Perspective article

Functions of hyaluronan in wound repair

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Hyaluronan is a major carbohydrate component of the extracellular matrix and can be found in skin, joints, eyes and most other organs and tissues. It has a simple, repeated disaccharide linear copolymer structure that is completely conserved throughout a large span of the evolutionary tree, indicating a fundamental biological importance. Amongst extracellular matrix molecules, it has unique hygroscopic, rheological and viscoelastic properties. Hyaluronan binds to many other extracellular matrix molecules, binds specifically to cell bodies through cell surface receptors, and has a unique mode of synthesis in which the molecule is extruded immediately into the extracellular space upon formation. Through its complex interactions with matrix components and cells, hyaluronan has multifaceted roles in biology utilizing both its physicochemical and biological properties. These biological roles range from a purely structural function in the extracellular matrix to developmental regulation through effects of cellular behavior via control of the tissue macro- and microenvironments, as well as through direct receptor mediated effects on gene expression. Hyaluronan is also thought to have important biological roles in skin wound healing, by virtue of its presence in high amounts in skin. Hyaluronan content in skin is further elevated transiently in granulation tissue during the wound healing process. In this review, the general physicochemical and biological properties of hyaluronan, and how these properties may be utilized in the various processes of wound healing: inflammation, granulation and reepithelization, are presented. **(WOUND REP REG 1999;7:79–89)**

Hyaluronan is a linear polymer of glucuronic acid *N*-acetylglucosamine disaccharide. It was originally discovered in the vitreous body of the eye but subsequently found in most parts of the body, including synovial fluid of joints and in the skin. Most cells in the body have the capability to synthesize hyaluronan during some point of their cell cycles, implicating its function in several fundamental biological processes.

It is generally accepted that hyaluronan is associated with the tissue repair process. Evidence of this association comes from many sources. Studies of hyaluronan in other biological processes such as morphogenesis and oncology[1–4] have also provided valuable insights into how hyaluronan may function in tissue repair. Although hyaluronan may participate in many and diverse tissue repair biological processes, on the whole, despite many years of intensive research, the detailed mechanisms of how it functions are not entirely clear and are only beginning to be elucidated. Some of these functions may be attributed to its role as an integral part of the extracellular matrix where it provides primarily a structural role. Because of its unique hygroscopic, rheologic and viscoelastic properties, hyaluronan may also affect cellular behavior by affecting the macro- and microenvironment around cells through its complex interactions with cells and other extracellular matrix components. Thirdly, hy-

IαI	Inter-α-inhibitor
ICAM-1	Intercellular adhesion molecule-1
IL-1β	Interleukin-1β
LFA-1	Lymphocyte function associated-1
TNF-α	Tumor necrosis factor-α
TSG6	TNF-stimulated gene 6

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aluronan and its oligosaccharides may directly affect cell function through receptor binding events that directly lead to alteration of specific gene expression.

Because of its unique physicochemical properties, and, most importantly, nonimmunogenicity of the highly purified form, hyaluronan has already found medical applications for many years, primarily in ocular and joint surgery.[5,6] More recently, the reported benefits of exogenously-applied hyaluronan in tissue repair have resulted in hyaluronan-based biomaterials being developed for tissue repair purposes. This article aims to review the current knowledge of hyaluronan biology and how it may function in tissue repair through its biological interactions and physicochemical properties.

PHYSICOCHEMICAL PROPERTIES

Hyaluronan is one of the most hygroscopic molecules in nature. This single primary characteristic is probably the key contributor to many of its attributed biological functions, and can be further modified by its interaction with cells as well as other components of the extracellular matrix. The main physicochemical properties of hydrated, free colloidal hyaluronan are reviewed extensively elsewhere,[7] so they are only summarized below.

