Cl, however, these are known as ClC (Fahlke, 2001). The ClC constitute a large family of $Cl^-$ selective channels (Jentsch, 2002). In humans, have been described nine isoforms of ClCs. The first branch of this gene family encodes plasma membrane channels (ClC-1, -2, -Ka and -Kb) and others two branches (ClC-3, -4 and -5; ClC-6/-7) which encode for proteins found on intracellular vesicles (Jentsch, 2005).

In the plasma membrane, the main functions of ClCs are regulation cell volume and ionic homeostasis, transepithelial transport and excitability. Channels in intracellular organelles facilitate the exchange of anionic substrates between the biosynthetic compartments involved in acidification of vesicles in the endosomal pathway (Jentsch, 2002; 2007).

Different diseases have been associated with anionic channels. The loss of ClC-5 is related to Dent's disease (Lloyd, 1996), while the disruption of ClC-3, -6, or -7 in mice promotes the development of neurodegenerative disorders in the central nervous system (Kasper, 2005; Poët, 2006), and ClC-7 mutations have been related with osteopetrosis and lysosomal storage disease (Kasper, 2005; Poët, 2006).

### 4.1 ClC and chondrocytes proliferation

OA is a complex morphology reflect the severity of damage to articular structures. The histopathological parameters in OA include cartilage degradation with formation of

fibrocartilage, fissures, denudation with exposure, repair and remodeling of subchondral bone. In addition, chondrocytes suffer proliferation and apoptosis (Pritzker, 2006) (Fig. 1).

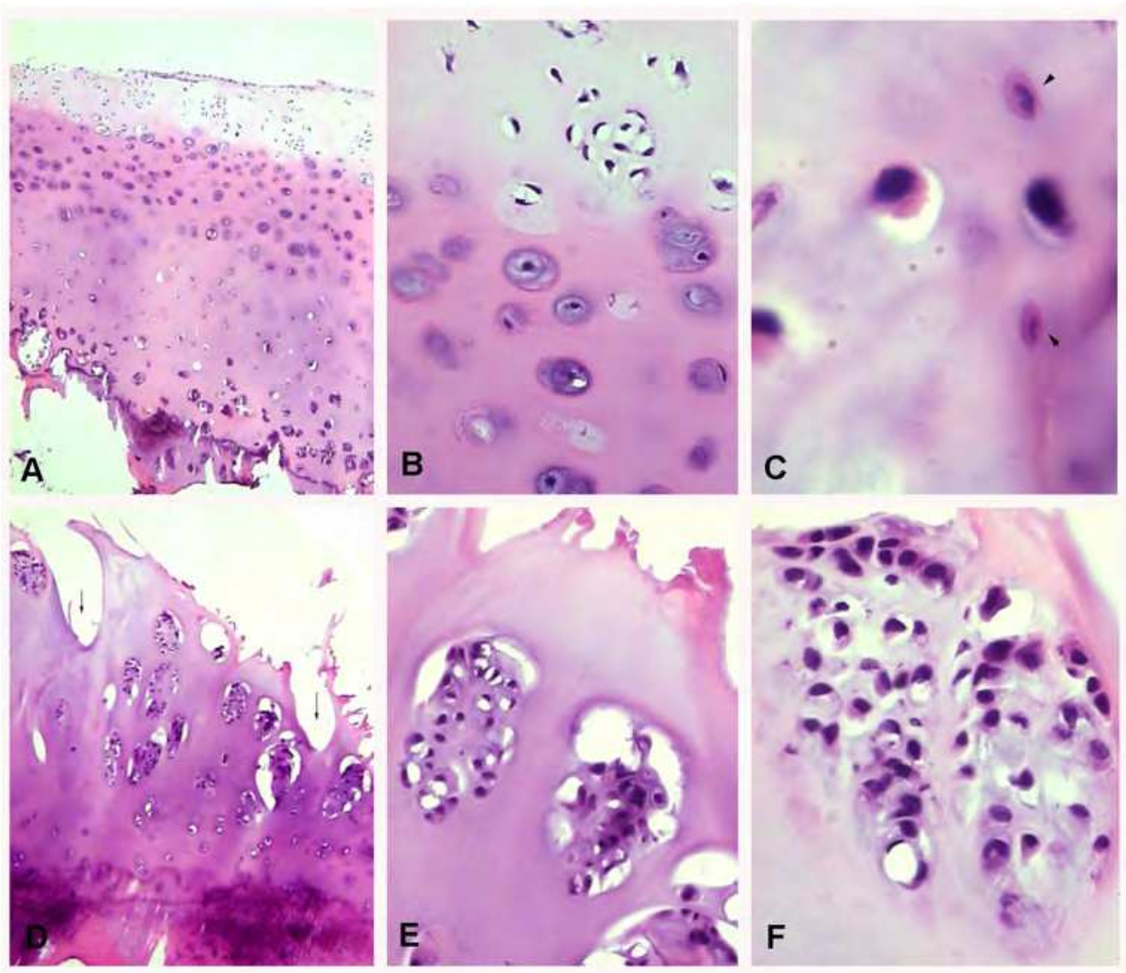



Fig. 1. OA cartilage morphology. A-B fibrillation zone, C apoptotic chondrocytes, D vertical fissures, E-F "clones" or chondrocytes aggregates. Hematoxylin and eosin staining. 10x, 20x and 40x.

