REVIEW ARTICLE

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The Role of Hyaluronic Acid in Wound Healing

Assessment of Clinical Evidence

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Abstract

Hyaluronic acid (hyaluronan), a naturally occurring polymer within the skin, has been extensively studied since its discovery in 1934. It has been used in a wide range of medical fields as diverse as orthopedics and cosmetic surgery, but it is in tissue engineering that it has been primarily advanced for treatment. The breakdown products of this large macromolecule have a range of properties that lend it specifically to this setting and also to the field of wound healing. It is non-antigenic and may be manufactured in a number of forms, ranging from gels to sheets of solid material through to lightly woven meshes. Epidermal engraftment is superior to most of the available biotechnologies and, as such, the material shows great promise in both animal and clinical studies of tissue engineering. Ongoing work centers around the ability of the molecule to enhance angiogenesis and the conversion of chronic wounds into acute wounds.

1. Background

In recent years, research into wound healing has expanded dramatically. This has been fueled by a number of sentinel discoveries, particularly over the last 25 years. Techniques described in the last quarter of a century include human keratinocyte culture in 1975,[1] the first dermal analog in 1979,[2] and the discovery of a variety of cytokines and inflammatory mediators that modulate wound healing (see Martin[3]). The opening of each field led to explosions in technology, which have had ramifications in almost all branches of medicine. Within wound healing alone, tissue-engineered products range from simple wound dressings (the original application of Integra®, Johnson & Johnson)[1] to fully formed bilaminar skin substitutes formed as composite cultures (e.g. Apligraf®, Organogenesis Inc.; Novartis Pharma AG, Basel, Switzerland). Bio-engineered materials have also been assessed in fields as diverse as orthopedic,[4] spinal cord,[5] and tracheal surgery,[6] although they are not yet in common use. In general, research has been concentrated in two areas. The first of these, the complex interactions based upon inflammatory mediators and cytokines, is beyond the remit of this discussion, but is an expanding field in which, for instance, manipulation of specific molecules may affect wound healing.[7,8] The second large field

1 The use of trade names is for product identification purposes only and does not imply endorsement.

under study is the extracellular matrix and its interactions with cells. However, it is fair to say that in recent years both lines of research are beginning to coalesce and current work includes the study of bio-engineered materials that contain bio-active molecules.

Research into the extracellular matrix has generally been divided into two materials: collagen and hyaluronic acid (hyaluronan) matrices. The first collagen matrix was developed by Bell et al.[2] in the 1980s and is commercially available as Apligraf®. Yannas et al.[9] developed a matrix composed of collagen and chondroitin sulfate with a silastic membrane. This material has since evolved into the commercial product Integra®, now commonly used as a dermal scaffold for regeneration. All collagen products used in this way are xenogenic, usually utilizing bovine collagen with another product (e.g. Integra® uses shark fin-derived chondroitin-6-sulfate).

In contrast to collagen, hyaluronic acid materials are derived from the same base product, which is highly conserved between species. Chemical modification is necessary in order to manufacture a stable polymer, but the material is essentially the same regardless of its origin. Furthermore, the material is relatively unique within the field of tissue engineering since its degradation products appear to be proactive in wound healing. This has led to a wealth of research within wound healing and has allowed the material to be used in a variety of ways throughout medicine that are as diverse as scaffolds for the growth of dermis,[10] cartilage defects,[11] glial cells,[12] and even as a substrate for the assessment of spermatic motility.[13]

2. Physico-Chemistry of Hyaluronic Acid (Hyaluronan)

Hyaluronic acid was first discovered in the vitreous humor of the eye in 1934[14] and was subsequently synthesized *in vitro* in 1964.[15] It is a polymer based upon a double unit of two sugars: *D*-glucuronic acid and *N*-acetyl-glucosamine (figure 1). It forms non-branching polymers that, when extracted, typically weigh several million daltons[16] and may consist of >30 000 repeating units;[17] as such, it is one of the larger extracellular matrix components. Hyaluronic acid can be sourced from a broad range of tissues and animals and its structure, when purified, is identical throughout species and phyla. It has been documented in such diverse settings as *Pseudomonas* slime,[18] *Ascaris* worms,[19] rats, rabbits,[20] and humans.[21] Equally, it has been documented in tissues as diverse as the skin,[21] aorta, cartilage,[20] and even the brain.[22]