Hyaluronan's viscoelasticity is particularly relevant in its cushioning and lubricating effects as a component of the eye (aqueous humor) and synovial fluid. This unique rheologic property is exploited in the application of hyaluronan in ophthalmic surgery.[8,9]

Because hyaluronan is a hygroscopic macromolecule, hyaluronan solutions are highly osmotic, a property further increased in the presence of serum albumin as found in many tissue fluids.[10] This osmotic property is particularly relevant as an osmotic buffer in the kidney. In the skin, this property is likely to be relevant in controlling tissue hydration during periods of change, such as embryonic development and during the inflammatory process (such as response to tissue injury) when hyaluronan levels are elevated. This is also of particular relevance for cell proliferation and migration, when hyaluronan synthesis contributes to local foci of tissue hydration. This results in weakening of cell anchorage to the extracellular matrix, allowing temporary detachment to facilitate cell migration and division.[11]

In the hydrated state, much of the water around the hyaluronan molecule is immobilized. This results in restriction of movement of water and small molecules.[12] Larger molecules, such as proteins, are excluded from the hyaluronan matrix by steric exclusion.[13,14] The highly viscous nature of hyaluronan also contributes to retardation of viral and bacterial passage through the hyaluronan-rich pericellular zone.[15,16]

Hyaluronan is fully ionized in physiological conditions. As a pericellular matrix, it may have effects on ion flux which are important in cellular signaling through membrane ion channels. Hyaluronan also serves as a scavenger of free radicals and as an antioxidant. These functions of hyaluronan may be particularly important in skin physiology, as a protectant against solar radiation. In inflammation, hyaluronan may also have a moderating effect through free-radical scavenging,[17–19] antioxidant effect,[20] as well as through exclusion of tissue degrading enzymes from the immediate cellular environment and from other structural components of the extracellular matrix.[7,17]

BIOLOGICAL PROPERTIES

These physicochemical properties of hyaluronan may be further modified by specific binding to cells and extracellular matrix to modulate the physicochemical and biological properties of specific local environments.

Cell surface receptors

Hyaluronan binds to cells via three main classes of cell surface receptors: CD44, RHAMM and ICAM-1. CD44 is very widely distributed in the body and is recognized to be the major cell surface receptor for hyaluronan.[21,22] CD44-mediated cell interaction with hyaluronan has been implicated in a variety of physiologic events, including cell-cell and cell-substrate adhesion, cell migration, proliferation, and activation, as well as hyaluronan uptake and degradation. The precise biological role of CD44 in vivo in various tissues remains to be determined, but recent studies by Kaya et al.[23] have suggested that the two major functions of CD44 in skin may be the regulation of keratinocyte proliferation in response to extracellular stimuli and the maintenance of local hyaluronan homeostasis.

The expression of the RHAMM (Receptor for HyaluronAn Mediated Motility) on cell surfaces is associated with cell locomotion, and has been identified in a wide variety of mobile cells, including migrating fibroblasts and highly metastatic tumor cells.[24–28]

Intracellular adhesion molecule-1 (ICAM-1) was originally thought to be a metabolic receptor for hyaluronan, effecting its uptake by cells and subsequent

breakdown in the intracellular space.[29] However, ICAM-1 is also a cell adhesion molecule widely distributed on endothelial cells, macrophages, and other cells. The binding of hyaluronan to ICAM-1 may affect its binding to other receptors such as the leukocyte integrins lymphocyte function associated-1 (LFA-1)[30] and Mac-1.[31] Endothelial cell binding to leukocytes through interaction of ICAM-1 with LFA-1/Mac-1 is an important early step in inflammatory activation[32] and so it is possible that ICAM-1 binding to hyaluronan may contribute to the control of ICAM-1-mediated inflammatory activation.

