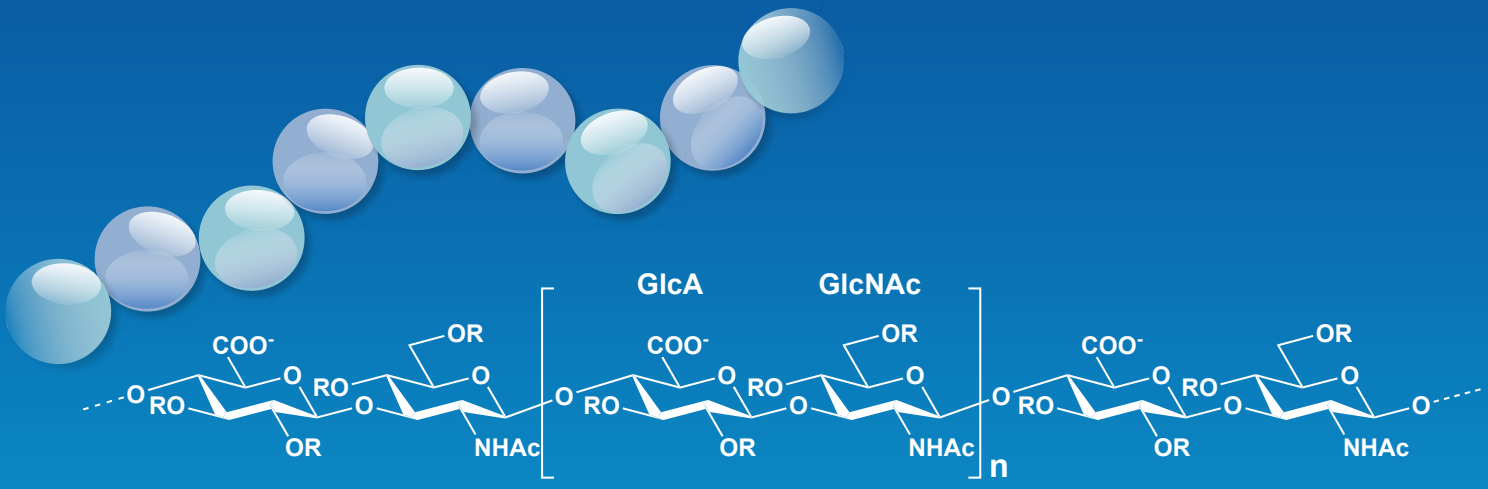
LIFE SCIENCE

Sulfated Hyaluronic Acids
—Cell Culture Applications—

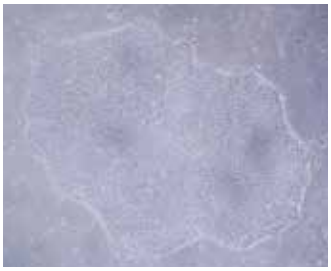


R = H or SO_3^-

Hyaluronic Acid, High-Sulfated 10mg [H1739]
Hyaluronic Acid, Low-Sulfated 10mg [H1740]

Maintaining the undifferentiated state of hiPS cells

Differentiated (control)



Undifferentiated (Hyaluronic Acid, High-Sulfated)

Sulfated hyaluronic acid maintains the undifferentiated state of hiPS cells under feeder-free and FGF2-free conditions.[1)]

These data were kindly provided by Prof. Shoko Nishihara and Dr. Taichi Miura, Soka University.