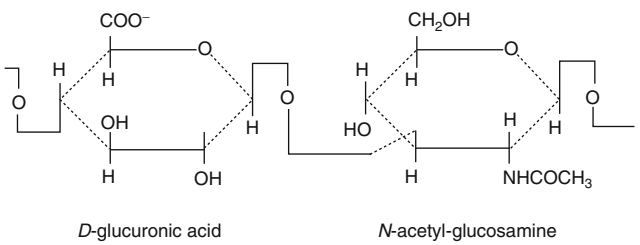

Fig. 1. Chemical structure of hyaluronic acid, a polymer based upon a double unit of *D*-glucuronic acid and *N*-acetyl-glucosamine.

The hyaluronic acid molecule is readily soluble in water, producing a viscous liquid or gel (figure 2) that behaves as a lubricant. The viscosity appears to be related to the length of the chains; longer chains appear to become entangled and thus have increased viscosity.[23] Concurrently, the large-chain molecule demonstrates hygroscopic properties and adsorbs water from the immediate environment, forming a gel at low concentrations[24] and conferring homeostatic properties to the material.

The solubility of hyaluronic acid in water of has proven to be a hindrance to the development of polymers for tissue engineering; when a sheet of purified hyaluronic acid is placed in even a small amount of water, it liquefies. This has beneficial effects in some applications (e.g. orthopedic surgery), but within the field of tissue engineering more structural stability is required. Chemical modification of the molecule has been necessary in order to circumvent this problem. The most common method of stabilization of the molecule is by alcohol esterification, particularly using ethyl and benzyl alcohol (reviewed in detail by Campoccia et al.[16]). In brief, alcohol esterification (usually benzyl) cross-links the polymer to a variable degree depending on the circumstances of the reaction. This leads to molecules with differing solubilities[25] that may be described by their percentage esterification; for example, the HYAFF® materials may be described as HYAFF®-11p75 or HYAFF®-11p95, indicating 75% and 95% esterification of the

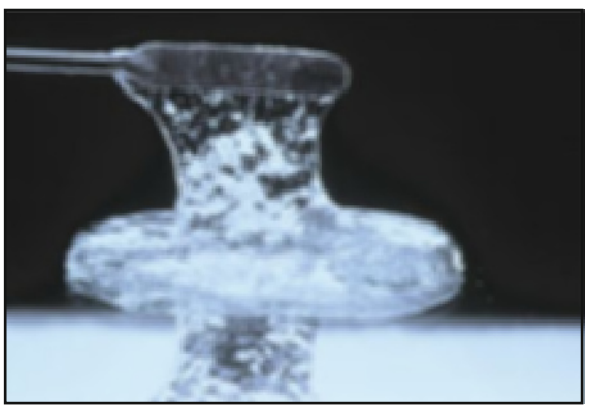

Fig. 2. Hyaluronic acid dissolved in water to produce a viscous liquid or gel. (Reproduced courtesy of Fidia Advanced Biopolymers s.r.l., via Ponte della Fabbrica No. 3/B, 35031 Abano Terme, Italy.)

benzyl ester of hyaluronic acid, respectively. It is thought that the esterification prevents water ingression into the macromolecule, which has the effect of rendering it less soluble. An adverse effect of this is to prevent fibroblast binding and migration along the molecule meaning that the cell is less able to degrade the molecule at will. This delays degradation to a variable extent; the 75% esterified material degrades over the course of 7–14 days, while the 95% esterified product may take up to 2 months to degrade.[16] Once rendered insoluble the polymer may be manufactured in a wide range of forms, including ropes and sheets (figure 3).

