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Mini-review

Hyaluronan and its catabolic products in tissue injury and repair

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Abstract

Hyaluronan is an unbiquitous glycosaminoglycan present in most tissues. Under homeostatic conditions hyaluronan exists as a high molecular mass polymer that has important roles in tissue structural integrity. Under conditions of stress such as following tissue injury, hyaluronan becomes depolymerized and lower molecular mass polymers are generated. The biological properties of these hyaluronan fragments appear to be distinct from the larger precursor molecules. This review examines the biological role of hyaluronan fragments in tissue injury and repair. © 2002 Elsevier Science B.V./International Society of Matrix Biology. All rights reserved.

1. Introduction

Hyaluronan (HA) is an ubiquitous glycosaminoglycan found in almost all tissues. Hyaluronan was first characterized from the vitreous of the eye (Meyer and Palmer, 1934) and shown to contain a hexuronic acid, an amino sugar and acetyl groups with no sulfo-ester content. HA was subsequently isolated from umbilical cord tissue, and glucuronic acid and glucosamine sugar constituents were identified (Meyer and Palmer, 1936). The actual linkages of the repeating disaccharide motif (-β-1,4-glucuronic acid-β1,3-*N*-acetylglucosamine-)$_n$ was described in 1954 (Weissman and Meyer, 1954). The number of repeat disaccharides can approach 30 000 (a molecular mass of 10×10^6 Da) in tissues such as synovial fluid. In addition to regulating physiologic processes in normal tissues, HA undergoes dynamic regulation under conditions of tissue injury and inflammation. The purpose of this review is to discuss the emerging roles of HA in tissue injury, inflammation and repair, with an emphasis on the lower MW forms of the molecule.

2. Hyaluronan as a signaling molecule: its potential role in initiating the host response to tissue injury

Hyaluronan is a remarkable polymer that appears to have distinct biological functions depending on the circumstances under which it is produced. Under physiologic conditions, HA exists as a high molecular weight polymer in excess of 10^6 Da. However, following tissue injury, HA fragments of lower molecular mass accumulate. The potential functional significance of the generation of HA fragments has been suggested by in vitro studies (Hodge-Dufour et al., 1997; Horton et al., 1999; McKee et al., 1996, 1997; Noble et al., 1993, 1996). The observation that HA may interact differently with various cells and produce distinct biological effects depending on the poly-

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Abbreviations: ROI, Reactive Oxygen Inter Intermediates; ECM, Extracellular Matrix.

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mer molecular mass was initially made with endothelial cells (West and Kumar, 1989). Oligomers of 8–16 disaccharides prepared by enzymatic digestion of native HA induce angiogenesis in a chick corneal assay, while the native high molecular weight polymer does not.

A number of other laboratories have since identified a similar phenomenon using different cell types, different polymer sizes and examining different biological effector functions (Rooney et al., 1995). In general, the ability of cells to respond to HA of differing sizes appears to vary with cell type. Generally, native high molecular mass polymers of $3–6 \times 10^6$ Da do not induce inflammatory or proliferative genes. However, high molecular weight HA can activate protein tyrosine cascades in endothelial cells (Lokeshwar and Selzer, 2000) although at low levels. Furthermore, although endothelial cells are able to activate protein tyrosine kinase cascades with high molecular weight HA, activation is several-fold greater in the presence of HA fragments (Lokeshwar and Selzer, 2000).

Studies with inflammatory macrophages have shown that fragmented HA with a molecular mass with a peak in the range of 2.5×10^5 Da, but not the high molecular mass precursor, can induce the expression of inflammatory genes (Hodge-Dufour et al., 1997; Horton et al., 1998, 1999; McKee et al., 1996, 1997; Noble et al., 1993, 1996). Similar results have been shown with renal tubular epithelial cells (Beck-Schimmer et al., 1998), T-24 carcinoma cells (Fitzgerald et al., 2000) and eosinophils (Ohkawara et al., 2000). The critical importance of excluding contaminating substances from HA preparations has recently been brought to light (Filion and Phillips, 2001). The biological relevance of these studies is supported by reports demonstrating that fragmented HA that induces inflammatory gene expression in vitro is in the same size range as HA that accumulates under inflammatory conditions in vivo (McKee et al., 1996). In contrast, a different size requirement is observed with dendritic cells where HA oligosaccharides in the 6–20 size range, but not the 2.5×10^5 Da or higher molecular weight, induce inflammatory gene expression (Termeer et al., 2000). The common theme appears to be that high MW HA does not initiate a program of gene expression geared toward cell proliferation, migration, or activation, whereas a variety of genes that regulate biological properties are expressed in response to fragmented lower molecular mass HA. Hyaluronan fragmentation in vivo may result from regulated expression of secreted hyaluronidases (Csoka et al., 1997) or from oxidation (Uchiyama et al., 1990), and this fragmentation is required for acquisition of a signaling function for HA. Generation of HA fragments under conditions of tissue injury may serve the function of signaling to the host that normal homeostasis has been profoundly disturbed.