This is a condition in which it was reported that the proliferative activity of chondrocytes is low compared with its absence in normal cartilage (Rothwell, 1973; Hulth, 1972). Apparently, the osteoarthritic chondrocytes have a greater access to proliferation factors due to alterations in the ECM (Lee, 1993). It is also possible that aggregates of chondrocytes or clones are a manifestation of the proliferative activity (Horton, 2005).

Moreover, apoptotic cell death is a mechanism widely described in association with OA (Blanco, 1998; Hashimoto, 1998a, 1998b; Kim, 2000; Kouri, 2000). The classic morphologic appearance of this process is characterized by fragmentation and nuclear condensation, and formation of apoptotic bodies (Aigner, 2002). In general, the response of osteoarthritic chondrocytes to the metabolic imbalance (Sandell, 2001), phenotypic modulation (Aigner, 1997) and cell death induces proliferation that compensate the cell loss and the demand of synthetic activity (Aigner, 2001; Rothwell, 1973; Hulth, 1972).

Processes such as proliferation and cell death have been linked to the involvement of ion channels. In this regard, it has been described the association between the activity of $K^+$ channels and the proliferation of Schwann cells and B lymphocytes (Deutsch, 1990), keratinocytes (Harmon, 1993), melanoma (Nilius, 1994), neuroblastoma and astrocytoma cells (Lee YS, 1993). It also has been associated intracellular free $Ca^{2+}$ concentration and cell proliferation (Wohlrab, 1998).

In chondrocytes, there are changes in the membrane potential of human chondrocytes in response to modulators of ion channels such as tetraethylammonium (TEA), 4-aminopyridine (4-AP), 4′,4′diisothiocyanato-stilbene-2,2′-disulfonic acid (DIDS), 4-acetamido-4′-isothiocyano-2,2′-disulfonic acid (SITS), verapamil and lidocaine. About this, it was reported an increase in DNA synthesis with lidocaine and 4-AP after 12 days in chondrocytes culture (Wohlrab, 2002). Moreover, the exposure of chondrocytes to high concentrations of SITS induced necrosis while that the use of 4-AP caused cytotoxic effects and suppression of proliferation on the same system (Wohlrab, 2004).

### 4.2 CLIC proteins

The chloride intracellular channel (CLIC) proteins belong to the glutathione S-transferase (GST) superfamiliy and these are group of proteins with possible role of anion channels. However, they differ from classical GSTs because they contain an active site with cysteine residue, reactive for the protein itself and not through a thiol group (Littler, 2010). The CLICs are proteins highly conserved in vertebrates and these are referred to as CLIC1–CLIC6.

These proteins are present in soluble and membrane-inserted form. CLICs have been reported in membranous organelles, cytoplasmic and vesicular compartments and the nucleus (Valenzuela, 1997; Duncan, 1997; Chuang, 1999). The functions of CLICs include pH-dependent ion channel activity (Tulk, 2002; Littler, 2005) and enzymatic which likely to involve a glutathione (GSH) related cofactor (Littler, 2010). They could also be involved in maintaining the structure of intracellular organelles and their interaction with cytoskeleton proteins (Singh, 2007).

Functions of CLICs reported in the musculoskeletal system involve these proteins in the acidification processes in bone resorption (Edwards, 2006; Schlesinger, 1997). Despite their involvement in different systems with activities of ClC, has not been possible to attribute the channel protein function permanently.

CLICs proteins are implicated in cell cycle regulation, cell differentiation, and apoptosis. Specifically, CLIC4 has been linked to apoptosis and differentiation of fibroblasts into myofibroblasts (Fernandez-Salas, 2002; Ronnov-Jessen, 2002). In addition, it was reported that CLIC3 interacts with ERK7, a mitogen-activated protein kinase, allowing the regulation of the phosphatases or kinases (Qian, 1999).

### 4.3 CLIC6 protein

CLIC6 consist of 704 aminoacids with decapeptide repeats (Friedli, 2003) and and reportedly bind to the dopamine D(2)-like receptors (Griffon, 2003). It is also suggested that CLIC6 could be involved in the regulation of water and secretion of hormones (Nishizawa, 2000).

In chondrocytes, recently, we reported the identification of CLIC6 protein from proteomic analysis of rat normal articular cartilage (Perez, 2010). In human cartilage obtained from total knee arthroplasty, we found immunoreactivity for CLIC6 protein largely restricted to the aggregates of chondrocytes (clones or clusters) in the superficial zone (Fig. 2).