Binding to matrix components: Structural and biological functions

Hyaluronan is also an integral part of the extracellular matrix. In particular, it forms the backbone for the organization of proteoglycans.[33,34] It also forms associations with collagen, fibrin and other matrix molecules. Early response to tissue injury includes formation of a temporary matrix rich in hyaluronan and fibrin which supports the influx of fibroblasts and endothelial cells into the wound site and subsequent formation of granulation tissue.[35–37]

Whether hyaluronan is bound to cells or to extracellular matrix components, its hydrophilic nature creates an environment permissive for migration of cells to new tissue sites, while its free- radical scavenging and protein exclusion properties offer protection to cells and extracellular matrix molecules against free-radical and proteolytic damage. These represent some of the fundamental properties that may mediate the healing of both acute and chronic wounds.

In cartilage, hyaluronan forms the backbone in the complex proteoglycan structures that are immobilized in the collagen network. This complex matrix superstructure is responsible for the structural as well as mechanical characteristics of this semi-rigid tissue.[33,34]

Hyaluronan-binding proteins

Hyaluronan-binding proteins, also known as hyaladherins, are widely distributed in the body and have diverse functions.[38] The general feature of hyaladherins is the binding of hyaluronan with other cell or matrix components and thus are important in mediation of matrix assembly, cell- matrix and cell–cell interactions.

Besides their structural and organizational functions, of particular interest in terms of connective tissue dynamics during inflammation and tissue repair is the discovery of hyaladherins that can form complexes with proteinase inhibitors. Tumor necrosis factor–stimulated gene 6 (TSG-6) is a hyaladherin closely related to the hyaluronan receptor CD44. While it binds to hyaluronan, it also forms a stable complex with inter-α-inhibitor (IαI), a serine proteinase inhibitor in serum. TSG-6 expression in neutrophils is induced by tumor necrosis factor-α (TNF-α). The TSG-6/IαI complex is an inhibitor of serine proteinases. These proteinases, which include plasmin, trypsin and cathepsin G, can cause connective tissue degradation directly and through activation of matrix metalloproteinase proenzymes.[39–42] They can also activate latent transforming growth factor-β,[43] which is an important inflammatory mediator, and overactivity of which may lead to scarring complications.[44] Thus, the TSG-6/IαI complex, which may be additionally organized by matrix hyaluronan, may form an important negative feedback mechanism in the control of inflammation and stabilization of the extracellular matrix during the latter part of the inflammation process.[45]

Recent evidence also shows that IαI can form a stable, covalently linked complex with hyaluronan, and has an important role in formation of the pericellular matrix.[46]

Hyaluronan, hyaluronan oligosaccharides and direct effects on cell behavior

Hyaluronan oligosaccharides have been shown to promote angiogenesis in a variety of models.[47–49] This is a property which can potentially benefit the healing of acute and chronic wounds. The mechanisms by which hyaluronan oligosaccharides mediate angiogenesis are not known. However, soluble hyaluronan fragments have been shown to upregulate expression of several cytokines such as interleukin 1β (IL-1β), TNF-α and insulin-like growth factor-1,[50] and induce the expression of several inflammatory genes[51–53] in macrophages through a CD44 receptor-mediated mechanism, and enhance the production of collagens by endothelial cells.[48] These properties are consistent with the view that hyaluronan can directly affect cellular activity through a receptor-mediated mechanism.

Kobayashi and Terao[54] have also shown a dose-dependent increase of the proinflammatory cytokines TNF-α, IL-1β and IL-8 production by human uterine fibroblasts at hyaluronan concentrations of 10 μg/ml to 1 mg/ml via a CD44 mediated mechanism.

Hyaluronan synthesis

Hyaluronan is unique among matrix macromolecules in that following synthesis, it is directly secreted into

the extracellular space. Hyaluronan synthase is located on the cell membrane.[55–57] Newly synthesized hyaluronan, protruding directly into the extracellular environment, provides a highly hydrated microenvironment at the sites of synthesis. This may represent a dynamic role by which hyaluronan synthesis may facilitate cell detachment during mitosis and migration.