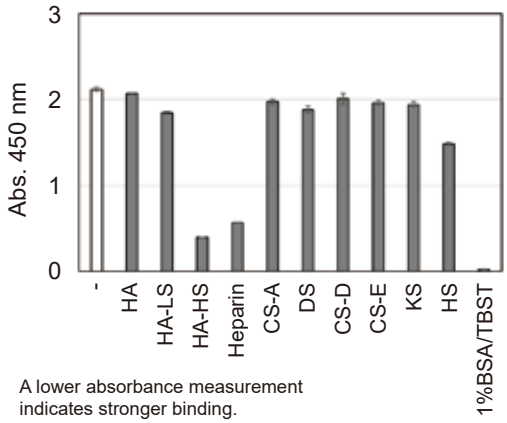
We offer Sulfated Hyaluronic Acids prepared by chemically modifying hyaluronic acid with sulfate groups. The degree of this sulfation is controllable by adjusting the reaction, allowing us to offer two separate products with differing sulfation degrees currently, both of which are animal-derived component free. Recent studies have revealed that our sulfated hyaluronic acids can protect growth factors from degradation and demonstrate functions similar to heparin. Given these properties, the development of novel applications of sulfated hyaluronic acids within the wide variety of fields such as cell culture, tissue engineering and regenerative medicine are to be expected in the coming years.

This work was supported by Saitama Prefecture's New Technology and Product Commercialization Costs Subsidy in 2016.

Glycosaminoglycans (GAGs) are important polysaccharide components of the extracellular matrix found both within tissues as well as on the surface of cells. Hyaluronic acid, one of the GAGs, is found in the body in an unbound form, and comprises repeating disaccharide units of glucuronic acid (GlcA) and *N*-acetylglucosamine (GlcNAc). GAGs such as heparin have sulfate groups and physically interact with growth factors and other various functional molecules. Heparin binds to FGF2 to both protect it from degradation and stimulate receptor binding, resulting in physical responses including cell proliferation.[2)] Hyaluronic acid itself does not contain sulfate groups, however our artificially sulfated hyaluronic acids have been found to possess various functions.

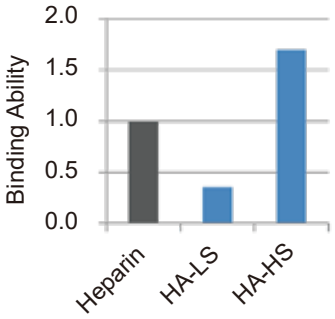
Binding of Sulfated Hyaluronic Acids to FGF2

Binding of Various GAGs to FGF2 (Competitive ELISA)



A lower absorbance measurement indicates stronger binding.

Evaluation of sulfated hyaluronic acid binding to FGF2

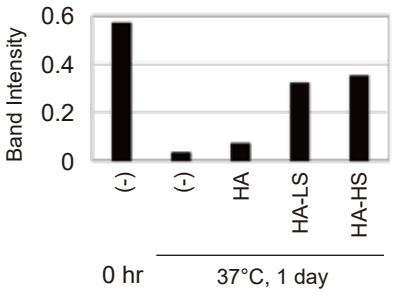


The FGF2 binding ability of heparin and sulfated hyaluronic acids was evaluated competitively and normalized to that of heparin.

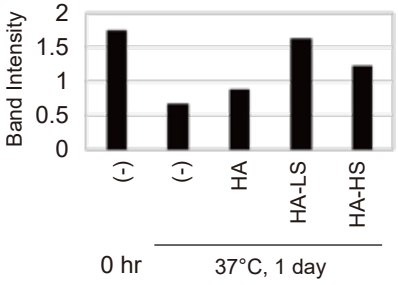
Low-sulfated hyaluronic acid showed weaker, and highly sulfated hyaluronic acid showed stronger binding to FGF2 than heparin.

Protection of FGF from Degradation by Sulfated Hyaluronic Acids

FGF1



FGF2



An Example of Protective Effects on Each Protein

	FGF1	FGF2	KGF	BMP2	IL-6
HA	—	—	—	—	—
HA-LS	++	++	+	+	—
HA-HS	++	+	+	—	+

Left: The ability of each sulfated hyaluronic acid to stabilize FGF1 and FGF2 was examined by mixing each pair together and incubating.
This data shows that sulfated hyaluronic acid protects unstable FGF from degradation.

