Proteoglycans with an E-unit structure

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1. What are proteoglycans?

Proteoglycans (PGs), such as collagen and hyaluronic acid, are important components of the extracellular matrix and are widely distributed in connective tissues, such as cartilage, skin, ligaments, and basement membranes[1].

The function of PGs is usually lubrication and buffering, due to its water retention ability, but in recent years, various other functions have been elucidated.

The structure of PGs consists of a core protein (proteo) to which many polysaccharides (glycans) are bound, but in the case of animal PGs, amino sugars (glycosaminoglycans) are bound as polysaccharides (glycans) to the core protein (proteo).

In Japan, PGs have been attracting attention since the 1970s, but they can only be obtained from limited parts of mammals (such as bovine tracheal cartilage and chicken combs). Therefore, they are very expensive, and practical applications are far from being achieved. In 1998, the mass extraction of PGs with C-unit structures from salmon nasal cartilage (salmon head) enabled significant cost reductions, resulting in many health food and cosmetic products being launched on the market[2),3)]. In 2017, highly functional PGs with E-unit structures were extracted from squid orbital cartilage, and PGs have since attracted increasing attention.

2. Differences in unit structures of PGs

The molecular structure of animal PGs is not uniform, but rather, there are various structures depending on the types of core proteins and amino sugars and their bonds. The chondroitin sulfate structure, which is a representative glycosaminoglycans, is a structural component that determines the diverse functions of PGs. In other words, the basic structure comprises a unit (disaccharide) of the N-acetylgalactosamine (GalNAc) and the glucuronic acid (GlcA), which are bonded in a chain shape.

Furthermore, there are PGs with an A-unit structure in which a sulfate group is bound to

the 4th position of GalNAc, PGs with a C-unit structure in which a sulfate group is bound to the 6th position, and PGs with an E-unit structure in which a sulfate group is bound to both the 4th and 6th positions[4),5)] (Figure 1 and Table 1).

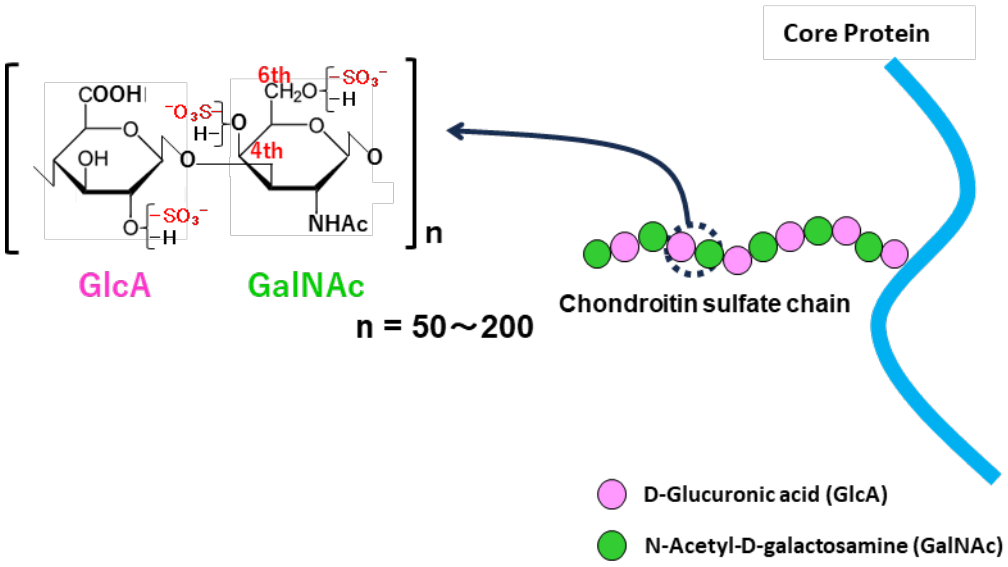

Figure 1. Chondroitin sulfate structures in proteoglycans

Table 1. Proteoglycans with various unit structures

Type	Position of sulfate group in the disaccharide	Origin
A-unit structure	GlcA-GalNAc (sulfation at the 4th position)	Bovine tracheal cartilage, Chicken comb
C-unit structure	GlcA-GalNAc (sulfation at the 6th position)	Shark cartilage, Salmon nasal cartilage
E-unit structure	GlcA-GalNAc (sulfation at the 4th and 6th positions)	Squid orbital cartilage