Observations of exogenous hyaluronan on wound healing

Many reports have attested to the effects of exogenous hyaluronan in producing beneficial wound healing outcome. In animal experiments, topically applied hyaluronan has been shown to accelerate skin wound healing in rats[58,59] and hamsters.[60] Similar results have been observed in the healing of perforated tympanic membranes in rats.[61] Corneal epithelial wound healing is also reported to be stimulated by exogenously applied hyaluronan.[62]

A prolonged presence of hyaluronan has been reported to be associated with the scarless quality of fetal tissue repair. Hyaluronan content in fetal wounds remains high for longer periods than in adult wounds, leading to the suggestion that hyaluronan may, at least in part, reduce collagen deposition and therefore lead to reduced scarring.[63] These suggestions are in agreement with the work of Laurent et al.,[29] who showed that applied hyaluronan resulted in scarless healing of tympanic membranes, and with Balasz and Denlinger[5] who hypothesized that a hyaluronan-rich environment inhibits the matrix cells responsible for fibrous scars. In a recent paper, West et al.[64] showed that in adult and late gestation fetal wound healing, removal of hyaluronan results in fibrotic scarring.

In chronic wounds, such as venous leg ulcers, hyaluronan application has been shown to promote healing.[65] It is accepted that in many chronic wounds, direct tissue damage is one of the consequences of prolonged inflammation mediated through oxygen free radicals and matrix degrading enzymes. Hyaluronan may have a protective effect on this type of tissue damage, as suggested by the work of Foschi et al.[59] who showed that hyaluronan prevents free radical damage to granulation tissue in rats. Ialenti and Di Rosa[66] have also directly demonstrated the inflammation-moderating effect of hyaluronan in standard models of acute and chronic inflammation, also in the rat.

It is clear that the function of hyaluronan in tissue repair is complex and cannot be specifically attributed to any single one of its many properties. However, by taking the current knowledge of the chemistry and biology of hyaluronan, and by drawing on the results of studies in related biological processes such as morphogenesis, oncology and inflammation, the putative mechanistic role of hyaluronan in the various stages of wound healing may be elucidated.

ROLE OF HYALURONAN IN WOUND HEALING PROCESSES

Many of the biological processes mediated by hyaluronan are also central in the wound healing process. Following injury, wound healing follows a series of tightly regulated, sequential events. These are inflammation, granulation tissue formation, reepithelization and remodeling, as described in Figure 1. Hyaluronan is likely to have a multifaceted role in mediation of these cellular and matrix events, summarized in Table 1. The putative roles of hyaluronan in this sequence of wound healing events are described in more detail in the following sections.

Inflammation

Inflammation generates many of the factors required for the subsequent steps of wound healing. These include growth factors, cytokines, eicosanoids, etc. which promote migration of inflammatory cells, fibroblasts and endothelial cells into the wound site.

The wound tissue in the early inflammatory phase of wound repair is rich in hyaluronan, probably a reflection of increased synthesis.[36,37] Hyaluronan has multiple roles in inflammation. It can act as a promoter of early inflammation that is important in the wound healing process. In a murine air pouch model of carrageenan/IL-1-induced inflammation, hyaluronan was shown to enhance cellular infiltration.[45] Kobayashi and Terao[54] have shown a dose-dependent increase of the proinflammatory cytokines TNF-α, IL-1β and IL-8 production by human uterine fibroblasts at hyaluronan concentrations of 10 μg/ml to 1 mg/ml via a CD44 mediated mechanism. Endothelial cells, in response to inflammatory cytokines such as TNF-α and IL-1β, and bacterial lipopolysaccharide, also synthesize hyaluronan and this has been shown to facilitate primary adhesion of cytokine-activated lymphocytes expressing the hyaluronan-binding variants of CD44[67] under laminar and static flow conditions. Interestingly, this phenomenon is restricted to microvascular endothelial cells. Large vessel endothelial cells do not display this phenomenon.