3. Hyaluronan depolymerization in tissue injury

Hyaluronan is a normal constituent of basement membrane, and in its native form, HA exists as a high molecular weight polymer, typically in excess of 10^6 Da. Hyaluronan plays a role in maintaining the structural integrity of tissues such as the joint where it is responsible for maintaining the viscosity of joint fluid. In addition to existing as a soluble polymer, HA is bound to large proteoglycans such as aggrecan and versican. Hyaluronan side chains of aggrecan are important in cartilage organization and recent data have suggested that HA is essential for maintaining cartilage integrity (Knudson, 1993; Nishida et al., 1999). At sites of inflammation, such as during inflammatory arthritis or in wound healing, HA becomes depolymerized into lower molecular weight forms.

There appear to be two mechanisms for depolymerizing HA, enzymatic and non-enzymatic (Laurent and Fraser, 1992). The enzymes that degrade HA are hyaluronidases, chondroitinases and hexosaminidases (Laurent and Fraser, 1992). Most hyaluronidases are lysosomal enzymes and require an acid pH for maximal activity (Kreil, 1995). However, the hyaluronidase PH-20, found in sperm, is active at pH 7 (see article by Cherr et al. in this mini-review series). Recently, a soluble form of PH-20 has been identified (Gmachl and Kreil, 1993; Gmachl et al., 1993; Li et al., 1997; Meyer et al., 1997).

In addition, a novel hyaluronidase (Hyal-2) that generates HA fragments of $10–20 \times 10^3$ Da has been described (see article by Lepperdinger et al. in this mini-review series). Hyal-2 is expressed in fibrotic lung injury (Lepperdinger et al., 1998; Li et al., 2000).

Hyaluronan can also be degraded into smaller fragments by exposure to ROI (Deguine et al., 1998). This is an important mechanism for generating HA fragments at sites of inflammation (Saari, 1991). Interestingly, hyaluronidases are endoglucosaminidases whereas ROIs fragment HA randomly at internal glycoside linkages.

Hyaluronan degradation products appear to have biological functions distinct from the native high molecular weight polymer. Oligosaccharides of less than 20 disaccharides have been shown to be angiogenic (West et al., 1985). Low and intermediate molecular weight HA (2×10^4–4.5×10^5 Da) stimulate gene expression in macrophages, endothelial cells, eosinophils and certain epithelial cells (McKee et al., 1996, 1997; Oertli et al., 1998; Slevin et al., 1998). Hyaluronan degradation products are purported to contribute to scar formation (West et al., 1997). Fetal wounds heal without scar formation and wound fluid HA is high molecular weight (Mackool et al., 1998; Sawai et al., 1997). When hyaluronidase is added to generate HA fragments, there is increased scar formation (West et al., 1997). Collectively, these data support the concept that high molecular weight HA promotes cell quiescence and supports tissue integrity, whereas generation of HA breakdown products is a signal that injury has occurred and initiates an inflammatory response. Interestingly, whether it be wound healing, liver injury or lung injury, there is a potent mechanism for clearing HA following tissue injury. This suggests that while the generation of HA breakdown products may be important in initiating the inflammatory response, removal of these fragments may be critical for the resolution of the repair process.

The mechanisms by which HA accumulates in tissue injury have been studied. Elegant work from Swedish investigators has demonstrated that growth factors such as PDGF and TGF-β that accumulate following bleomycin lung injury, stimulate lung fibroblasts to produce HA. However, whether increases in HA are due to increased production or decreased degradation were difficult to sort out at that time because the genes encoding HA synthases were unknown.