The length of the disaccharide chain is 50 to 200 units, and the sulfate group bonds are nonuniform. In other words, PGs are diverse molecules due to the mixture of various unit structures. This is a major difference from DNA and RNA, which have uniform sequences.

3. Mechanisms of action of PGs

PGs are present in many organs and are known to regulate various physiological activities through chondroitin with various unit structure. In other words, they are thought to interact with various physiologically active factors, such as cell growth factors[6),7)], cell differentiation factors[7)], and cell adhesion factors[8)], and exert various functions, such as cell proliferation, tissue formation, and organ formation.

PGs with an E-unit structure, in which two sulfate groups are bonded, are thought to have special functions, and they have been reported to be involved in promoting neurite outgrowth[9)], angiogenesis, and cancer metastasis[10)].

4. Action of chondroitin with the E-unit structure

Chondroitin with an E-unit structure ("E-unit structure chondroitin") is extracted from squid orbital cartilage. Its extraction rate is 2%, making it a very rare ingredient. In addition to being significantly more physiologically active than chondroitin with A, C-unit structures ("A, C-unit structure chondroitin"), it has been found to have many useful functions not seen in chondroitin with other unit structures. These functions include (1) strengthening cartilage, bones, and joints; (2) anti-inflammatory effects and joint pain relief; (3) promoting male hormone and insulin secretion; and (4) nerve cell elongation.

(1) Strengthening cartilage, bones, and joints

E-unit structure chondroitin promotes the production of (1) bone morphogenetic protein (BMP) and osteocalcin (OCN) which are cartilage and bone formation hormones and (2) collagen and hyaluronic acid, thus strengthens cartilage, bones, and joints[11)-14)]. These hormones are secreted by osteoblasts. This function is only seen in E-unit structure chondroitin (Figures 2 and 3).

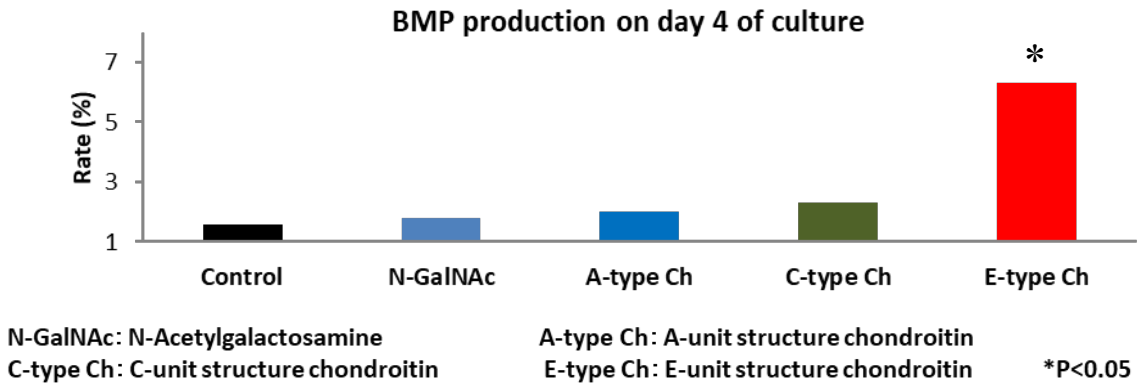

Figure 2. Production of bone morphogenetic proteins (BMPs) by chondroitins with various unit structures