In a somewhat contradictory role, hyaluronan can also moderate the inflammatory response, which may contribute to the stabilization of granulation tissue matrix, as reviewed below.

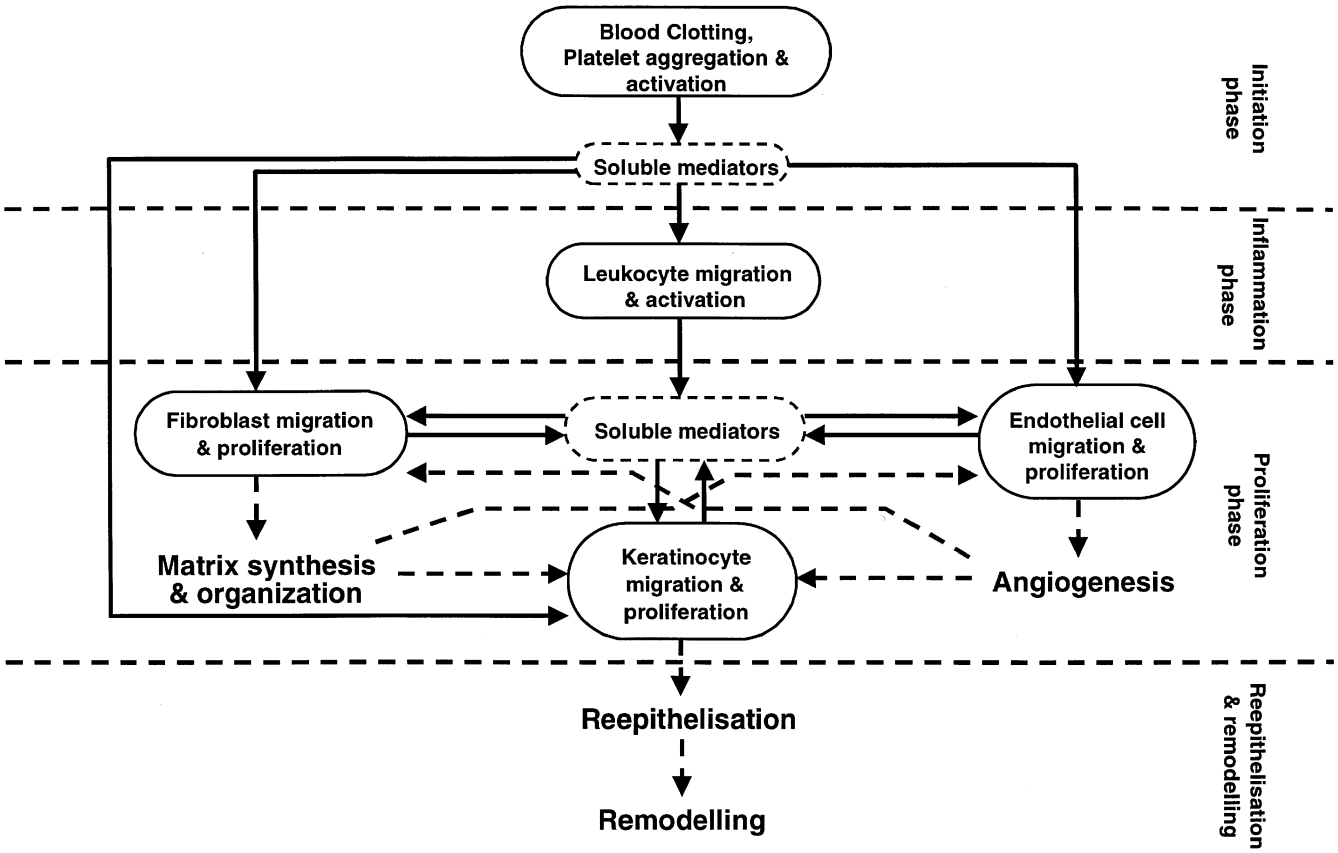

Figure 1. Cellular and matrix events that occur during the normal wound healing process.

