wjpmr, 2017,3(11), 206-213

SJIF Impact Factor: 4.103

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

INFLUENCING OF STEROID TO HA-CD44 INTERACTION AND DIVERTS ITS CANCER GROWTH

Fakihi Mohamed*[1], Prof. L. V. Huixia[2] and Linus Onyinyechi Loveth[3]

[1,2]Departement of Pharmaceutics, China Pharmaceutical University.
[3]Departement of Pharmacognosy, China Pharmaceutical University.

***Corresponding Author: Fakihi Mohamed**
Departement of Pharmaceutics, China Pharmaceutical University.
Email ID: fakihimed@yahoo.fr,

Article Received on 19/10/2017 **Article Revised on 10/11/2017** **Article Accepted on 01/12/2017**

ABSTRACT

Catabolism of Hyaluronic acid plays a major pharmacological action since several pathologies were proven. Indeed, induction of pro- angiogenic and inflammatory were enhanced while enzyme imparts different sizes of molecular weight to HA degradation. Research studies emphasized to those enzymes which were played major palliative in reducing the inflammation and damage released onto the extra-matrix cellular that initiate several pathologies. CD44 receptor to HA evoke to play pro- angiogenic and inflammatory actions in breast and ovarian cancer or thyroid associated ophthalmopathy (TAO) and cancer stem cells (CSCs). HA and its binding proteins CD44 regulate the expression of inflammatory genes and beset the intracellular microenvironment phosphate kinase pathway. Thus, interaction HA-CD44 fostered the self-renewal of cancer stem cells (CSCs) and imparts the multidrug resistance due to the ion charge of the HA likewise efflux transporters P-gp. However, steroid compound was found to inhibit Hyaluronic acid action. Furthermore, hyaluronidase was found to facilitate drug absorption by promoting spread. Steroid will suppress HA-CD44 interaction in a fragment minimizing the tumor progression or the multidrug resistance. Indeed, the genetic material was involved in the influence. It is mainly explained with the substitution and traduction of CD variants. Consequently, steroid may contradict the microenvironment pathway by inhibiting the phosphate kinase and enhances the stability of genetic material. Researches should mainly emphasizing the affinity of steroid compound to target the of Hyaluronic acid catabolism and abrogate the stage that involves the labile function of cytoskeleton.

KEYWORDS: HA, CD44, CSCs, TAO, GAGs, ECM, COX-2, HYAL-2, PGI2, RHAMM, RTKs, HNSCC, ROS, NASHA, MDR, EMT.

INTRODUCTION

Hyaluronic acid (HA), a linear nonsulfated glycosaminoglycan, is a major component of the extracellular matrix (ECM) and is abundant in the human body.[1] The carboxyl group of D-glucuronic acid is dissociated at physiological pH values, resulting in the formulation of a negatively charged polymer that combines with the most prevalent extracellular cation, Na^+ to form sodium hyaluronate. Hence, standing for "hyaluronic acid has been widely accepted. Hyaluronan belongs to the family of glycosaminoglycans (GAGs). Hyaluronan is a non-sulfated polymer consisting of a variably-sized but larger molecule of up to 25,000 disaccharide units, giving a molecular mass of up to 10 MDa. Over half of the total body hyaluronan occurs in the skin. Moreover, it is found in connective tissue, synovial fluid, vitreous body of the eye and intervertebral discs. Hyaluronan is also found in high concentrations during embryogenesis: in fetal tissues, amniotic fluid, as a major constituent of fetal structures. Interestingly, hyaluronan is abundant in malignancies.[2,3,4] Moreover we can find in other tissues and organs. Hyaluronan (hyaluronic acid) belongs to the family of glycosaminoglycans (GAGs), but it differs from the other members. Hyaluronan is a non-sulfated polymer consisting of a variably-sized but larger molecule of up to 25,000 disaccharide units, giving a molecular mass of up to 10 MDa. Within the structure of the extracellular matrix (ECM), all the GAGs, apart from hyaluronan, are covalently linked with a protein core, creating structures known as proteoglycans. Hyaluronan constitutes a frame for coordinately attached proteoglycans or the other GAGs, creating huge aggregates.[2] As well as know that the connectivity with the CD44 it has shown as good functionality and an involvement to tumor proliferation due to the interaction induced through the MAP kinase proteins. To date, several work remained unclear while HA-CD44 interactions impart a huge pathologies via phosphate kinase and inflammatory reaction. Apart the aberrant function; HA-CD44 has various functions in cell division, migration, adhesion, and signaling. CD44 arbitrate the human epidermal growth factor receptor (HER) and common cell signaling pathways regulates

cell division (MET) receptor tyrosine kinase. HA fragments have been shown to induce RhoA-ROK pathway-specific effects on keratinocyte functions (eg, proliferation and/or migration). RhoA-activated ROK also phosphorylates the cytoplasmic domain of CD44 while steroid overwhelmed the HA action and mainly act to the genetic material, biochemical pathway and enzymatic action of hyaluronidase should bypass pro-oncological and avoid relapsing the phenomenon of inflammation, induction of cancer and phosphate catabolism pathway. Processing the inactivation of low molecular weight (LMW) is likely to improve the proper direction of palliative and raise the affinity could rearrange the dysfunctional of phosphate pathway namely RhoA-ROK pathway or phosphoinositide 3-kinase (PI3K)/Akt pathway.