HA: Hyaluronic Acid
HA-LS: Hyaluronic Acid, Low-Sulfated
HA-HS: Hyaluronic Acid, High-Sulfated

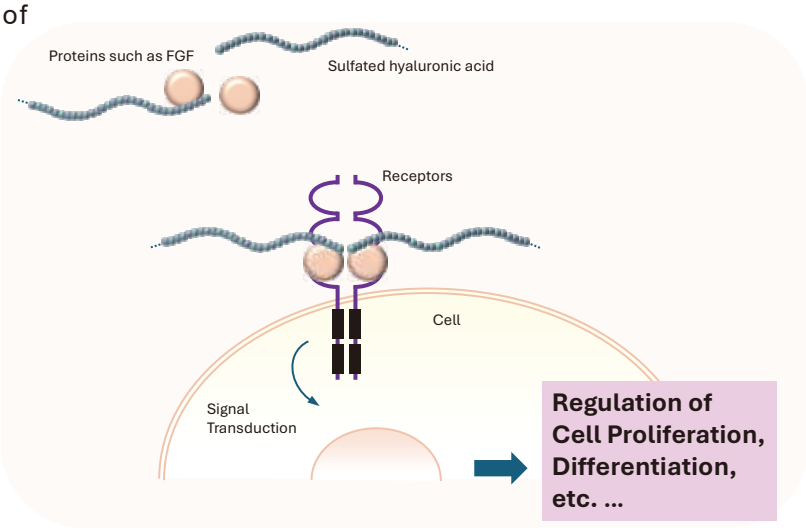
Examples of Applications of Sulfated Hyaluronic Acids

Prof. Shoko Nishihara, Dr. Taichi Miura, *et al.* of Soka University successfully cultured human iPS cells in an undifferentiated state under feeder-free and FGF2-free conditions through the addition of highly sulfated hyaluronic acid to their cell culture medium (see photographs on first page). Their study showed that highly sulfated hyaluronic acid promotes FGF2 signaling in human iPS cells.[1)]

In addition, a more recent study revealed that administration of FGF1 in combination with highly sulfated hyaluronic acid ameliorates radiation-induced intestinal damage, and highly sulfated hyaluronic acid, unlike heparin, only possesses a weak anti-coagulant effect. These results suggest that highly sulfated hyaluronic acid may be a promising radioprotective agent with a low risk of hemorrhage which will be a problem in the combination of FGF1 and heparin (reported by Dr. Fumiaki Nakayama, Group Leader, and Dr. Taichi Miura of the Regenerative Therapy Research Group, Department of Radiation Regulatory Science Research, National Institute of Radiological Sciences (NIRS), and the Institute of Glycotechnology of Tokyo Chemical Industry Co., Ltd. (TCI)).[3)]

Sulfated hyaluronic acids have also been found to inhibit hyaluronidase, an enzyme that degrades hyaluronic acid.

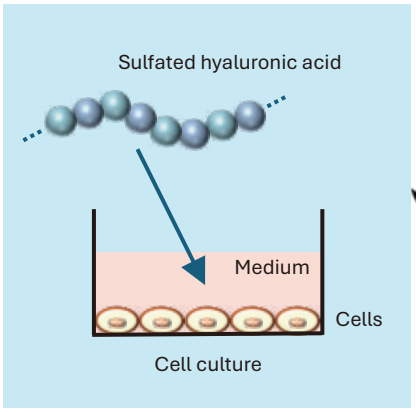
Furthermore, it has been reported that sulfated hyaluronic acids inhibit the activity of heparanase, an enzyme that cleaves heparan sulfate and macromolecular heparin and which is essential for cancer cell invasion. It was also shown that highly sulfated hyaluronic acid inhibited heparanase-mediated extension protrusion of cancer cells in a 3D-culture system.[4)]



Hypothesized Model of Action of Sulfated Hyaluronic Acid

Future Outlook

Given these various functions, our sulfated hyaluronic acids show potential to be used as alternatives for sulfated polysaccharides in various fields such as large-scale cell culture, regenerative medicine, wound healing, and cancer therapy.