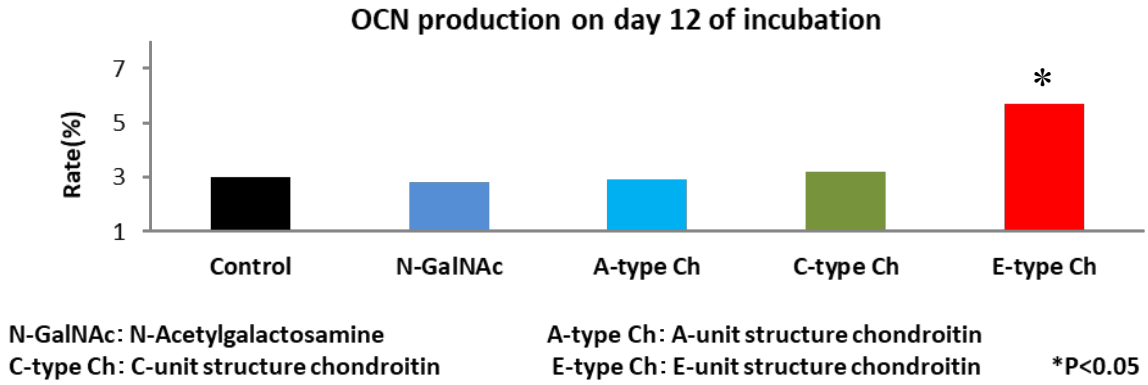

Figure 3. Production of osteocalcin (OCN) by chondroitins with various unit structures

(2) Anti-inflammatory effects and joint pain relief

E-unit structure chondroitin (1) seizes the inflammatory factor midkine (MK)[15),16)], (2) suppresses the attacking factor TGF-β[17)], (3) improves immune parameters (Th1/Th2 cell ratio)[18),19)], and (4) cleaves CD44[8)], thereby suppressing inflammation and relieving joint pain. These effects have only been observed for E-unit structure chondroitin (Figures 4 and 5).

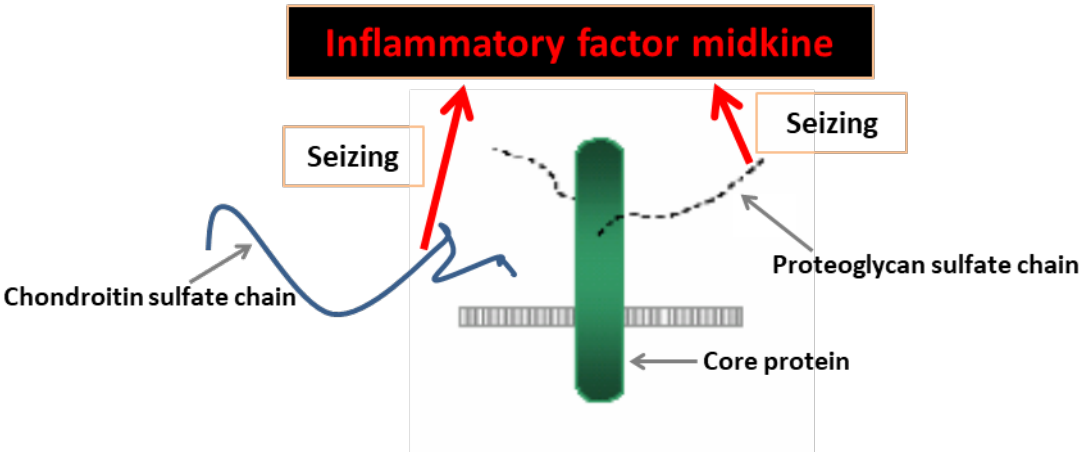

Figure 4. Seizing of the inflammatory factor midkine (MK)