Granulation and organization of the granulation tissue matrix

Granulation tissue matrix is rich in hyaluronan.[36,37] The hyaluronan-rich matrix may contribute to a variety of cell functions that are essential for tissue repair. These include facilitation of cell migration into the provisional wound matrix, cell proliferation and organization of the granulation tissue matrix. Of course, initiation of inflammation is important for the formation of granulation tissue so the pro-inflammatory role of hyaluronan as reviewed above also contribute to this stage of wound healing.

Hyaluronan and cell migration

Cell migration is essential for the formation of granulation tissue. A hyaluronan-rich extracellular matrix, characteristic of early granulation tissue, is regarded as a conducive environment for migration of cells into this provisional wound matrix. Hyaluronan may function in cell migration through its physicochemical properties as well as through direct interactions with cells. In the former, hyaluronan provides an open, hydrated matrix that facilitates cell migration[2,3] whereas in the latter, through specific cell interaction via cell surface hyaluronan receptors, directed migration and control of the cell locomotory mechanisms are mediated. The principal cell surface receptors include CD44, ICAM-1 and RHAMM. RHAMM, in particular, forms links with several protein kinases associated with cell locomotion, e.g., extracellular signal-regulated protein kinase (ERK), $p125^{fak}$, and $pp60^{c-src}$.[26,68,69] During fetal development, the migration path through which neural crest cells migrate is rich in hyaluronan.[1,70] Increased cell movement in response to hyaluronan can also be demonstrated experimentally in other cell types,[2,71,72] whereas cell movement can be inhibited, at least partially, by hyaluronan degradation or blocking hyaluronan receptor occupancy.[73–77]

Hyaluronan synthesis has also been shown to correlate with cell migration.[74,78–81] Hyaluronan synthesis may itself provide the dynamic force to facilitate cell migration. It is synthesised at the plasma membrane and released directly into the ex-

Table 1. Summary of wound healing biological processes involving hyaluronan

Stage	Process	Mechanism	Reference
Inflammatory phase	Inflammation activation	Enhancement of cell infiltration	45
		Increase of proinflammatory cytokines TNF-α, IL–1β and IL-8 via a CD44-mediated mechanism	54
		Facilitates primary adhesion of cytokine-activated lymphocytes to endothelium	67
	Inflammation moderation	Free radical scavenging and antioxidant properties	17–20, 59
		TSG-6 and IαI mediated inhibition of inflammatory proteinases	45, 46, 85
Granulation phase	Cell proliferation	Hyaluronan synthesis facilitates cell detachment and mitosis	81-84
	Cell migration	Increased hyaluronan synthesis	73, 77–80
		Hyaluronan-rich granulation tissue provides open, hydrated matrix that facilitates cell migration	2, 3
		Receptor mediated cell migration, e.g., CD44, RHAMM	2, 26, 68–76
	Angiogenesis	Angiogenic properties of low molecular weight hyaluronan oligosaccharides	48, 50-53, 87-92
Reepithelization	Keratinocyte functions	Hyaluronan-rich matrix is associated with proliferating basal keratinocytes	94–98
		Facilitates keratinocyte migration via a CD44-mediated mechanism	23, 37
Remodeling	Scarring	Hyaluronan-rich matrix may reduce collagen deposition, leading to reduced scarring as seen in fetal wound healing	29, 63–64

tracellular environment.[55–57] This may provide the hydrated microenvironment at sites of synthesis to facilitate cell detachment essential for cell migration.

Hyaluronan and cell proliferation

Cell proliferation is also an essential part of tissue repair. It has been shown that increased hyaluronan occurs and is essential for fibroblast detachment from the matrix and mitosis.[82,83] Although hyaluronan has been shown to facilitate cell detachment,[84,85] it has not been shown to have direct mitogenic activity. However, through facilitating cell mitosis in response to mitogenic factors, which are abundant during the early phases of tissue repair, hyaluronan may have an important, albeit indirect, role in cell proliferation too.