As a material used for research or medical purposes hyaluronic acid may be extracted from a number of sources.[14] The two most common sources are rooster combs and the *Streptococcus* bacterium. The former is most commonly used in research and the majority of medical applications, while the latter is the form found in Restylane® rejuvenation products. The two products, when used commercially, appear to have differing rheologic properties, possibly because of the manufacturing process.[26] In animals hyaluronic acid is formed, possibly uniquely, at the cell surface of fibroblasts by extrusion into the extracellular matrix in close association with a dedicated receptor, CD44. There are a number of dedicated synthetic enzymes that form a family known as the hyaluronic acid synthase (HAS) proteins,[27] and synthesis appears to be enhanced in conditions of high lactate.[28] Although there are at least three dedicated cell surface receptors – CD44, RHAMM (receptor for hyaluronic acid mediated motility), and intercellular adhesion molecule-1 (ICAM-1) – CD44 is the main cell surface-binding receptor[29] (particularly the extracellular domain).[30] This receptor and its interaction with hyaluronic acid have been implicated in a number of cell-migration pathologies, particularly the movement of malignant cells.[31,32] As well as manufacturing the macromolecule, fibroblasts also elaborate hyaluronidase, the enzyme responsible for its degradation, and are able to internalize both the original molecule and, particularly, its breakdown products.[33] Hyaluronidase cleaves the macromolecule into a number of smaller polymers, each comprised of short repeating chains based upon the same repeating base pair unit. It is these degradation products that have been the focus of much of the work surrounding the molecule; unlike the collagen-based products mentioned in section 1, the breakdown products of hyaluronic acid appear to have properties that actively affect wound healing and cell kinetics. Studies have indicated that most of the effects attributed to the molecule are applicable to only a narrow range of degradation products and, for convenience, the fragments are now divided into short- and long-chain varieties, although there is no finite division.

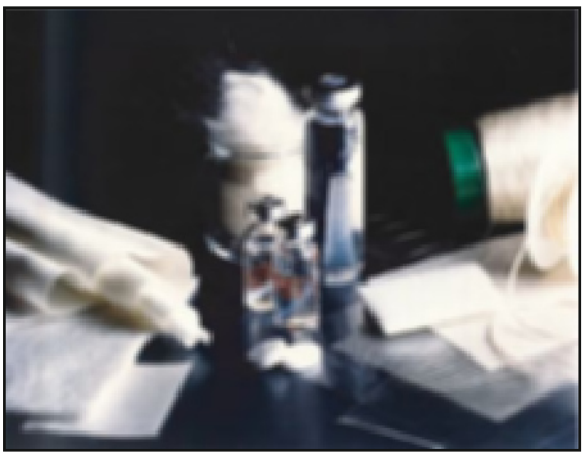

Fig. 3. Examples of different forms of soluble and insoluble hyaluronic acid, such as ropes and sheets. (Reproduced courtesy of Fidia Advanced Biopolymers s.r.l., via Ponte della Fabbrica No. 3/B, 35031 Abano Terme, Italy.)

3. Wound Healing and Hyaluronic Acid

In 1991, West et al.[34] demonstrated that the degradation products of hyaluronic acid were pro-angiogenic, and noted that this effect was limited to fragments of between 4 and 25 disaccharides in length. This was one of the first studies into wound modulation by hyaluronic acid and was soon followed by work that demonstrated other properties and the dependence of those properties upon given molecular length fragments. The angiogenic response was confirmed in 1994[35] and in 1997,[36,37] then subsequently attributed to an intracellular effect upon signaling pathways[38,39] enhanced by co-application of vascular endothelial growth factor.[40] This response has particular importance in tumor biology where it appears to be partly responsible for the enhanced angiogenesis seen within some cancers.[41] Paradoxically, high molecular weight hyaluronic acid appears to inhibit such gene transduction.[37] This polarity of response is a common phenomenon shared with, amongst others, epithelial cells; that is, markedly different responses are dependent upon hyaluronic acid levels.