1. Cluster of differentiation 44 (CD44) genetic material

Specifically CD44 is recognized by the HA. The human cell CD44 genetic material is located on the short arm of chromosome 11. It holds 50 KB of human DNA and its chromosome receptor CD44 is composed of 20 exons, and 12 of them have played a role in splicing. Exons 1-5 encode the constant region of the extracellular domain, whereas exons 6-15 exons are encoded for variable sides of the extracellular domain.[68,69,70] Furthermore splicing may be included to the varieties of gene sequences that induced more variants and standard then it can estimate more than 800 isoforms. The diversity of CD44 has induced several endpoints to binding linkage since angiogenesis was initiated by different binding cognate within outer cell and inner cell. In addition, the disengagement of CD44 to ligand was implicated when its variants is highly expressed. Herein, we can say that possible translocation can be substitute while using antisense however steroid may be ramified to act again in HA namely as known to inhibit the degradation of HA. Thereby, inherit the function of steroid into the antisense will improve the feasibility and promote the palliative enhancement through the phosphate kinase cascade pathway.

2. Cluster of differentiation 44 (CD44) receptor

To date, many works showed a progression on cancer when CD44-HA is highly observed since the only ligand which has recognized by HA and sparked different cascade of malignancies. Accordance to the interaction to HA-CD44 handled the pathway of several phosphate kinases. Moreover, it has contributing to cancer cell adhesion, migration, invasion and growth, triggers multiple intracellular signaling pathways. In the cytoplasmic environment has been observed apart kinase dysfunctional while activation of RhoA and Rac1, small GTPase proteins, results in myosin light chain phosphorylation. Consequently, calcium and pH are involved in the change then up-regulation of invasions and cancer cells growth.[6] The interaction between phosphate pathways remains the basic targeted area to deflect the tumor progression. On the other side, it is proved that CD44 linked with HA is involved in the inflammatory with thyroid associated ophthalmopathy (TAO). Induction on cyclooxygenase (COX)-2 expressions in patients with TAO was well understood that CD44 high level enhanced the activity of inducing the formation of prostacyclin (PGI2) and cyclooxygenase (COX)-2 expressions.[25] HA is the main molecule which is responsible of stimulating COX-2. Thus, cytokines were prompted to inflammatory process.[5] This is explained whilst HYAL-2 enhanced the catabolism of high molecular weight and CD44 variants synergic was urging the yield to cancer progression mainly in cancer stem cells (CSCs). In recent experiment, mutant mammary carcinoma cells lacking the ability to synthesize HA displayed a significant decrease in metastatic ability in an experimental model of lung metastasis. In that way, the restitution of HA yielded the HA ability to act in the adhesion, cell migration and tumor progression.[43] Furthermore inhibition of HA-CD44 can lead to drop the high connectivity and cut down the over expression of adhesiveness of human colon cancer cells to HA, cancer colony forming ability in soft agar assays, and xenograft tumorigenicity, while increasing susceptibility to etoposide-induced apoptosis[7] namely phosphoinositide 3-kinase (PI3K)/Akt.[7] Likewise steroid will inhibit inflammation yielded by the COX-2 while producing prostaglandin. This was proven in edema when steroid was administrated to minimize the drawbacks of hyaluronic acid esthetic fillers injection into the skin. Besides, the influence of cascade series realized near the binding of HA-CD44 variants turned into multi-resistant drug steroid by enhancing the anti-apoptosis and had urged the up-regulation function of MDR gene and enhanced ankyrin-regulated multidrug efflux. The reactive oxygen species (ROS) and cell damage and death were also implicated since cancer stem cells consume the energy by glycolysis however it is evaluate to up-regulation and elevation of CSCs. Thereby, it is indispensable for further emphasizing to deflect the aberrant of CD44 variants whose mainly involved in several pathologies which lead the damage of intracellular environment. In other word, interplaying in both HA-CD44 will assume the palliation and the impasse of up-regulation of HA. Hence, cell proliferation, migration, angiogenesis and tumor progression will be contradicted. Cancer stem cells implicated in the resistance of ROS then survival/up-regulate.

3. Catabolism of hyaluronic acid

HA catabolism split into two parts which has been degraded by two processes: enzymatic and non-enzymatic. It is well understood that hyaluronidases (HYALs) and isoenzyme played a major role in the degradation while isoenzyme hyaluronidase-2 (HYAL-2) caused low molecular weight and hyaluronidase-1(HYAL-1) involved in the catabolism of HA to high molecular weight. While HMWH is connected to the extracellular matrix then targeted CD44 ligand, HYAL-2 broke its down into low molecular weight (LMWH) to intermediate in length molecules (low molecular weight

hyaluronan – LMWH) of ~ 20 kDa (i.e., containing about 50 repeating disaccharide units).[8] HYAL-2 is involved in tumor progression when degrades the high molecular weight (HMWH), these pieces went through endocytosis by lysosomal and resistant to acidic pH[9] to the cytoplasmic microenvironment. However, low molecular weight was implied to induce tumor invasion, adhesion and cancer progression.