However, as stated above, three isoforms of HA synthase have recently been cloned (Weigel et al., 1997). The three isoforms exhibit different patterns of expression in developing embryos (Spicer et al., 1996, 1997a; Spicer and McDonald, 1998). HAS1 is expressed early from day 1-5, HAS2 is expressed throughout development, and HAS3 is expressed in late development. The three isoforms map to three distinct chromosomes, suggesting that they arose from ancient gene duplication (Spicer et al., 1997b).

Targeted deletion of HAS2 has recently been reported (Camenisch et al., 2000). HAS2 deletion results in an embryonic lethal condition, whereas HAS1 and HAS3 mice develop normally. The HAS2 deletion appears to present a similar phenotype to that described for a naturally occurring versican knockout (Mjaatvedt et al., 1998). There are major abnormalities in heart and blood vessel development. Interestingly, in vitro data have suggested that HAS1 and HAS2 produce high molecular weight HA, whereas HAS3 produces lower molecular weight HA (Itano et al., 1999).

4. Role of CD44 in hyaluronan signaling and host response to injury

CD44 is a polymorphic type I transmembrane glycoprotein and the main cell surface receptor for HA whose diversity is determined by differential splicing of at least 10 variable exons encoding a segment of the extracellular domain, termed exons v1–10, and cell type-specific glycosylation (Lesley et al., 1993). Most cells express the standard isoform which is a 85-kDa protein that undergoes post-translational modification (Lesley et al., 1993). CD44 is a HA-binding protein, and HA-CD44 interactions play an important role in development, inflammation, T cell recruitment and activation, and in tumor growth and metastasis (Lesley et al., 1993). Although glycosaminoglycan side chains associated with some CD44 isoforms can also bind a subset of heparin-binding growth factors, cytokines, and ECM proteins such as fibronectin, most of the functions ascribed to CD44 thus far can be attributed to its ability to bind and internalize HA (Sherman et al., 1994). Most cells including stromal cells such as fibroblasts and smooth muscle cells, epithelial cells and immune cells such as neutrophils, macrophages and lymphocytes all express CD44 (Sherman et al., 1994).

A fundamental step in elucidating the biological effects of HA on cell function is to understand the mechanisms that regulate the relationship between cell-surface binding and internalization (see the article by Knudson et al. in this mini-review series). Furthermore, it is critical to understand the contribution of HA receptors and also address the possibility that there may be non-receptor mediated mechanisms that contribute to HA internalization. There have been numerous studies demonstrating that HA binds to the surface of many cell types and can be internalized (Lee and Spicer, 2000). Depending on the cell type being studied, the binding affinity and rate of internalization varies.

Studies have recently shown that the avidity of binding of HA oligomers to CD44 increases with oligomer size up to 38 sugars (Lesley et al., 2000). In addition, in work examining the binding and internalization of labeled HA in permeabilized smooth muscle cells and fibroblasts, HA staining was seen in the cytoplasm as a diffuse, network and in vesicles. Both nuclear and lamellae HA staining can also be demonstrated (Collis et al., 1998; Evanko and Wight, 1999). This unusual pattern of uptake is most obvious following stimulation of serum-starved 3T3 cells or in sub-confluent, mutant active ras-transfected fibroblasts. Hyaluronan uptake into these novel compartments is associated with enhanced cell motility (Collis et al., 1998). These observations and the growing list of intracellular HA-binding proteins, exemplified by RHAMM, suggests that HA not only occurs in intracellular sites, but may regulate signaling events from these intracellular or intranuclear locations.

The role of CD44 in HA-binding and signaling has recently been investigated in hematopoietic cells from

CD44-deficient mice (Protin et al., 1999; Schmits et al., 1997). CD44-deficient mice develop normally and exhibit minor abnormalities in hematopoiesis and lymphocyte recirculation (Protin et al., 1999; Schmits et al., 1997). Induction of inflammatory gene expression in response to hyaluronan was observed in the absence of CD44 in bone marrow cultures and dendritic cells (Khaldoyanidi et al., 1999; Termeer et al., 2000). These data suggest that there are CD44-independent mechanisms for induction of gene expression by HA. Important studies are underway to examine the relationship between HA internalization and signal transduction pathways under CD44-deficient conditions.