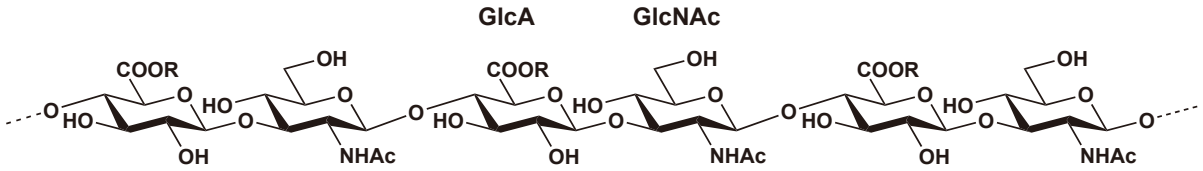


As an animal-derived component free biomaterial which enhances FGF activity to regulate cell differentiation and proliferation

- As an additive to cell culture medium
- For industry applications that require sustainable large-scale cell culture
- As a heparin alternative
- Applicable to developmental biology, bioengineering, animal cell engineering
- To aid physiological processes that require tissue repair such as wound healing
- In regenerative medicine, including regeneration of skin and teeth

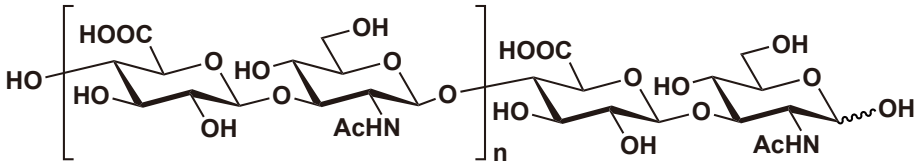
Related Products

Hyaluronic Acids



R=H	**Hyaluronic Acid** from Bacteria	1g **[H1807]**
R=Na	**Hyaluronic Acid Sodium Salt** from Bacteria	100mg / 1g **[H1791]**
R=K	**Hyaluronic Acid Potassium Salt** from Bacteria	1g **[H1808]**
R=H	**Hyaluronic Acid** from Cockscomb	1g **[H0595]**
R=Na	**Hyaluronic Acid Sodium Salt** from Cockscomb	100mg / 1g **[H0603]**
R=K	**Hyaluronic Acid Potassium Salt** from Cockscomb	1g **[H0652]**

Oligo Hyaluronic Acids: $[GlcA\beta(1\text{-}3)GlcNAc\beta(1\text{-}4)]_n\text{-}GlcA\beta(1\text{-}3)GlcNAc$



n=1	**Hyaluronate Tetrasaccharide**	1mg / 5mg **[H1284]**
n=2	**Hyaluronate Hexasaccharide**	1mg / 5mg **[H1285]**
n=3	**Hyaluronate Octasaccharide**	1mg **[H1148]**
n=4	**Hyaluronate Decasaccharide**	1mg **[H1149]**
n=5	**Hyaluronate Dodecasaccharide**	1mg **[H1666]**

Other Glycosaminoglycans

Heparin Sodium Salt from Hog intestine	100mg / 1g **[H0393]**
Chondroitin Sulfate Sodium Salt	25g / 100g **[C0335]**
Dermatan Sulfate Sodium Salt	20mg / 100mg **[D3672]**

Abbreviations and Synonyms

FGF: Fibroblast Growth Factor
FGF1: acidic FGF (aFGF)
FGF2: basic FGF (bFGF)
KGF: Keratinocyte Growth Factor (FGF7)
BMP2: Bone Morphogenetic Protein 2
IL-6: Interleukin-6
CS: Chondroitin Sulfate
KS: Keratan Sulfate
HS: Heparan Sulfate

References

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