Cell adhesion within the extracellular matrix also appears to be closely related to the CD44 receptor and hyaluronic acid. There is clear evidence that this is the preferential means of attachment for fibroblasts, and may be the means by which cells first attach to substrates regardless of subsequent motility.[42] Furthermore, hyaluronic acid has been shown to contribute to the regulation of locomotion in ras-transformed cells.[43]

Collagen deposition by fibroblasts is one of the key factors in reconstitution of the supporting matrix at the site of a scar and it is

the nature of this deposition that largely determines the quality of the scar. Application of long-chain hyaluronic acid to gingiva results in decreased fibroblast proliferation,[44] a finding mirrored *in vitro* with cultured fibroblasts.[45,46] It prevents adhesion formation in a variety of areas as diverse as peripheral nerves[47] and spinal laminae,[48] and decreases the total amount of collagen deposited at the scar site by adult dermal fibroblasts[49] (but not fetal – see following paragraph). There is also evidence that extracellular matrix remodeling following application of hyaluronic acid matrices is enhanced and collagen deposition is more ordered[50-52] with less degradation.[53] Confusingly, keloid fibroblasts appear to synthesize increased levels of hyaluronic acid compared with normal (resting) cells,[54] although wound healing cells are probably inherently different to the resting population in their *in vitro* properties,[55] and vascular fibroblasts may demonstrate increased contractility *in vitro*.[56] Fibroblast production of hyaluronic acid may be affected by a number of growth factors.[57] In summary, transforming growth factor (TGF)β-1, basic fibroblast growth factor (b-FGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) all stimulate hyaluronic acid production by fibroblasts. Furthermore, their effects appear to be synergistic and not related to mitosis (and, by extension, proliferation). It would, therefore, appear that at least some of the effects of these growth factors upon cell proliferation and migration are mediated via the hyaluronic acid pathway. The situation is, therefore, not clear-cut but, on balance, there would appear to be benefits from exogenous application of hyaluronic acid on extracellular matrix remodeling.

This latter concept has been extensively studied in the fetal wound healing environment in which prolonged elevation of hyaluronic acid levels has been demonstrated in comparison with adult wounds.[58] In particular, the macromolecule does not appear to be degraded within the fetal environment. Sawai et al.[59] have demonstrated increased levels of hyaluronic acid in sponges implanted in a fetal model and have postulated that this may be related to the rheologic effects. West et al.[60] have demonstrated that application of hyaluronidase (and, by extension, increased levels of hyaluronic acid fragments) causes increased scarring, while persistently raised levels of the macromolecule decrease fibroblast contraction.[61] In addition, fetal and adult fibroblasts react differently to hyaluronic acid,[62] with the former demonstrating greater migration in response to applied hyaluronic acid *in vitro*. The same study demonstrated that fetal cells do not appear to be sensitive to many exogenously applied growth factors such as EGF, PDGF, and acidic-FGF. A further *in vitro* study has shown that fetal fibroblasts proliferate less and produce more extracellular matrix proteins when exogenous hyaluronic acid is added to the culture;[46] when fetal forelimbs are cultured *in vitro* and wounds are created, application of exogenous hyaluronic acid decreases scarring.[63] Recognition that higher levels of CD44 and RHAMM expression are associated with adult wounds may, in part, explain the increased scarring demonstrated in *in utero* studies.[64] It is worth noting that the proportions of hyaluronic acid in normal skin do not appear to change from fetal life to old age, although the degree to which they are bound within the extracellular matrix increases.[65] One final consideration is that at one extreme of tissue inflammation, the rejection response to transplanted tissue, hyaluronic acid fragment levels appear to be increased.[66] In summary, it appears that high levels of macromolecular hyaluronic acid lead to decreased scarring, whilst the adult phenotype is characterized by increased numbers of breakdown products and smaller molecules. Clinically, hyaluronic acid-protein complexes have been used to ameliorate scarring in an adult rat model; treatment was associated with an increased rate of healing, scar remodeling, and peri-wound neutrophil levels but decreased macrophage counts.[67]