CD44-deficient mice challenged in models of tissue injury have revealed important roles for CD44 in mediating pathogenesis of host injury (Chen et al., 2001; Rafi-Janajreh et al., 1999). Depending on the mechanism of pathogenesis and the predominant cell types that mediate the host injury, differing effects of CD44 are observed. In a model of endothelial cell injury mediated by IL-2, CD44-deficient mice are protected from endothelial injury (Rafi-Janajreh et al., 1999). This protection is suggested to be due to a decrease in IL-2-induced lymphocyte-activated killer cell activity. However, in a model of hepatocellular injury due to administration of Con A, CD44-deficient mice exhibit enhanced hepatitis (Chen et al., 2001). The increased susceptibility to hepatocyte injury correlates with the observation that T cells from CD44-deficient animals are resistant to activation-induced cell death. Hyaluronan turnover has not been evaluated in CD44-deficient mice to date. Future studies in CD44-deficient mice will elucidate the importance of HA homeostasis in models of tissue injury and repair.

References

Beck-Schimmer, B., Oertli, B., Pasch, T., Wuthrich, R.P., 1998. Hyaluronan induces monocyte chemoattractant protein-1 expression in renal tubular epithelial cells. J. Am. Soc. Nephrol. 9, 2283–2290.

Camenisch, T.D., Spicer, A.P., Brehm-Gibson, T. et al., 2000. Disruption of hyaluronan synthase-2 abrogates normal cardiac morphogenesis and hyaluronan-mediated transformation of epithelium to mesenchyme. J. Clin. Invest. 106, 349–360.

Chen, D., McKallip, R.J., Zeytun, A. et al., 2001. CD44-deficient mice exhibit enhanced hepatitis after concanavalin A injection: evidence for involvement of CD44 in activation-induced cell death. J. Immunol. 166, 5889–5897.

Collis, L., Hall, C., Lange, L., Ziebell, M., Prestwich, R., Turley, E.A., 1998. Rapid hyaluronan uptake is associated with enhanced motility: implications for an intracellular mode of action. FEBS Lett. 440, 444–449.

Csoka, T.B., Frost, G.I., Stern, R., 1997. Hyaluronidases in tissue invasion. Invas. Metas. 17, 297–311.

Deguine, V., Menasche, M., Ferrari, P., Fraisse, L., Pouliquen, Y., Robert, L., 1998. Free radical depolymerization of hyaluronan by Maillard reaction products: role in liquefaction of aging vitreous. Int. J. Biol. Macromol. 22, 17–22.

Evanko, S.P., Wight, T.N., 1999. Intracellular localization of hyaluronan in proliferating cells. J. Histochem. Cytochem. 47, 1331–1342.

Filion, M.C., Phillips, N.C., 2001. Pro-inflammatory activity of contaminating DNA in hyaluronic acid preparations. J. Pharm. Pharmacol. 53, 555–561.

Fitzgerald, K.A., Bowie, A.G., Skeffington, B.S., O'Neill, L.A., 2000. 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. 164, 2053–2063.

Gmachl, M., Kreil, G., 1993. Bee venom hyaluronidase is homologous to a membrane protein of mammalian sperm. Proc. Natl. Acad. Sci. USA 90, 3569–3573.

Gmachl, M., Sagan, S., Ketter, S., Kreil, G., 1993. The human sperm protein PH-20 has hyaluronidase activity. FEBS Lett. 336, 545–548.

Hodge-Dufour, J., Noble, P.W., Horton, M.R. et al., 1997. Induction of IL-12 and chemokines by hyaluronan requires adhesion-dependent priming of resident but not elicited macrophages. J. Immunol. 159, 2492–2500.

Horton, M.R., Burdick, M.D., Strieter, R.M., Bao, C., Noble, P.W., 1998. Regulation of hyaluronan-induced chemokine gene expression by IL-10 and IFN-gamma in mouse macrophages. J. Immunol. 160, 3023–3030.

Horton, M.R., Olman, M.A., Noble, P.W., 1999. Hyaluronan fragments induce plasminogen activator inhibitor-1 and inhibit urokinase activity in mouse alveolar macrophages: a potential mechanism for impaired fibrinolytic activity in acute lung injury. Chest 116, 17S.

Itano, N., Sawai, T., Yoshida, M. et al., 1999. Three isoforms of mammalian hyaluronan synthases have distinct enzymatic properties. J. Biol. Chem. 274, 25085–25092.

Khaldoyanidi, S., Moll, J., Karakhanova, S., Herrlich, P., Ponta, H., 1999. Hyaluronate-enhanced hematopoiesis: two different receptors trigger the release of interleukin-1beta and interleukin-6 from bone marrow macrophages. Blood 94, 940–949.