4. HA action in tumor progression

Hyaluronic acid is a polymer whose composition is repeated disaccharide units composed of D-glucuronic acid and D-N-acetylglucosamine. The disaccharide unites is mainly hydrophilic and possess a high osmotic pressure.[10,11] Moreover, the physical characteristic of HA is promoted by its hydrophobicity and since paste decades several works showed pro-inflammatory due to the linkage in different receptor involved likewise CD44 interaction. Hyaluronic acid promoted pro-inflammatory circumstances in different cases such as s pulmonary fibrosis, diabetes, and intervertebral disc degeneration.[12,13] Recent studies has marked that low molecular weight of HA has been degraded by HYAL-2 induced through the cytoplasmic environment cascade of phosphate kinases as well as the activation of RhoA and Rac1, small GTPase proteins, results in myosin light chain phosphorylation when high molecular weight is metabolized. These ones will improve the feasibility to target the HYAL-2. The medication of steroid will play onto the inhibition of high molecular weight degradation or incorporate to the modification of the genetic material namely mRNA transcription in that condition steroid is holds a carrier as substrate to bind it ligand coenzyme to escape the multidrug resistance. So cytokine productions won't be output neither inflammation nor phosphate kinases pathway destabilization. Thus coenzyme HYAL-2 would exchange with steroid medicine while high molecular weight assumed to bind HA-CD44 and goes through normal function. Nonetheless CD44 was castigated to stimulate inflammatory and breast cancer due to its variability likewise RHAMM.[14,15] Unlike CD44, RHAMM is found abundant in the cytoplasm which interferes into the cell cycle (G2/M) and co-stimulates the signal transduction pathways as ERK1, 2, which are initiated by growth factor.[16] Whereas CD44 and RHAMM are mainly involving the joint activity in certain conditions such as stroma, settling the medication in both HA-RHAMM seemed to improve the stability inside cytoplasm and outside ECM.

5. HA fragmentation results

In mammals, catabolism of HA undergoes to three types of enzymes: hyaluronidase (hyase), D-glucuronidase, and β-N-acetyl-hexosaminidase. Within the body these enzymes act differently hyase cleaves high molecular weight HA into smaller oligosaccharides while β-d-glucuronidase and β-N-acetylhexosaminidase further degrade the oligosaccharide fragments by removing nonreducing terminal sugars.[17] Hyaluronidase disrupted hyaluronic acid by splitting the glucosaminidic bond between carbon-1 of the glucosamine moiety and carbon-4 of glucuronic acid. To this, oligosaccharides and low molecular weight hyaluronan yielded to pro-angiogenic properties while high molecular weight prone to anti-inflammatory proprieties.[18] HA is hygroscopic then able to induce damage while disconnected with the extracellular matrix. Therefore, thus the activation of signaling phosphate kinase pathways is activated and influenced to the generated cell migration, proliferation, and gene expression.[19] Since HA is degraded in two parts, HYAL-2 isoenzyme takes in charge with the high molecular weight to degrade it in small particles called low molecular weight (LMW) which seemed to be involved in many balance of pathological and pharmacological dysfunction. Thereby, high molecular weight (HMW) undergoes depletion outside the cell into low molecular weight through endocytosis carried by vesicles.[20] Therefore depletion of molecular degradation was created when oxidation of free radical was released and Reactive oxygen species – ROS (and/or reactive nitrogen species – RNS) occurred in the cytoplasm. In same case it happens in rheumatoid arthritis. A recent laboratory studies had showed and proved the involvement of small molecular weight in the dysfunction related on phosphate pathway. High molecular weight found to be inactive while low molecular weight to CD44 has induced phosphorylation of MAP kinase proteins (MEK1/2, ERK1/2 and c-Jun) within 30 min. these ones were explained when using anti-CD44 monoclonal antibody, the concentration level remained decreased. As far as possible sustained the tumor cell invasion could be more perplexed while several in vitro animal studies showed a promise in monoclonal antibody (Anti-CD44). However, since steroid had great affinity to inhibit the hyaluronic acid and the constraint of CD44 variants is highly implicated that should be targeted. Since CD44 variants implicated in tumor progression.[22] The progression of head and neck squamous cell carcinoma (HNSCC) is a witness of CD44 variants.[21] Those isoforms played a great role in tumor progression and metastatic. The outer cell and inner cell had encountered basic modification where transcription in stem-cell is the key factor of the progression for instance Sox2, Klf4, Oct4, and Nanog are mainly observed in human cancers.[23,24] Other study used hyaluronic acid to treat arthritis found being effective to protect the cartilage. The hygroscopic proprieties of HA induced the attractive linked between extracellular matrix and the low molecular weight where it had played an action of cell invasion, cell migration, proliferation, and gene expression. Furthermore, HMW-HA is one of the principle components which acts due to its molecular size as anti-inflammatory and since its extension in the cell matrix which took stock of inhibitor of proliferation cell and prevention intra-matrix damage.[25,26,27] In recent studies, it came to question the action of the mitochondrial that reactive oxygen species (ROS) is involved. It is at this moment that phosphoric links encourage the offshoring of connectivity. It depends of the molecular chain of HA, these is bypassed