The interaction of keratinocytes with hyaluronic acid is complex. There is a body of evidence that suggests that the molecule lies within normal epithelia in fixed distribution. Furthermore, within an *in vitro* monolayer there seems to be preferential colocation with CD44 at apical and lateral aspects of the cell. This is displaced, selectively, by fragments >10U but not <10U.[68] The interaction between cell and peri-cellular hyaluronic acid probably depends upon the cell's response to EGF,[69] and actively proliferating cells express higher levels of CD44 than mature cells.[70] Furthermore, upregulation of hyaluronic acid production has been demonstrated in association with mitosis,[71] suggesting that the hyaluronic acid-CD44 axis may be, in part, responsible for cell proliferation, and recently a novel, hyaluronic acid-specific endocytic pathway has been described.[72] The net effect is that exogenous hyaluronic acid application has been shown to enhance corneal keratinocyte proliferation, both *in vitro* and *in vivo*.[73] Corneal cell migration *in vitro* is enhanced by the addition of hyaluronic acid, an effect that appears to be enhanced by the further addition of fibronectin or EGF.[74] Application of EGF to organotypic cultures results in upregulation of epidermal cell HAS and subsequent production of hyaluronic acid, which further results in increased motility and proliferation[75] (in the same study, TGFβ inhibited such responses, an interesting finding given our understanding of scarring in wounds that are slow to heal). The EGF-dependent production of hyaluronic acid is associated with deposition of hyaluronic acid around the cell and high levels of

uptake,[76] giving rise to the possibility that it may be acting in an autocrine or paracrine fashion.

There is, therefore, a large body of evidence from scientific studies to indicate that hyaluronic acid might affect, predominantly in a beneficial manner, several of the components of wound healing. With this in mind hyaluronic acid has been used *in vivo* for a number of applications resulting in some qualified success.

4. Clinical Experience

Observations regarding the distribution of hyaluronic acid in both normal[77] and disease states[78,79] were recorded as early as 1968 shortly after the first description of the material in the vitreous humor.[14] The earliest therapeutic use, namely treatment of a burn with purified hyaluronic acid in Italy, appears to have taken place in the same year.[80] Since that time, the hyaluronic acid system has found application in almost every field of medicine. Most commonly, hyaluronidase has long been advocated as an addition to subcutaneous fluid administration in order to enhance absorption and subsequently as a means of ameliorating extravasation of chemotherapeutic agents.[81]

Clinical application of hyaluronic acid products falls into two groups: those treatments based upon tissue engineering (particularly wound healing) that generally require the application of a sheet or mesh of the material; and those applications in which the material is instilled into a cavity to effect a change in function of that cavity (particularly for joint conditions). Finally, hyaluronic acid derivatives have been used as markers for clinical conditions, for example, in intraperitoneal inflammation.[82]

5. Tissue Engineering Using Hyaluronic Acid

The advent of a reliable method for culturing human keratinocytes in 1975[83] appeared to herald the onset of a new era in which skin would be produced in virtually limitless quantities and the practice of split-thickness skin grafting would be abolished. The cold reality was that cultured sheets of keratinocytes had exceptionally poor take rates, repeatedly blistered up to late time-points, and were not by any means universally adopted. The Cuono technique[84] of allogenic whole skin grafting followed by autologous keratinocyte grafting increased the take rates of the technology, but not to a degree where it ever realistically threatened to supersede skin grafting. Cuono did, however, appreciate the need for a dermal construct within tissue-engineered whole skin, a concept eventually confirmed scientifically in 1993 by Kangesu et al.[85] Interestingly, this is the very concept upon which Reverdin developed pinch grafting in 1869, although he did not realize its importance.[86] Accordingly, tissue engineering has followed this concept and readers will be familiar with collagen-based lattices such as Integra®, which was developed by Yannas[87] in the 1980s. In keeping with these concepts, two very different hyaluronic acid-derived products have been developed for wound healing, mainly by Fidia Advanced Biopolymers (Padua, Italy) in association with the BRITE-Euram European Union Research Project. The first is a keratinocyte culture/transfer device (Laserskin®) while other products are aimed at dermal regeneration.