Knudson, C.B., 1993. Hyaluronan receptor-directed assembly of chondrocyte pericellular matrix. J. Cell Biol. 120, 825–834.

Kreil, G., 1995. Hyaluronidases — a group of neglected enzymes. Protein Sci. 4, 1666–1669.

Laurent, T.C., Fraser, J.R., 1992. Hyaluronan. Fed. Am. Soc. Exp. Biol. J. 6, 2397–2404.

Lee, J.Y., Spicer, A.P., 2000. Hyaluronan: a multifunctional, megaDalton, stealth molecule. Curr. Opin. Cell Biol. 12, 581–586.

Lepperdinger, G., Strobl, B., Kreil, G., 1998. HYAL2, a human gene expressed in many cells, encodes a lysosomal hyaluronidase with a novel type of specificity. J. Biol. Chem. 273, 22466–22470.

Lesley, J., Hyman, R., Kincade, P.W., 1993. CD44 and its interaction with extracellular matrix. Adv. Immunol. 54, 271–335.

Lesley, J., Hascall, V.C., Tammi, M., Hyman, R., 2000. Hyaluronan binding by cell surface CD44. J. Biol. Chem. 275, 26967–26975.

Li, M.W., Cherr, G.N., Yudin, A.I., Overstreet, J.W., 1997. Biochemical characterization of the PH-20 protein on the plasma membrane and inner acrosomal membrane of cynomologus macaque spermatozoa. Mol. Reprod. Dev. 48, 356–366.

Li, Y., Rahmanian, M., Widstrom, C., Lepperdinger, G., Frost, G.I., Heldin, P., 2000. Irradiation-induced expression of hyaluronan (HA) synthase 2 and hyaluronidase 2 genes in rat lung tissue accompanies active turnover of HA and induction of types I and III collagen gene expression. Am. J. Respir. Cell Mol. Biol. 23, 411–418.

Lokeshwar, V.B., Selzer, M.G., 2000. Differences in hyaluronic acid-mediated functions and signaling in arterial, microvessel, and vein-derived human endothelial cells. J. Biol. Chem. 275, 27641–27649.

Mackool, R.J., Gittes, G.K., Longaker, M.T., 1998. Scarless healing. The fetal wound. Clin. Plastic Surg. 25, 357–365.

McKee, C.M., Penno, M.B., Cowman, M. et al., 1996. Hyaluronan (HA) fragments induce chemokine gene expression in alveolar macrophages. The role of HA size and CD44. J. Clin. Invest. 98, 2403–2413.

McKee, C.M., Lowenstein, C.J., Horton, M.R. et al., 1997. Hyaluronan fragments induce nitric-oxide synthase in murine macrophages through a nuclear factor kappaB-dependent mechanism. J. Biol. Chem. 272, 8013–8018.

Meyer, K., Palmer, J.W., 1934. J. Biol. Chem. 107, 629–634.

Meyer, K., Palmer, J.W., 1936. J. Biol. Chem. 114, 689–703.

Meyer, M.F., Kreil, G., Aschauer, H., 1997. The soluble hyaluronidase from bull testes is a fragment of the membrane-bound PH-20 enzyme. FEBS Lett. 413, 385–388.

Mjaatvedt, C.H., Yamamura, H., Capehart, A.A., Turner, D., Markwald, R.R., 1998. The Cspg2 gene, disrupted in the hdf mutant, is required for right cardiac chamber and endocardial cushion formation. Dev. Biol. 202, 56–66.

Nishida, Y., Knudson, C.B., Nietfeld, J.J., Margulis, A., Knudson, W., 1999. Antisense inhibition of hyaluronan synthase-2 in human articular chondrocytes inhibits proteoglycan retention and matrix assembly. J. Biol. Chem. 274, 21893–21899.

Noble, P.W., Lake, F.R., Henson, P.M., Riches, D.W., 1993. Hyaluronate activation of CD44 induces insulin-like growth factor-1 expression by a tumor necrosis factor-alpha-dependent mechanism in murine macrophages. J. Clin. Invest. 91, 2368–2377.

Noble, P.W., McKee, C.M., Cowman, M., Shin, H.S., 1996. Hyaluronan fragments activate an NF-kappa B/I-kappa B alpha autoregulatory loop in murine macrophages. J. Exp. Med. 183, 2373–2378.