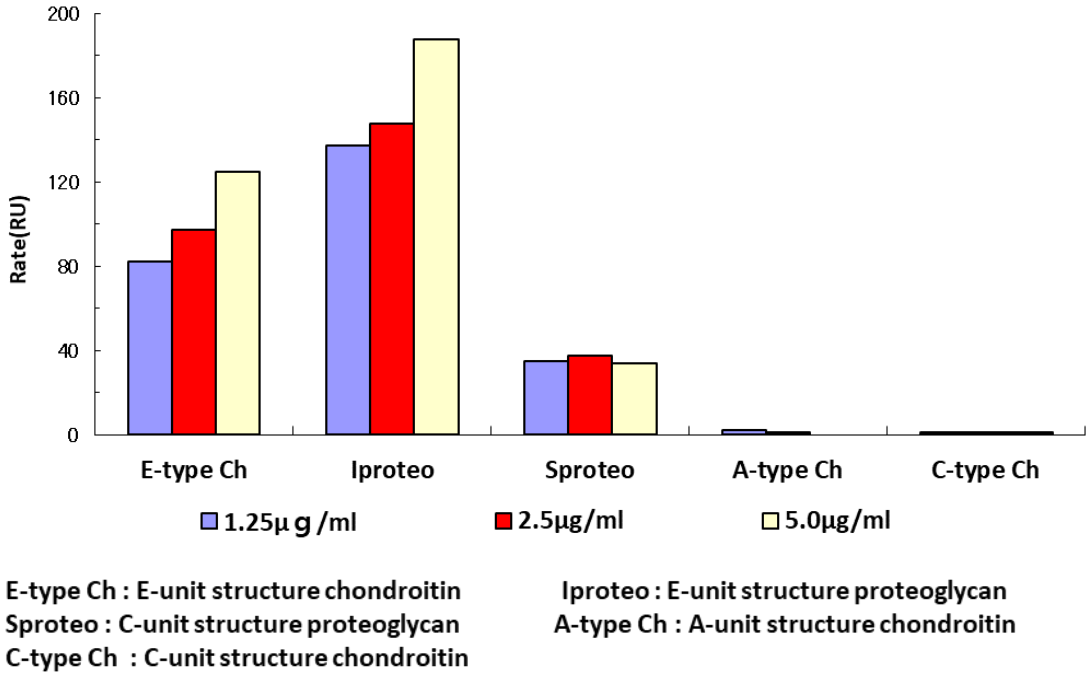

Figure 5. Seizing of midkine (MK) by proteoglycans (PGs) and chondroitins with various unit structures

(3) Increase in testosterone and insulin by OCN

Recently, it has been reported that OCN increases the secretion of testosterone (male hormone)[20] and insulin[21)-23)]. E-unit structure chondroitin also increases the secretion of testosterone and insulin by promoting the production of OCN. Only E-unit structure chondroitin significantly increases testosterone and insulin production[24] (Figures 6 and 7).

