# Magnesium and connective tissue

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# Magnesium and connective tissue

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Summary

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**Summary :** Magnesium ($Mg^{2+}$) is the fourth most abundant cation and the second most abundant **intracellular** cation in vertebrates. Magnesium plays a critical role in cellular functions such as: -- Cell adhesion via integrins on various macromolecular substrats. -- Cell migration -- DNA transcription and protein synthesis

**Pictures**

ARTICLE

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The cells which constitute tissue of vertebrates are in charge of the synthesis and remodelling during the life of the four extracellular macromolecules contained in the connective tissue. Magnesium stimulates collagen synthesis expressed by fibroblasts in culture. Magnesium inhibits prolyl and lysyl hydroxylases and could be considered as antifibrotic. Magnesium is associated with elastin and plays a protective role in maintaining the extensibility of elastin. Magnesium associated proteoglycans in cartilage prevent the swelling and degradation of this tissue. Magnesium regulates the functional activity of integrins. This non exhaustive list of some properties linked to magnesium makes it a potential leader in physiological and pathological situations which occur at the level of the connective tissue and also at the level of the matrix associated cells.

## Magnesium and connective tissue

Magnesium ($Mg^{2+}$) is the fourth most abundant cation and the second most abundant intracellular cation in vertebrates. The normal adult total $Mg^{2+}$ content is estimated at 25g (for 70 kg body weight) of which about 53% is found in bone [1]. Magnesium plays an essential role in a wide range of biological processes and is crucial for life. $Mg^{2+}$ is essential for many enzymatic reactions and develops two interactions (table I): (1) $Mg^{2+}$ binds to the substrate thereby forming a complex with which the enzyme interacts, for example enzymes that utilize ATP do so with Mg ATP, and (2) $Mg^{2+}$ binds to the enzyme and plays an allosteric activator role [2]. Furthermore Mg is critical for some cellular functions such as DNA transcription and protein synthesis [3]. Extracellular $Mg^{2+}$ accounts for about 1% of total $Mg^{2+}$ content [4]. The distribution of $Mg^{2+}$ in the body shows that about 53% of $Mg^{2+}$ is present in the skeleton and 46% in soft tissues, in other words 99% of $Mg^{2+}$ is associated with the connective tissue [5] (table II). Extracellular matrix is a complex integrated system responsible for the biological and mechanical properties of our tissues. The extracellular matrix is in constant remodelling and tissue homeostasis is a dynamic process involving a balance between protein synthesis and degradation. Cells, which constitute the tissues of vertebrates, are in charge of the synthesis and renewal of the four extracellular macromolecules which compose the connective tissue: two fibrillar components, collagens and elastin and two other families of macromolecules which do not belong to the fibrillar component, namely proteoglycans and structural glycoproteins.

**Table I.** Example of the role of magnesium in enzymatic reactions

| **Binding to the substrate**<br>**Enzyme substrate ATP Mg, GTP Mg** |
|---|
| ATPase |
| Kinase |
| Cyclase |
| **Enzyme activation** |
| Adenylate cyclase |
| Creatinine kinase |
| Lipoprotein lipase |
| Phospholipase C |

Nb: This list is not exhaustive.

**Table II.** Distribution of magnesium in the Body

| **Tissue or organ** | **% of total body Mg** |
|---|---|
| Muscle | 19 |
| Non mineralized tissue | 27 |
| Bone | about 53 |