Laserskin® is sheets of maximally esterified hyaluronic acid with laser-drilled perforations (figure 4) in rows of 40μm and 500μm holes.[16] The material was initially designed as a transfer mechanism from *in vitro* to *in vivo* for keratinocytes. Cells were applied to the surface of the material and proliferated across it, eventually migrating down the perforations. It would then be applied to the wound bed with the (differentiated) cell surface most superficial, allowing the proliferating cells to populate the wound bed through the pores. The material was first used in isolated clinical cases in the 1990s and was studied in formal research trials from 1997, showing take rates averaging 48.5% in the pig[88] and subsequently assessed in the rat.[89] The latter study demonstrated complete take in 80% of wounds but this result has not been matched in subsequent studies. In 1998 Harris et al.[90] described pre-confluent grafting, where the Laserskin® material was seeded with keratinocytes but these were not allowed to reach confluence. This minimized stratification of the cells and, by extension, differentiation. The Laserskin® could then be applied in an inverted fashion, effectively applying more proliferative cells to the wound since the entire surface of the material could be used for transfer rather than (in effect) the surface area of the pores. This

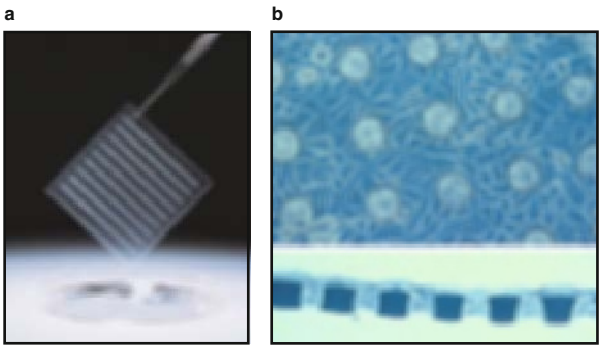

Fig. 4. Laserskin®, a hyaluronan-derived keratinocyte culture/transfer device for wound healing. (**a**) Macroscopic appearance. (**b**) Microscopic view of human keratinocyte cultured on the membrane around the pores and a cross-section below. (Reproduced courtesy of Fidia Advanced Biopolymers s.r.l., via Ponte della Fabbrica No. 3/B, 35031 Abano Terme, Italy.)

proved successful and had the benefit of a reduced *in vitro* time, and has since been adopted by other authors.[91]

Clinical studies into Laserskin® application have centered around chronic wounds. Lobmann et al.[92] have undertaken preliminary studies investigating resurfacing of diabetic ulcers. They compared take rates with this system when used with keratinocytes alone or with a number of fibroblast sources, and demonstrated high rates of healing with co-cultured systems. It is not clear from the article whether the Laserskin® was used inverted or in its traditional orientation; however, they reported wound closure after a single grafting technique in 11 of 14 patients and postulated that the associated arterial disease found in the remainder prevented keratinocyte take. These results are superior to those found by Lam et al.[89] in a burn wound, although the principle of co-culture with fibroblasts to enhance take was demonstrated in this study. Hollander et al.[91] have used Laserskin® in the treatment of chronic leg ulcers to good effect.

The question of why chronic wounds fail to heal has been the source of much debate and there is now a body of evidence to suggest that the micro-environment is abnormal; fibroblasts exhibit abnormal proliferative and functional responses to cytokines[93-99] and this may underlie their inability to heal. The addition of a healthy epidermis, actively secreting cytokines and growth factors is believed to underlie the ability of this technology to heal wounds. Native cells are probably not required as experience with Apligraf® has demonstrated good wound healing with allogenic cells[100-102] without a clinical rejection pattern, although these cells almost certainly do not survive.[103]

Epidermolysis bullosa is a disorder in which essential components of the basement membrane, particularly collagen VII, are manufactured in an abnormal state.[104] Keratinocytes cultured from such patients demonstrate abnormal responses to stress *in vitro*,[105,106] but skin graft wounds (in such patients) treated conservatively and with cultured keratinocytes demonstrate few differences in healing.[107] Although the disorder is at a genetic level and, therefore, would be unlikely to be cured by autologous grafting, Wollina et al.[108] have shown good response rates to autologous Laserskin® grafting in patients with epidermolysis bullosa and have also used the technology in a single case of pyoderma gangrenosum.[109]