through cell monocytes and platelets of way or membership. Depending on the composition of the molecule degraded many studies focused on the blockbuster of the chemical elements that can be questioned of being stimulating of gene transcription namely TNF-α, IL-12, IL-1β, and matrix metalloproteinases.[28–29] Oligomers of around 7 disaccharide units inhibit anchorage- independent growth of several tumor cell types and induce apoptosis in vitro[30] but in other side an interplaying was found to small oligosaccharides between 3 and 9 disaccharide units, because of their shortness, exhibit only monovalent binding to CD44, displacing any hyaluronan polymer from membrane bound receptors (receptor antagonists).[31] The interaction of high molecular weight of HA with Toll-like receptor 4 (TLR4) also is synergized on biological activities[32] by increasing these secretion of suppressor of cytokine signaling 3 (SOCS3), that underplayed the proinflammatory cytokine expression. The redirection of Toll-like receptor 4 (TLR4) to target HA likewise steroid to inhibit HA assessed the pattern of suppressing the pro-inflammatory and other pharmacological cascades.

6. HA study

Hyaluronic acid is a major component of extracellular matrices and cell surface receptors of HA which is mainly work as cell proliferation, migration, and invasion. Moreover, its binding to CD44 receptor raised several pharmacological and pathological effects. Likewise CD44, HA-mediated motility (RHAMM) revealed as a ligand of HA whose acts in biological function in human and interfered in malignancies. These interactions as soon as induced markedly modifying the phosphate kinase pathways. In recent studies, it was shown that HA is found in pericellular matrices attached to the HA-synthesizing enzymes or its receptors and is also present in intracellular degradation compartments.[33,34,35,36] Whilst, in other animals played a role such resistance and strength in cancer when using antisense techniques suppresses tumor growth. So to this model explained that high level of HA may included in cancer suppression in naked mole rate.[37] The HA and its degraded were accumulated in the cytoplasm by endocytosis through lysosome vesicles and induced inflammatory genes with renal tubular epithelial cells T-24 carcinoma cells and eosinophils.[38,39,40] HA of 40–400kDa interact with HA-receptors to activate the NFκB-mediated gene expression for endocytosis likewise HA-RHAMM by intracellular signaling pathways.[41,42,43] Consequently, these pathways involve wound healing and tissue remodeling,[44,45,46] tissue morphogenesis[44,47] matrix organization, and much inflammatory pathology.[47,48,49,50,51,52,53]

7. NASHA (Non Animal Stabilized Hyaluronic Acid)

NASHA comes from purified preparations of AH of bacteria and several product manufactured in this type had approved commercialization when indorsed by FDA in 2002 such as Restylane®. Despite of the effectiveness of non-animal stabilized hyaluronic acid but local inflammatory reactions immediately non-allergic diatoms (erythema, swelling) are frequent and they disappear without treatment.[66] Contrariwise, common hyaluronic acid injection doesn't show any similar action. NASHA is largely used in facial esthetic injection to treat skin aging due to lack of hyaluronic acid, collagen, fatty tissues and elastic fibers. It provides loss of volume and appearance of wrinkle. However, it eliminates wrinkles and skin folds and reshapes facial contours.[67]

8. The epithelial-mesenchymal transition (EMT)

The epithelial-mesenchymal transition (EMT) was found to be correlated in the dysfunction when HA is overexpressed. Therefore, using transgenic mice while introducing HAS2 gene raised the up-regulation and interference between several endpoint of epithelial phenotype in tumor cells.[54] Consequently, as soon as HA is concerned with to EMT and further modification were found to be included in both connectivity. So HA induced overproduction up-regulated Snail and Twist expression in a mammary carcinoma cell.[55] It was explained by the secretion of cytokines and growth factors. These can be explained by autocrine/paracrine cytokine loops in controlling HA-induced EMT. Obviously, TGF-β was found to be responsible of stromal and tumor cells when interfering with EMT. In fact HAS2 was implicated to stimulate TGF-β to act as inducer and promote dysfunction such as fibronectin, Snail, and Zeb1.[56]

9. Deflection of HA-CD44

The ligand binding of HA-CD44 or HA-CD44v can be deflected. In addition steroid compound when used its action can induce inhibition to the catabolism of HA as well as the linkage between HA-CD44 may be prohibited. Indeed, the linkage was responsible of receptor tyrosine kinases (RTKs) damaging. RTKs are sensitive and more active since it has catabolic site where phosphate compound has interconnection and may be responsible of several cascade. Pathological action observed in RTKs to CD44 is due to the intervention of HA fragments resulted in malignant colon, prostate, and breast carcinoma cells. So far induction of COX-2 and MDR is major part of HA-CD44 high level. This interaction enhances the stimuli and development of several pathologies such as ERBB2, ErbB3, EGFR, IGF1R-β, PDGFR-β, and c-MET, as well as assembly of lipid-raft integrated signaling complexes containing these activated RTKs, CD44, ezrin, PI3-kinase (PI3K) and the chaperone molecules HSP90 and CDC37, which upgrades apoptosis resistance in cancer cells.[57,58,599,60–61] In breast tumor cell migration CD44v3 mainly up-regulates the phosphorylation while well known to be responsible of these pathologies. In other side, RhoA-activated ROK also phosphorylates the cytoplasmic domain of the CD44v3 isoform.[62] It is well-known that CD44v sponsored the cascade and intervention of HA within phosphorylation kinases chain reaction. Notion that HGF-initiated c-Met signaling that required association

of the CD44 cytoplasmic tail with ezrin/radixin/moesin family members to regulate MEK and Erk signaling pathways was caused by a variant CD44 receptor.[63] Previously, rather than CD44v6 its counterpart CD44v3 promoted the CSCs involvement when drew the binging of HB–EGF precursor and matrilysin/MMP7 while degrading the matrix connectivity and induced the cancer resistance.[89] Indeed, the antisense when insert to modify the transcription of CD44v can be repaired.

