# Hyaluronic acid

Hyaluronic acid (HA; conjugate base hyaluronate), also called hyaluronan, is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is unique among glycosaminoglycans in that it is nonsulfated, forms in the plasma membrane instead of the Golgi apparatus, and can be very large: human synovial HA averages about 7 million Da per molecule, or about twenty thousand disaccharide monomers, while other sources mention 3–4 million Da.

One of the chief components of the extracellular matrix, hyaluronan contributes significantly to cell proliferation and migration, and may also be involved in the progression of some malignant tumors.

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Hyaluronic acid (HA), is an important component of the extracellular matrix in the tumor microenvironment, which abnormally accumulates in a variety of tumors. However, the role of abnormal HA accumulation in glioma remains unclear. A study indicated that HA, hyaluronic acid synthase 3 (HAS3), and a receptor of HA named CD44 were expressed at high levels in human glioma tissues and negatively correlated with the prognosis of patients with glioma. Silencing HAS3 expression or blocking CD44 inhibited glioma cell proliferation in vitro and in vivo. The underlying mechanism was attributed to the inhibition of autophagy flux and maintaining glioma cell cycle arrest in the G1 phase. More importantly, 4-methylumbelliferone (4-MU), a small competitive inhibitor of Uridine diphosphate (UDP) with the ability to penetrate the blood-brain barrier (BBB), also inhibited glioma cell proliferation in vitro and in vivo. Thus, approaches that interfere with HA metabolism by altering the expression of HAS3 and CD44 and the administration of 4-MU potentially represent effective strategies for glioma treatment [1)].

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Osteoarthritis (OA) poses a major clinical challenge owing to limited regenerative ability of diseased or traumatized chondrocytes in articular cartilage. Previous studies have determined the individual therapeutic efficacies of hyaluronic acid (HA) and platelet-rich plasma (PRP) on OA; however, the underlying mechanism is still lacking. Therefore, Chiou et al., investigated mechanistic approach of HA+PRP therapy on chondrocyte apoptosis in IL-1β+TNF-α (I+T) treated in vitro OA model, in addition to in vivo anterior cruciate ligament transection-OA mice model. MTT assay showed an enhanced chondrocyte proliferation and viability in HA+PRP-treated group, compared to I+T, I+T/HA, I+T/PRP, I+T/HA+PRP groups. Further, HA+PRP also significantly suppressed ROS, apoptotic cleaved caspase-3 and PARP, p53 and p21 and MMP-1; whereas, cell cycle modulatory proteins including p-ERK, cyclin B1, D1, and E2 were upregulated. The sub-G1 population and TUNEL assay confirmed the higher abundance of healthy chondrocytes in HA+PRP group. A significantly decreased ARS staining in HA+PRP group was also noted, indicating reduced cartilaginous matrix mineralization compared to other groups. Conclusively, compared to HA or PRP, the combined HA+PRP might be a promising therapy for articular cartilage regeneration in osteoarthritic pathology, possibly via augmented anti-inflammatory, anti-oxidative chondrocyte proliferation and inhibited MMP-1 activity and matrix calcification [2)].

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Previous work with chondrocytes and mesenchymal stem cells demonstrated that hydrogels based on

hyaluronic acid (HA) are effective at promoting matrix production and the development of functional material properties. However, this material has not been evaluated in the context of NP cells. Therefore, to test this material for NP regeneration, bovine NP cells were encapsulated in 1%w/vol HA hydrogels at either a low seeding density (20×10(6)cellsml(-1)) or a high seeding density (60×10(6)cellsml(-1)), and constructs were cultured over an 8week period. These NP cell-laden HA hydrogels showed functional matrix accumulation, with increasing matrix content and mechanical properties with time in culture at both seeding densities. Furthermore, encapsulated cells showed NP-specific gene expression profiles that were significantly higher than expanded NP cells prior to encapsulation, suggesting a restoration of phenotype. Interestingly, these levels were higher at the lower seeding density compared to the higher seeding density. These findings support the use of HA-based hydrogels for NP tissue engineering and cellular therapies directed at restoration or replacement of the endogenous NP [3].

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