Hyaluronan and moderation of the inflammatory response

Although inflammation is an integral part of granulation tissue formation, for normal tissue repair to proceed, inflammation needs to be moderated. The initial granulation tissue formed is highly inflammatory with a high rate of tissue turnover mediated by matrix degrading enzymes and reactive oxygen metabolites that are products of inflammatory cells. Inflammation needs to be moderated in order to allow stabilization of the granulation tissue matrix. In a somewhat contradictory role to its inflammatory stimulation functions as described above, hyaluronan may also function as moderator of inflammation. Hyaluronan protects against free-radical damage to cells.[17–19] This is probably mediated through a free-radical scavenging property, a physicochemical characteristic of large polyionic polymers. In a rat model of free-radical-induced inflammation, hyaluronan has been shown to reduce damage to the granulation tissue.[59]

In addition to the free-radical scavenging role, hyaluronan may also, through its specific biological interactions with the biological constituents of inflammation, function in the negative feedback loop of inflammatory activation. TNF-α, an important cytokine generated in inflammation, stimulates the ex-

pression of TSG-6 in fibroblasts and inflammatory cells. TSG-6, a hyaluronan-binding protein, also forms a stable complex with the serum proteinase inhibitor IαI with a synergistic effect on the latter's plasmin-inhibitory activity. Plasmin is involved in activation of the proteolytic cascade of matrix metalloproteinases and other proteinases leading to inflammatory tissue damage. Therefore, the action of TSG-6/IαI complex, which may be additionally organized by binding to hyaluronan in the extracellular matrix, may serve as a potent negative feedback loop to moderate inflammation and stabilize the granulation tissue as healing progresses.[86] In the murine air pouch model of carragenan/IL-1-induced inflammation where hyaluronan has been shown to have a proinflammatory property[45] (see above), administration of TSG-6 results in reduction of inflammation comparable with systemic dexamethasone treatment.[45]

Angiogenesis

Hyaluronan may also have a role in the control of angiogenesis. High molecular weight hyaluronan in the extracellular matrix has been shown to inhibit angiogenesis.[87,88] However, low molecular weight hyaluronan oligosaccharides have been shown to promote angiogenesis in several experimental models,[89–92] and enhance the production of collagens by endothelial cells.[48] Hyaluronan oligosaccharides may mediate endothelial cell function through binding to the ICAM-1 receptor.[92] Hyaluronan oligosaccharides bind to the CD44 receptor on macrophages and induce the expression of several inflammatory genes including TNF-α and IL-1β.[50–53] This can lead to upregulation of ICAM-1 and further predispose the endothelial cell to stimulation by hyaluronan oligosaccharides. However, high molecular weight hyaluronan also binds to these receptors and so, how they have different effects on cells in comparison to hyaluronan oligosaccharides is not clear. Nevertheless, observations of angiogenesis coinciding with an increase of hyaluronidase and degradation of matrix hyaluronan in several in vivo systems,[88,93] and hyaluronidase digestion of fetal wound hyaluronan leading to fibroplasia and capillary formation[94] are in general agreement with the hypothesis of a physiological role hyaluronan and its oligosaccharides have in the control of angiogenesis.

Reepithelization

Hyaluronan has important functions in normal epidermis. Its functions as an integral part of the extracellular matrix of basal keratinocytes, its free-radical scavenging function and its role in keratinocyte proliferation and migration strongly implies an important role in the reepithelization process as well.