From Elin [5] 1987

## Collagens and magnesium

The connective tissue exists in a wide variety of specialized forms; the most abundant and ubiquitous element of the extracellular matrix is the collagen family. Among this family, the classical fibrous collagens (types I, II, III, and V) are found in greatest amounts and type I collagen is quantitatively the most important [6]. The biosynthesis of the collagen molecule is a complex process with intra and extracellular phases. Intracellularly the principal events are the hydroxylation of prolyl and lysyl residues on the one hand and the glycosylation of hydroxylysyl residues on the other. They are caused by the actions of hydroxylases and glycosyl transferases [7]. It has been reported that hydroxy prolyl residues are essential for the folding and stabilization of the newly synthesized procollagen polypeptide chain into the triple helical conformation. Prolyl hydroxylase is a target for pharmacological modulation as a potential means of control fibrotic diseases in which collagen is over produced [8]. Chinese authors [9] screened several Chinese medicinal herbs for the presence of antifibrotic agents. An aqueous extract of Salvia *miltorrhizae* Radix was found to inhibit collagen secretion by human skin cultured fibroblasts, but DNA and non collagenic protein synthesis were unaffected. They identified the inhibitory activity as magnesium lithospermate. This compound decreased by about 50% the extent of Prolyl and Lysyl hydroxylations in collagen. Furthermore Magnesium lithospermate given orally to mice led to a significant reduction of prolyl hydroxylation in newly synthesized skin collagen. The authors concluded that magnesium lithospermate could be used beneficially in the treatment of fibrotic diseases such as scleroderma and keloid lesions.

It has been shown that ascorbic acid stimulates collagen synthesis in dermal fibroblasts by increasing the rate of collagen gene transcription, but unfortunately experiments involving the use of ascorbic acid require daily supplementation of this molecule [10] due to its instability. Geesin [11] and co-workers have reported that magnesium ascorbyl 2 phosphate was equivalent to ascorbic acid in stimulating collagen synthesis even after nine days of culture, owing to its great stability.

## Proteoglycans and magnesium

The collagen fibers form a network which appears to be formed by individual fibers interacting with neighboring fibers via other matrix constituents. Small leucine rich proteoglycans, also named decorans [12] have interesting functions. For example decorin have been shown to bind to fibril forming collagens in vitro and to inhibit the formation of collagen fibers [13]. Decorin

and fibromodulin have been demonstrated localized over the collagen fibers, and one function of these molecules may be to provide a coat to favor interaction with other collagen fibrils [14]. One of the main functions of proteoglycans decorin and biglycan is to bind TGFβ via their protein core [15] thus they can serve as a reserve for growth factors in order to release them when the proteoglycans are degraded. It is known that TGFβ is a key mediator of extracellular matrix accumulation in sclerotic kidney disease due to responding mesangial cells. It has been reported [16] that decorin can disrupt TGFβ/smad dependent transcriptional events in human mesengial cells, $Mg^{2+}$ could be active at the level of protein kinase II.
The cartilage is a highly specialized connective tissue, essentially avascular, the main matrix components are type II collagen and large aggregating proteoglycans (aggrecan), not binding covalently to hyaluronic acid and forming a macromolecular complex with a relative mass exceeding $3\ 10^6$kDa. Hyaluronan-aggrecan complex forms a domain with high charge density and therefore high osmotic pressure. The principal function of this complex is to provide resistance to compression of the cartilage. In disease, turn over of aggrecan may be accelerated due to proteolytic cleavage of the molecule by the enzyme like matrix metalloproteinase stromelysin [17]. Swelling is associated with increased degradation of proteoglycans and these effects are prevented by divalent cations, particularly $Mg^{2+}$ as demonstrated by Campo [18]. It has been reported [19] with cultured chondrocytes in magnesium deficient media that glycosaminoglycan synthesis was reduced. Thus we can propose that magnesium maintains the structure and function of the cartilage.