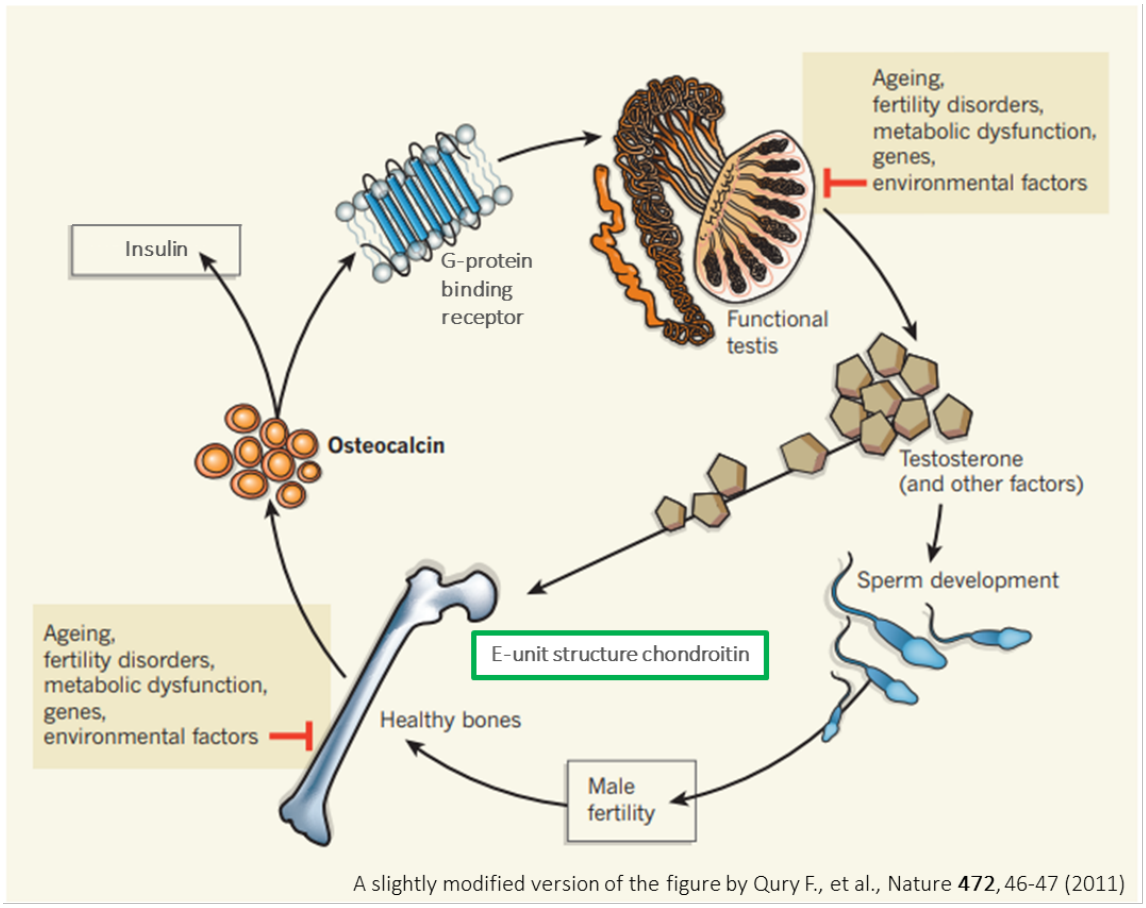

Figure 6. Action of E-unit structure chondroitin

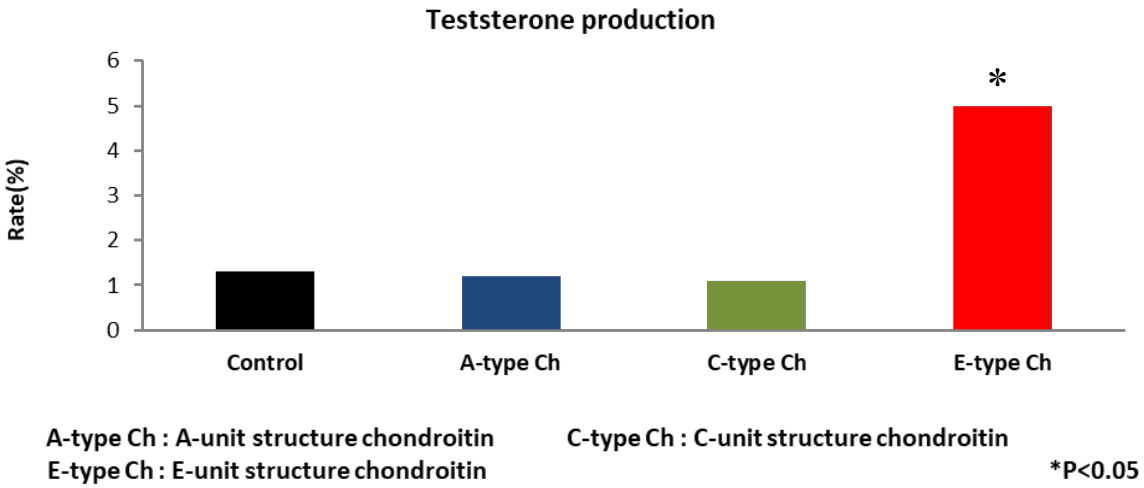

Figure 7. Testosterone production by chondroitins with various unit structures

Insulin acts on osteoblasts to first produce inactivated OCN. This OCN is then activated by osteoclasts, and activated OCN acts on pancreatic β cells to increases insulin secretion. E-unit structure chondroitin increases the secretion of OCN, which increases insulin (Figure 8). This effect is only observed for E-unit structure chondroitin.

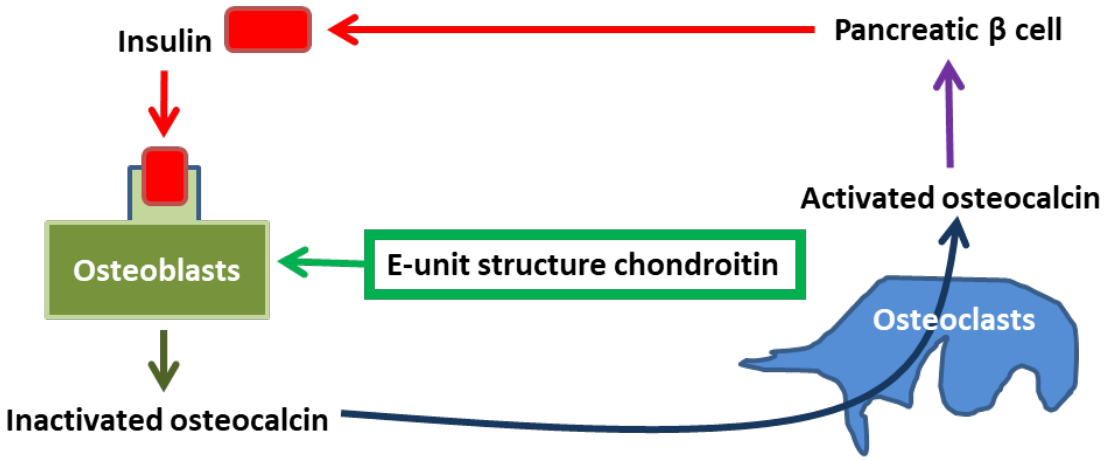

Figure 8. Insulin secretion by Osteocalcin (OCN)

(4) Elongation of nerve cells

E-unit structure chondroitin has also been shown to promote the elongation of nerve

processes in nerve cells[25),26)]. This action repairs central nervous system damage and is expected to improve memory, prevent dementia, and improve eyesight[27)]. This action has only been observed for chondroitin with an E-unit structure.

5. Conclusions

The reason why E-unit structure chondroitin has higher physiological activity than other-unit structure chondroitin is thought to be due to its polysulfide structure. Unlike C-unit structure chondroitin (shark-derived) and A-unit structure chondroitin (pork-derived), which have only one sulfate group on N-acetylgalactosamine, E-unit structure chondroitin which has two sulfate groups on N-acetylgalactosamine, is thought to bind to various proteins and exhibit important physiological activity in humans.

In addition, the daily dosage of C-unit structure chondroitin in pharmaceuticals, functional foods, and health foods for "relieving joint pain" varies, but is usually 1,000 mg to 1,500 mg[28)]. Meanwhile, the daily dosage of C-unit structure PG is 5 mg[29)]. In other words, C-unit structure PG is more active than C-unit structure chondroitin.

Furthermore, as mentioned above, the daily dosage of C-unit structure chondroitin is high, but the daily dosage of E-unit structure chondroitin is 150 mg to 250 mg, and it is effective with a small amount[30),31)].

Therefore, E-unit structure PG is expected to be higher effective than other PGs against symptoms other than inflammation and joint pain, and further research is expected to further clarify their effects.

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