10. Multidrug resistance (MDR)

The anticancer drugs have been largely used to shrink the tumor progression. Treatment of malignant diseases is rather focused on targeting the growth factors, specific signaling pathway, angiogenesis and tumor antigens. Nevertheless, no acquired in some tumors are refractory to drugs due to the sensitivity. Recent studies showed the nuclear translocation and efflux phenomena by reflecting the medicine through membrane bilayer pump. In addition, these hindrances were found to malignant melanomas, bronchogenic carcinoma (non small cell). Indeed, cancer stem cells had more potent to be out of neutralization the CSCs and apoptosis. The degradation of ECM has supported the evasion of angiogenesis. Elsewhere, translocation of multidrug resistance gene indicated as promoter which has been co-stimulated Nanog and Stat-3 dependent MDR1 gene expression. The HA-CD44 interaction altered the microenvironment then translocation and cascade phosphate pathway was enhanced when a high concentration level accumulated steadily which leaded to anti-apoptosis.[64,65] In addition steroid (corticosteroid) administration into osteoarthritis patients showed a good result that found to palliate the reduction of pain likewise the inflammatory cascade compared to the treatment by hyaluronic acid even if the later observation into the group administrated showed not far difference of effective results. In addition, when administrating steroid a visual response was quick observable with a consistency of dosage.

11. CONCLUSION AND PERSPECTIVES

Hyaluronic acid is an anionic, nonsulfated glycosaminoglycan widely distributed in different part of the body. It is unique for CD44 receptor binging and play a great role in cell adhesion, migration, anti-aging, penis elongation and wound healing. Besides, it is assessed to be potent in osteoarthritis intra-articular in intra-articular injection. Moreover, the extracellular matrix damage assessed by the involvement of tumor cell-associated proteases (MMP.s-2, MMPs-9, urokinase-type plasminogen activator (uPA), serine protease) and tissue inhibitors of gelatinase (TIMP-2) which are amid to the extracellular matrix degradation.

Ultimately, different pathologies were encountered and possible therapies are suspected since corticosteroids were found highly potent in different treatments as well as to find a new direction for its use as antisense. Meanwhile, steroids could play a great role while translation may inhibit the CD44 variants and HA enzymes (HYAL) which was suspected to break up HA into low molecular weight. This one enhanced the proinflammatory action, cell migration, tumor progression ….etc. In this review some instance showed the profile of steroid effectiveness compared to intra-articular hyaluronic acid injections of in the treatment of osteoarthritis. To date, different perspective emphasized to limit the phosphate kinase pathway which could be inhibit from the linkage of CD44 onto MAP kinase proteins (MEK1/2, ERK1/2 and c-Jun). Accordingly, devoid of human chondrosarcoma cells likewise other cancer pathologies. Therefore the following scientific research could predict the transcription of micro-RNA modification loci since steroid introduction into the nucleus acts immediately to translate mRNA for further protein synthetase. Thus, substitution of nucleotides from mRNA transcription may direct for further protein translation and assess the inhibition of extracellular matrix. So that autocrine action would inhibit the damage of intracellular compartment.

REFERENCES

1. Fraser JRE, Laurent TC, Laurent UBG. Hyaluronan:its nature, distribution, functions and turnover. J Intern Med, 1997; 242: 27-33; PMID:9260563; http://dx.doi.org/10.1046/j.1365-2796.1997.00170.x.
2. NowakJZ:Hyaluronan:biochemicaland functional aspects (Polish). Mag Lek Okul, 2010; 4: 37–49.
3. Sironen RK, Tammi M, Tammi R, Auvinen PK, Anttila M, Kosma VM: Hyaluronan in human malignancies. Exp Cell Res, 2011; 317: 383–391.
4. Stern R: Association between cancer and "acid muco-polysaccharides": an old concept comes of age, finally. Semin Cancer Biol, 2008; 18: 238–243.
5. Vondrichova T, de Capretz A, Parikh H, et al. COX-2 and SCD, markers of inflammation and adipogenesis, are related to disease activity in Graves' ophthalmopathy. Thyroid, 2007; 17: 511–517.
6. Bourguignon LY, Singleton PA, Diedrich F, Stern R, Gilad E: CD44 interaction with Na + -H^+ exchanger (NHE1) creates acidic microenvironments leading to hyaluronidase and cathepsin B activation and breast tumor cell invasion. J Biol Chem, 2004; 279: 26991–27007.
7. Subramaniam V, Vincent IR, Gilakjan M, Jothy S. Suppression of human colon cancer tumors in nude mice by siRNA CD44 gene therapy. Exp Mol Pathol, 2007; 83(3): 332–40. doi:10.1016/j.yexmp.2007.08.013.
8. Lepperdinger G, Mullegger J, Kreil G: Hyal2-less active, but more versatile Matrix Biol, 2001; 20: 509–514.
9. Sironen RK, Tammi M, Tammi R, Auvinen PK, Anttila M Kosma VM: Hyaluronan in human malignancies. Exp Cell Res, 2011; 317: 383–391.
10. Hansen C, Rouhi R, Forster G, Kahaly GJ. Increased sulfatation of orbital glycosaminoglycans in Graves'