There are a number of methods available for reconstructing dermis. In its simplest form, application of an epidermis will eventually generate a limited amount of support tissue although this will take years; clinicians will recognize the long-term appearance of skin grafts applied to, for example, fascial surfaces, in which there appears to be a limited amount of dermis-like tissue beneath the epidermis. Formal reconstruction of the dermal layer may be undertaken by grafting allogenic dermis, as in the Cuono technique (discussed earlier), or by application of novel tissue in the form of bio-engineered substrates. In essence, two materials are currently available in the latter group. The first (which has the longer history) is collagen. The first collagen lattice, based upon bovine material, was described *in vitro* by Bell and coworkers.[2,110] Problems with early degradation led to the addition of shark-fin chondroitin-6-sulfate[9] to produce a material that demonstrated good neo-dermal regeneration. This was subsequently covered in a silicone sheet and is currently marketed as Integra®. For reasons that remain unclear, this material accepts cultured keratinocytes poorly and is currently used with split-thickness autograft, although Chan et al.[111] have successfully engrafted keratinocytes using Laserskin®.

The hyaluronan-based dermal scaffolds that are available have been assessed *in vitro* and *in vivo* in animal models. The material is presented in the form of a loose-woven mesh, which looks very similar to white felt, with a silicone membrane to provide an element of barrier function in the same way as for collagen products (figure 5). Differing levels of esterification are available, with corresponding degradation profiles, although remnants of both partial and total esters may be seen for some time when buried in muscle,[112] suggesting that complete degradation may take some time. Our experience with skin suggests that the HYAFF-11p75 (partial benzyl ester) is almost completely degraded within 7–10 days when applied to a full-thickness wound bed.[113] The angiogenic effects of the material may be quite pronounced and leave the wound bed in a position to undergo epithelial engraftment after 14 days, a time-point that is also convenient for tissue culture techniques. Mouse studies have demonstrated accel-

Fig. 5. Hyaluronan-based dermal scaffold applied onto a full thickness wound in a pig model with chambers. The loose-woven mesh form resembles white felt and contains a silicone membrane that acts as a barrier.

erated wound healing, without excessive wound contraction, when hyaluronic acid-based biopolymers are used as a treatment for full-thickness wounds.[114]

Dermal matrices derived from hyaluronic acid have also been assessed in chronic wounds. Hollander et al.[115] have used a HYAFF mesh co-cultured with dermal fibroblasts and subsequently grafted with Laserskin® onto three patients with traumatic loss of skin, following their experience of use of these products in chronic wounds.[91] Vasquez et al.[116] have used a hyaluronic acid matrix in diabetic, neuropathic ulcers on the weight-bearing surface of the foot. The mean age of the patients was 60 years and 75% of wounds healed by secondary intention during the 20-week study. No epidermal grafting was used. Enhanced epithelial migration and decreased time-to-healing have also been demonstrated in mastoid wounds after application of hyaluronic acid matrices.[117]

In vitro studies of biopolymers have revealed that co-culture with fibroblasts significantly alters the composition of the matrix. Landeen et al.[118] have clearly demonstrated the pattern of molecular replacement towards a more 'normal' extracellular matrix in such conditions. With this in mind, a number of dermal technologies now utilize a period of co-culture with fibroblasts; a prime example is Apligraf®, a collagen matrix composed of neonatal foreskin fibroblasts and keratinocytes. More recently, pre-treatment with fibroblasts has been used in hyaluronic acid matrices to generate a dermis-like material that has been applied to human wounds.[119] This effectively generated a neo-dermis, as assessed by histology, and allowed both split-thickness grafting and secondary healing. Most recently, endothelial cells have been added to hyaluronic acid matrices by Tonello et al.[120] and although this particular construct has yet to be trialed in either an animal or human model, the angiogenic effects of hyaluronic acid have been used to enhance skin graft revascularization,[121] suggesting this to be a potentially interesting line of research.

6. Summary

Hyaluronic acid is a naturally occurring polymer with a highly conserved molecular structure. It has been used extensively in a number of fields, including ophthalmic and joint surgery and particularly wound healing. Hyaluronic acid has important rheostatic and viscosity-controlling properties as a macromolecule, and its degradation products have important modulating effects on the healing wound. It enhances keratinocyte proliferation and migration, as well as the angiogenic response from the wound bed. Although the material is not the panacea against all evils, it clearly demonstrates excellent potential within the fields of tissue engineering and therapeutics. We look forward to the further development of this important biopolymer.

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