## Elastin and magnesium

Elastic recoil is a critical property of several tissues and organs; such as lungs, aorta, and skin... Elastic fibers are found in the extracellular matrix of the connective tissue providing elasticity and resilience to tissue which have the ability to deform repetitively and reversibly. Elastic fibers are made of two major components: elastin and microfibrils [20]. Deposition of tropoelastin (soluble elastin) into the extracellular space occurs at specific sites on the cell surface, then tropoelastin is incorporated into the forming elastic fiber. Before elastin deposition into the extracellular space, microfibrils are secreted. It was suggested that the microfibrils are a scaffold upon which elastin is deposited and thus directs the form of the growing fiber [21]. The highly conserved C-terminus domain of tropoelastin is necessary for a correct elastic fibre formation. The binding site between the microfibrillar protein, MAGP-1, and tropoelastin has been localized at the C-terminus of tropoelastin [22]. It is still unknown how the other microfibrillar proteins contribute to elastin fibrillogenesis. It has been reported that $Mg^{2+}$ is associated with the elastin core of elastic fibers and not with the associated microfibrils namely oxytalan fibers [23]; and that $Mg^{2+}$ plays a protective role in maintaining the extensibility of elastin [24]. Elastin degradation is extensive in many physiological processes such as growth, wound healing, and tissue remodeling [25]. Furthermore inappropriate elastolysis can be destructive particularly in arterial pathologies such as atherosclerosis in which elastolysis can be enhanced by lipids [26]. Interestingly it has been shown that increased elastolytic activities are connected with the severity of atherosclerosis and that enzymatic hydrolysis of aortic elastin is significantly increased by cholesterol and by magnesium [27]. So it appears that $Mg^{2+}$ is active in maintaining the structure and mechanical properties of elastic fibers and it is also actively involved in elastic fiber elastolysis.

## Glycoproteins and magnesium

Most of the proteins of the extracellular matrix can bind to specific transmembrane receptors belonging to a superfamily of cell surface proteins named integrins [28]. Integrins are α-β heterodimeric glycoproteins, both chains of which are transmembrane polypeptides. α subunits appears to be involved in both divalent cation ($Ca^{2+}$, $Mg^{2+}$) dependent ligand recognition and interaction with cytoskeleton [29]. During wound healing directed migration of keratinocytes and fibroblasts is a fundamental prerequisite. Cation dependent affinity changes of integrins involved in cell adhesion on extracellular matrix components were shown to be implicated in driving cell migration. So it has been reported that the adhesion of keratinocytes and fibroblasts to type I collagen and to laminins (glycoproteins located in basement membrane) was enhanced by $Mg^{2+}$ in a concentration dependent manner, while $Ca^{2+}$ antagonized this effect [30, 31]. Integrin expression at the cell surface was not modified, and it was suspected that divalent cation dependent conformational changes of integrins regulate their functional activity. Recently co-localisation of integrins and matrix metalloproteinases (MMPs) in the extracellular matrix of cultured chondrocyte was reported [32]. A specific co-localisation of β1 integrins and MMP-1, MMP-3 and MMP-9 has been evidenced on the chondrocyte cell surface, in the pericellular space and between collagen fibrils in the extracellular matrix in cartilage. The function and origin of integrins in the cartilage and the functional significance of the association between MMPs and β integrins in cartilage is not known. Some years ago a competition was reported between $Ca^{2+}$ and $Mg^{2+}$ for binding to and regulating the activities of two gelatinases (totally or partially inhibited by EDTA) present in the sea urchin embryo [33]. If $Mg^{2+}$ is able to modulate matrix metalloproteinase activity in the vicinity of the cell and induce the conformational changes of integrins, the association between integrins and MMPs could favour cell migration. This non exhaustive list of some properties linked to magnesium make it a potential leader in physiological and pathological situation, which occur at the level of the connective tissue macromolecular components and also at the level of the matrix associated cells.

## Conclusion

Magnesium ($Mg^{2+}$) one of the most abundant cations in vertebrates was shown to be involved in fundamental cellular functions such as adhesion migration and also in protein synthesis (figure 1). Interestingly $Mg^{2+}$ is associated with elastin and collagen, two fibrillar components of the extracellular matrix, and also with non fibrillar macromolecules namely proteoglycans and glycoproteins. The cells which constitute the connective tissue are in constant dialogue with the extracellular matrix components. Due to $Mg^{2+}$ functions with cells and on extracellular macromolecule structuring, $Mg^{2+}$ can be considered a pivotal actor in tissue homeostasis.

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