In normal skin, hyaluronan is found in relatively high concentrations in the basal layer of the epidermis, where proliferating keratinocytes are found.[95,96] CD44 is colocated with hyaluronan in the basal layer of epidermis[97] where additionally it has been shown to be preferentially expressed on plasma membrane facing the hyaluronan-rich matrix pouches.[98] The primary function of hyaluronan in epidermis is the maintenance of the extracellular space, and to provide an open, hydrated structure for the passage of nutrients. Hyaluronan content increases upon treatment of skin with topical retinoic acid.[96,99] The reported effects of retinoic acid in reversing the effect of skin photodamage and aging[100–102] may be associated at least in part with an increase of skin hyaluronan content, leading to increase of tissue hydration. It has been suggested that the free-radical scavenging property of hyaluronan contributes to protection against solar radiation, supporting the role of CD44 acting as a hyaluronan receptor in the epidermis.

Epidermal hyaluronan is also implicated in the control of keratinocyte proliferation, which is essential in normal epidermal function, as well as during reepithelization during tissue repair. In healing wounds, hyaluronan is expressed in the wound margin, in the connective tissue matrix, and colocating with CD44 expression in migrating keratinocytes.[37] Kaya et al.[23] showed that suppression of CD44 expression by an epidermis-specific antisense transgene resulted in animals with defective hyaluronan accumulation in the superficial dermis, accompanied by distinct morphologic alterations of basal keratinocytes and defective keratinocyte proliferation in response to mitogen and growth factors. Decrease in skin elasticity, impaired local inflammatory response and impaired tissue repair were also observed. These observations are strongly supportive of the important roles hyaluronan and CD44 have in skin physiology and tissue repair.

Fetal wound healing and scarring

Fetal wound healing is characterized by lack of fibrous scarring. Hyaluronan content in fetal wounds remains high for longer periods than in adult wounds, leading to the suggestion that hyaluronan may, at least in part, reduce collagen deposition and therefore leading to reduced scarring.[63] These suggestions are in agreement with the work of Laurent et al.[29] who showed that applied hyaluronan resulted in scarless healing of tympanic membranes, and with Balasz

and Denlinger,[5] who hypothesized that a hyaluronan-rich environment inhibits the matrix cells responsible for fibrous scars. In a recent paper, West et al.[64] showed that in adult and late gestation fetal wound healing, removal of hyaluronan results in fibrotic scarring. The mechanisms by which hyaluronan affects the quality of fetal wound healing is however, not clear, but is very likely to be a result of a persistent hyaluronan-rich environment that may affect cell-cell and cell–matrix interactions. This in turn may lead to different activation and control of various cell populations in comparison to the adult environment where the hyaluronan-rich environment during tissue repair is transient.

CONCLUSIONS

Hyaluronan is a biological macromolecule that is remarkably conserved through evolution. This high degree of conservation implies fundamental importance in biological processes. Like other areas of biology, such as morphogenesis and metastasis,[1–4] hyaluronan has a multifaceted role in the mediation of the tissue repair process, from early in the inflammatory activation process through to granulation tissue formation and to the reepithelization process. It is unique in biological molecules in that its biological functions can be attributed to its physicochemical properties and to its specific interactions with cells and extracellular matrix. Much work still needs to be done in order to elucidate the biological mechanisms of hyaluronan in tissue processes.

Because of its unique physicochemical properties, hyaluronan has already seen biomedical applications. In tissue repair, its physicochemical properties, the promising results shown by in vivo experimental studies, and its currently known biological properties, strongly indicate applications in mediation of the wound healing process as well as a biomaterial for bioengineering purposes. Already in this field products have been developed for antiadhesion, wound healing, tissue implants and for moisturizing purposes.[6] These products are either based on pure hyaluronan, or derivatives of hyaluronan using cross-linking, esterification or other chemical modification techniques to improve their physical handling and stability characteristics.[103–105] These derivatives of hyaluronan can be manufactured into many physical forms including powders, fleece, fibers, semisolid gels and microspheres, without significant loss of biocompatibility.

Currently, hyaluronan-based medical products are designed to function as medical devices,[6] but applications to utilize its biological functions undoubtedly will also be developed when the biology of hyaluronan becomes better known.

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