Oertli, B., Beck-Schimmer, B., Fan, X., Wuthrich, R.P., 1998. Mechanisms of hyaluronan-induced up-regulation of ICAM-1 and VCAM-1 expression by murine kidney tubular epithelial cells: hyaluronan triggers cell adhesion molecule expression through a mechanism involving activation of nuclear factor-kappa B and activating protein-1. J. Immunol. 161, 3431–3437.

Ohkawara, Y., Tamura, G., Iwasaki, T., Tanaka, A., Kikuchi, T., Shirato, K., 2000. Activation and transforming growth factor-beta production in eosinophils by hyaluronan. Am J Respir Cell Mol Biol 23, 444–451.

Protin, U., Schweighoffer, T., Jochum, W., Hilberg, F., 1999. CD44-deficient mice develop normally with changes in subpopulations and recirculation of lymphocyte subsets. J. Immunol. 163, 4917–4923.

Rafi-Janajreh, A.Q., Chen, D., Schmits, R. et al., 1999. Evidence for the involvement of CD44 in endothelial cell injury and induction of vascular leak syndrome by IL-2. J. Immunol. 163, 1619–1627.

Rooney, P., Kumar, S., Ponting, J., Wang, M., 1995. The role of hyaluronan in tumour neovascularization. Int. J. Cancer 60, 632–636.

Saari, H., 1991. Oxygen derived free radicals and synovial fluid hyaluronate. Ann. Rheum. Dis. 50, 389–392.

Sawai, T., Usui, N., Sando, K. et al., 1997. Hyaluronic acid of wound fluid in adult and fetal rabbits. J. Pediatr. Surg. 32, 41–43.

Schmits, R., Filmus, J., Gerwin, N. et al., 1997. CD44 regulates hematopoietic progenitor distribution, granuloma formation, and tumorigenicity. Blood 90, 2217–2233.

Sherman, L., Sleeman, J., Herrlich, P., Ponta, H., 1994. Hyaluronate receptors: key players in growth, differentiation, migration and tumor progression. Curr. Opin. Cell Biol. 6, 726–733.

Slevin, M., Krupinski, J., Kumar, S., Gaffney, J., 1998. Angiogenic oligosaccharides of hyaluronan induce protein tyrosine kinase activity in endothelial cells and activate a cytoplasmic signal transduction pathway resulting in proliferation. Lab. Invest. 78, 987–1003.

Spicer, A.P., McDonald, J.A., 1998. Characterization and molecular evolution of a vertebrate hyaluronan synthase gene family. J. Biol. Chem. 273, 1923–1932.

Spicer, A.P., Augustine, M.L., McDonald, J.A., 1996. Molecular cloning and characterization of a putative mouse hyaluronan synthase. J. Biol. Chem. 271, 23400–23406.

Spicer, A.P., Olson, J.S., McDonald, J.A., 1997a. Molecular cloning and characterization of a cDNA encoding the third putative mammalian hyaluronan synthase. J. Biol. Chem. 272, 8957–8961.

Spicer, A.P., Seldin, M.F., Olsen, A.S. et al., 1997b. Chromosomal localization of the human and mouse hyaluronan synthase genes. Genomics 41, 493–497.

Termeer, C.C., Hennies, J., Voith, U. et al., 2000. Oligosaccharides of hyaluronan are potent activators of dendritic cells. J. Immunol. 165, 1863–1870.

Uchiyama, H., Dobashi, Y., Ohkouchi, K., Nagasawa, K., 1990. Chemical change involved in the oxidative reductive depolymerization of hyaluronic acid. J. Biol. Chem. 265, 7753–7759.

Weigel, P.H., Hascall, V.C., Tammi, M., 1997. Hyaluronan synthases. J. Biol. Chem. 272, 13997–14000.

Weissman, B., Meyer, K.J., 1954. Am. Chem. Soc. 76, 1753–1757.

West, D.C., Kumar, S., 1989. The effect of hyaluronate and its oligosaccharides on endothelial cell proliferation and monolayer integrity. Exp. Cell Res. 183, 179–196.

West, D.C., Hampson, I.N., Arnold, F., Kumar, S., 1985. Angiogenesis induced by degradation products of hyaluronic acid. Science 228, 1324–1326.

West, D.C., Shaw, D.M., Lorenz, P., Adzick, N.S., Longaker, M.T., 1997. Fibrotic healing of adult and late gestation fetal wounds correlates with increased hyaluronidase activity and removal of hyaluronan. Int. J. Biochem. Cell Biol. 29, 201–210.