ophthalmopathy. J Clin Endocrinol Metab, 1999; 84: 1409–1413.
11. Do Y, Nagarkatti PS, Nagarkatti M. Role of CD44 and hyaluronic acid (HA) in activation of alloreactive and antigen-specific T cells by bone marrow-derived dendritic cells. J Immunother, 2004; 27: 1–12.
12. Bollyky PL, Bogdani M, Bollyky JB, Hull RL, Wight TN. The role of hyaluronan and the extracellular matrix in islet inflammation and immune regulation. Curr Diab Rep, 2012; 12: 471–480.
13. Lennon FE, Singleton PA. Role of hyaluronan and hyaluronan-binding proteins in lung pathobiology. Am J Physiol Lung Cell Mol Physiol, 2011; 301: L137–147.
14. Tolg C, Mccarthy JB, Yazdani A, Turley EA. Hyaluronan and RHAMM in wound repair and the "cancerization" of stromal tissues. Biomed Res Int, 2014; 2014: 103923. doi: 10. 1155 /2014 /103923.
15. Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiol Rev, 2011; 91: 221–64. doi:10.1152/physrev.00052.2009.
16. Mohapatra S, Yang X, Wright JA, Turley EA, Greenberg AH. Soluble hyaluronan receptor RHAMM induces mitotic arrest by suppressing Cdc2 and cyclin B1 expression. J Exp Med, 1996; 183: 1663–8. doi:10.1084/jem.183.4.1663.
17. Leach and Schmidt, 2004.
18. Mio and Stern, 2002.
19. Turley et al. 2002; Taylor et al. 2004.
20. Early-response gene signalling is induced by angiogenic oligosaccharides of hyaluronaninendothelialcells. Inhibitionbynon-angiogenic, high molecular weight hyaluronan. Int J Cancer, 1997; 71(2): 251–6. doi:10.1002/(SICI)1097-0215(19970410)71:2<251::AID-IJC21>3.0.CO;2-J
21. Wang SJ, Wreesmann VB, Bourguignon LY. Association of CD44 V3-containing isoforms with tumor cell growth, migration, matrix metalloproteinase expression, and lymph node metastasis in head and neck cancer. Head Neck, 2007; 29(6): 550–8. doi:10.1002/hed.20544.
22. Wielenga VJ, Heider KH, Offerhaus GJ, Adolf GR, van den Berg FM, Ponta H, et al. Expression of CD44 variant proteins in human colorectal cancer is related to tumor progression. Cancer Res, 1993; 53(20): 4754–6.
23. Mathieu J, Zhang Z, Zhou W, Wang AJ, Heddleston JM, Pinna CM, et al. HIF induces human embryonic stem cell markers in cancer cells. Cancer Res, 2011; 71(13): 4640–52. doi:10.1158/0008-5472.CAN-10-3320.
24. Wang XQ, Ng RK, Ming X, Zhang W, Chen L, Chu AC, et al. Epigenetic regulation of pluripotent genes mediates stem cell features in human Hepatocellular carcinoma and cancer cell lines. PLOS One, 2013; 8(9): e72435. doi:10.1371/ journal.pone.0072435.
25. SlevinM, KrupinskiJ, GaffneyJ, MatouS, WestD, DelisserH, et al. Hyaluronan-mediated angiogenesis in vascular disease: uncovering RHAMM and CD44 receptor signaling pathways. Matrix Biol, 2007; 26(1): 58–68. doi:10.1016/j. matbio.2006.08.261.
26. Feinberg RN, Beebe DC. Hyaluronate in vasculogenesis. Science, 1983; 220(4602): 1177–9. doi:10.1126/science.6857242.
27. Deed R, Rooney P, Kumar P, Norton JD, Smith J, Freemont AJ, et al.
28. Taylor KR, Yamasaki K, Radek KA, Di Nardo A, Goodarzi H, Golenbock D, et al. Recognition of hyaluronan released in sterile injury involves a unique receptor complex dependent on Toll-like receptor 4, CD44, and MD-2. J Biol Chem, 2007; 282(25): 18265–75. doi:10.1074/jbc.M606352200.
29. DoY,Nagarkatti PS,Nagarkatti M. Role of CD44 and hyaluronic acid (HA) in activation of alloreactive and antigen-specific T cells by bone marrow-derived dendritic cells. J Immunother, 2004; 27(1): 1–12. doi:10.1097/00002371- 200401000-00001.
30. Ghatak S, Misra S. Toole BP: Hyaluronan oligosaccharides inhibit anchorage-independent growth of tumor cells by suppressing the phosphoinositide 3-kinase/Akt cell survival pathway. J Biol Chem, 2002; 277: 38013–38020.
31. Ghatak S, Misra S. Toole BP: Hyaluronan oligosaccharides inhibit anchorage-independent growth of tumor cells by suppressing the phosphoinositide 3-kinase/Akt cell survival pathway. J Biol Chem, 2002; 277: 38013–38020.
32. Lesley J, Hascall VC, Tammi M, Hyman R: Hyaluronan binding by cell surface CD44. J Biol Chem, 2000; 275: 26967–26975.
33. A.Asari,T.Kanemitsu,andH.Kurihara,"Oral administration of high molecular weight hyaluronan (900 kDa) controls immune system via toll-like receptor 4 in the intestinal epithelium," Journal of Biological Chemistry, 2010; 285(32): 24751–24758.
34. Misra S, Heldin P, Hascall VC, Karamanos NK, Skandalis SS, Markwald RR, et al. Hyaluronan-CD44 interactions as potential targets for cancer therapy. FEBS J, 2011; 278: 1429–43. doi:10.1111/j.1742-4658.2011.08071.x.
35. Ghatak S, Hascall VC, Karamanos NK, Markwald RR, Misra S. Targeting the tumor microenvironment in cancer progression. In Karamanos N, editor. Extracellular Matrix: Pathobiology and Signaling. Berlin: DeGruyter, 2012; 729-46.
36. Toole BP. Hyaluronan: from extracellular glue to pericellular cue. Nat Rev Cancer, 2004; 4: 528–39. doi:10.1038/nrc1391.
37. Tian X, Azpurua J, Hine C, Vaidya A, Myakishev-Rempel M, Ablaeva J, et al.nHigh-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. Nature, 2013; 499: 346–9. doi: 10.1038/nature12234.
38. Beck-Schimmer B, Oertli B, Pasch T, Wuthrich RP. Hyaluronan induces monocyte chemo-attractant