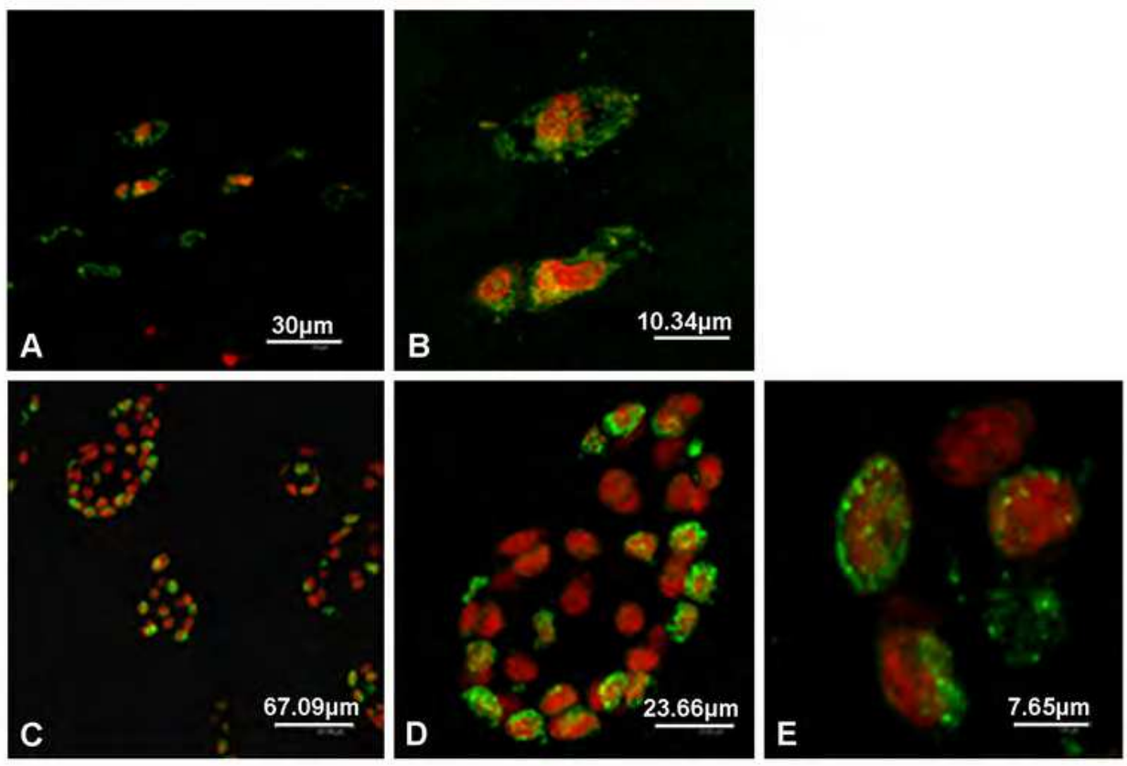



Fig. 2. CLIC6 immunostaining of NoAC and OAC. A-B Surface zone (NoAC), C-E Chondrocytes clusters (OAC). The anti-CLIC6 antibody was coupled to FITC (fluorescein-5-isothiocyanate) and the nucleus were counterstained with propidium iodide.

Immunolabelling was arranged in a coarse granular pattern located in the cytoplasm of most chondrocytes. Comparatively, chondrocytes of non osteoarthritic human articular cartilage (NoAC) showed scarse immunoreactivity predominantly in cells of superficial zones (unpublished data).
Although controversial, the formation of cell clusters in osteoarthritic cartilage (OAC) has been considered an event of repair and regeneration (Horton, 2005). However, electrophysiological and molecular investigations are required to define role of the CLIC6 protein on healthy and osteoarthritic chondrocytes.

## 5. Conclusion

The pathogenesis of OA includes homeostatic alterations that induce imbalance in the anabolic and catabolic processes. These have been associated with changes in the viability and chondrocytes proliferation. Previous studies have showed a low proliferative activity of OAC. However, the arrangement of the chondrocytes in groups (clones), a hallmark of OA, could possibly be considered a sign of proliferation.
CLIC6 protein expression in normal articular cartilage of rat, and immunolocalization in chondrocytes clusters removed from patients with OA, could suggest the involvement of this anion channel in the pathophysiologic processes of disease.

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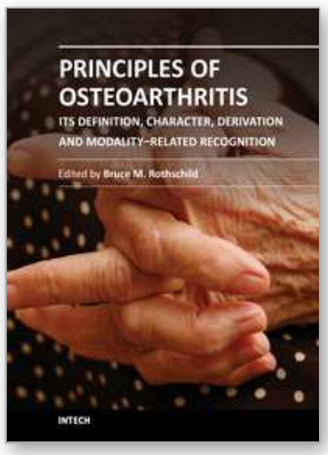
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**Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition**

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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