protein-1 expression in renal tubular epithelial cells. J Am Soc Nephrol, 1998; 9: 2283–90.
39. Fitzgerald KA, Bowie AG, Skeffington BS, O'Neill LA. Ras, protein kinase C zeta, and I kappa B kinases 1 and 2 are downstream effectors of CD44 during the activation of NF-kappa B by hyaluronic acid fragments in T-24 carcinoma cells. J Immunol, 2000; 164: 2053–63. doi:10.4049/jimmunol.164.4.2053.
40. Ohkawara Y, Tamura G, Iwasaki T, Tanaka A, Kikuchi T, Shirato K. Activation and transforming growth factor-beta production in eosinophils by hyaluronan. Am J Respir Cell Mol Biol, 2000; 23: 444–51. doi:10.1165/ajrcmb. 23.4.3875.
41. Day AJ, Prestwich GD. Hyaluronan-binding proteins: tying up the giant. J Biol Chem, 2002; 277: 4585–8. doi:10.1074/jbc.R100036200.
42. Misra S, Heldin P, Hascall VC, Karamanos NK, Skandalis SS, Markwald RR, et al. Hyaluronan-CD44 interactions as potential targets for cancer therapy. FEBS J, 2011; 278: 1429–43. doi:10.1111/j.1742-4658.2011.08071.x.
43. Entwistle J, Hall CL, Turley EA. HA receptors: regulators of signaling to the cytoskeleton. J Cell Biochem, 1996; 61: 569–77. doi:10.1002/(SICI) 1097-4644(19960616)61:4<569::AID-JCB10>3.0.CO;2-B.
44. Laurent TC, Fraser JR. Hyaluronan. FASEB J, 1992; 6: 2397–404.
45. West DC, Hampson IN, Arnold F, Kumar S. Angiogenesis induced by degradation products of hyaluronic acid. Science, 1985; 228: 1324–6. doi:10.1126/science.2408340.
46. Weigel PH, Frost SJ, Le Boeuf RD, Mc Gary CT. The specific interaction between fibrinogen and hyaluronan: possible consequences in haemostasis, inflammation and wound healing. Ciba Found Symp, 1989; 143: 248–61.
47. Toole BP. Hyaluronan in morphogenesis. J Intern Med, 1997; 242: 35–40. doi:10.1046/j.1365-2796.1997.00171.x.
48. Misra S, Heldin P, Hascall VC, Karamanos NK, Skandalis SS, Markwald RR, et al. Hyaluronan-CD44 interactions as potential targets for cancer therapy. FEBS J, 2011; 278: 1429–43. doi:10.1111/j.1742-4658.2011.08071.x.
49. Ghatak S, Hascall VC, Karamanos NK, Markwald RR, Misra S. Targeting the tumor microenvironment in cancer progression. In Karamanos N, editor. Extracellular Matrix: Pathobiology and Signaling. Berlin: DeGruyter, 2012; 729-46.
50. Ghatak S, Hascall VC, Markwald RR, Misra S. Stromal hyaluronan interaction with epithelial CD44 variants promotes prostate cancer invasiveness by augmenting expression and function of hepatocyte growth factor and androgen receptor. J Biol Chem, 2010; 285: 19821–32. doi:10.1074/jbc.M110. 104273.
51. Toole BP. Hyaluronan: from extracellular glue to pericellular cue. Nat Rev Cancer, 2004; 4: 528–39. doi:10.1038/nrc1391.
52. Toole BP. Hyaluronan in morphogenesis. J Intern Med, 1997; 242: 35–40. doi:10.1046/j.1365-2796.1997.00171.x.
53. Pilarski LM, Masellis-Smith A, Belch AR, Yang B, Savani RC, Turley EA. RHAMM, a receptor for hyaluronan-mediated motility, on normal human lymphocytes, thymocytes and malignant B cells: a mediator in B cell malignancy? Leuk Lymphoma, 1994; 14: 363–74. doi:10.3109/10428199409049691.
54. Koyama H, Hibi T, Isogai Z, Yoneda M, Fujimori M, Amano J, et al. Hyperproduction of hyaluronan in neu-induced mammary tumor accelerates angiogenesis through stromal cell recruitment: possible involvement of versican/PG-M. Am J Pathol, 2007; 170(3): 1086–99. doi:10.2353/ ajpath.2007.060793.
55. Chanmee T, Ontong P, Mochizuki N, Kongtawelert P, Konno K, Itano N. Excessive hyaluronan production promotes acquisition of cancer stem cell signatures through the coordinated regulation of twist and the transforming growth factor beta (TGF-beta)-snail signaling axis. J Biol Chem, 2014; 289(38): 26038–56. doi:10.1074/jbc.M114.564120.
56. Porsch H, Bernert B, Mehic M, Theocharis AD, Heldin CH, Heldin P. Efficient TGFbeta-induced epithelial-mesenchymal transition depends on hyaluronan synthase HAS2. Oncogene, 2013; 32(37): 4355–65. doi:10.1038/ onc. 2012.475.
57. Misra S, Hascall VC, De Giovanni C, Markwald RR, Ghatak S. Delivery of CD44 shRNA/nanoparticles within cancer cells: perturbation of hyaluronan/CD44v6 interactions and reduction in adenoma growth in Apc Min/+ MICE. J Biol Chem, 2009; 284: 12432–46. doi:10.1074/jbc. M806772200.
58. Misra S, Toole BP, Ghatak S. Hyaluronan constitutively regulates activation of multiple receptor tyrosine kinases in epithelial and carcinoma cells. J Biol Chem, 2006; 281: 34936–41. doi:10.1074/jbc. C600138200.
59. Zoller M. CD44: can a cancer-initiating cell profit from an abundantly expressed molecule? Nat Rev Cancer, 2011; 11: 254–67. doi:10.1038/nrc3023.
60. DeAngelis PL. Glycosaminoglycan polysaccharide biosynthesis and production: today and tomorrow. Appl Microbiol Biotechnol, 2012; 94: 295–305. doi:10.1007/s00253-011-3801-6.
61. Itano N, Kimata K. Mammalian hyaluronan synthases. IUBMB Life, 2002; 54: 195–9. doi:10.1080/15216540214929.
62. Bourguignon LY, Wong G, Xia W, Mao-Qiang M, Holleran WM Elias PM: Selective matrix (hyaluronan) interaction with CD44 and RhoGTPase signaling promotes keratinocyte functions and overcomes age-related epidermal dysfunction. J Dermatol Sci, 2013; 72: 32e44.

63. Orian-Rousseau V, Chen L, Sleeman JP, Herrlich P, Ponta H. CD44 is required for two consecutive steps in HGF/c-Met signaling. Genes Dev, 2002; 16(23): 3074–86. doi:10.1101/gad.242602.
64. Bourguignon LY, Spevak CC, Wong G, Xia W, Gilad E. Hyaluronan-CD44 interaction with protein kinase C(epsilon) promotes oncogenic signaling by the stem cell marker Nanog and the production of microRNA-21, leading to down-regulation of the tumor suppressor protein PDCD4, anti-apoptosis, and chemotherapy resistance in breast tumor cells. J Biol Chem, 2009; 284(39): 26533–46. doi:10.1074/jbc.M109.027466.
65. Ohashi R, Takahashi F, Cui R, Yoshioka M, Gu T, Sasaki S, et al. Interaction between CD44 and hyaluronate induces chemoresistance in non-small cell lung cancer cell. Cancer Lett, 2007; 252(2): 225–34. doi:10.1016/j. canlet.2006.12.025.
66. Romagnoli M, Belmontesi M. Hyaluronic acid-based fillers: theory and practice. Clin Dermatol, 2008; 26: 123-59.
67. Prager W, Wissmueller E, Havermann I, Bee EK, Howell DJ, Zschocke I, Simon. A prospective, split-face, randomized, comparative study of safety and 12-month longevity of three formulations of hyaluronic acid dermal filler for treatment of nasolabial folds. Dermatol Surg, 2012; 38: 1143-50.
68. Ponta H, Sherman L, Herrlich PA. CD44: from adhesion molecules to signaling regulators. Nat Rev Mol Cell Biol, 2003; 4: 33–45. doi: 10.1038/nrm1004.
69. Turley EA, Noble PW, Bourguignon LY. Signaling properties of hyaluronan receptors. J Biol Chem, 2002; 277: 4589–92. doi:10.1074/jbc.R100038200.
70. Naor D, Wallach-Dayan SB, Zahalka MA, Sionov RV. Involvement of CD44, a molecule with a thousand faces, in cancer dissemination. Semin Cancer Biol, 2008; 18: 260–7. doi:10.1016/j.semcancer.2008.03.015.