Regulatory roles of androgens in cutaneous wound healing

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Summary
Although the effects of androgens on wound healing are poorly characterised, the androgen receptor is expressed by inflammatory cells, keratinocytes and fibroblasts during wound healing, suggesting that androgens may regulate inflammatory and/or repair processes. In fact, it appears that endogenous testosterone inhibits wound healing and promotes inflammation. Since castration of male mice or systemic treatment with the androgen receptor antagonist flutamide accelerates cutaneous wound healing and reduces the inflammatory response. The aim of this review is to summarise our current knowledge about the regulation of tissue repair processes by androgens.

Keywords
Testosterone, androgen receptor, wound, castration, inflammation

Introduction
Large amounts of androgens are synthesised in humans locally in peripheral target tissues from the inactive adrenal precursors dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEA-S). The testis is the major site of androgen biosynthesis in the human male with only a very small contribution from the adrenals. In females, the ovaries and adrenal glands synthesise small amounts of androgens. Circulating testosterone levels are roughly ten times higher in males than in females and, whilst serum testosterone levels decrease slightly with ageing in males, there is no so-called 'andropause'.

The principal function of the skin is to protect the body from the external environment and so it is important that any damage that it sustains is rapidly repaired. Cutaneous wound healing is a complex process involving several overlapping phases. After an initial inflammatory response, wound closure is achieved by the processes of re-epithelialisation and contraction, while fibroblasts proliferate and deposit matrix proteins to replace the damaged tissue. The skin is an important target organ for androgens, whose normal physiological roles include the regulation of hair growth and sebum production. There is also a growing body of direct and indirect evidence to suggest that androgens influence wound repair processes.

It is well known that wound healing is delayed and impaired in the elderly, particularly in males who heal wounds more slowly than females with reduced matrix deposition and an increased inflammatory response. Whilst it is likely that cell ageing mechanisms contribute to impaired wound healing in the elderly, gender differences in various wound repair parameters suggest that differences in the circulating levels of sex hormones may also be involved. All available evidence suggests that, whilst estrogens have a positive effect on wound healing by reducing inflammation and accelerating wound closure, testosterone appears to have a detrimental effect. Moreover, from the in vitro studies and limited number of in vivo studies so far undertaken it appears that androgens influence all phases of wound healing from initial clot formation to long-term wound remodeling.

Androgen biosynthesis
The neutral lipid cholesterol may be transformed via a series of hydroxylation, oxidation and reduction reactions into a vast array of biologically active compounds including mineralocor-
ticos, glucocorticoids and steroid sex hormones. The majority of these conversions occur in the adrenal, testis and ovary although other tissues including liver, kidney, placenta, brain and skin are also involved (1). DHEA and DHEA-S are synthesised in the adrenal cortex and released into the bloodstream in response to the hormone adrenocorticotropic, secreted by the anterior pituitary gland (2). DHEA and DHEA-S circulate at very high concentrations in the blood of young adults. Indeed, plasma DHEA-S levels in adult men and women are some 100-500 times higher than those of testosterone and 1,000-10,000 times higher than those of 17β-estradiol, thus providing a large reservoir of substrate for conversion to androgens and/or estrogens in peripheral intracrine tissues including the skin (3).

The biosynthetic pathway for the conversion of DHEA and DHEA-S to androgens is outlined in Figure 1. DHEA-S is converted to DHEA by the enzyme steroid sulphatase expressed in various cell types including macrophages, keratinocytes and dermal fibroblasts (4-5). The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) is responsible for the conversion of DHEA and 5-DIOL and 4-DIONE and T. DHT is formed from T in a reaction catalysed by 5α-R. The enzyme aromatase converts 4-DIONE and T to the estrogens E1 and E2 respectively.

Figures 1 and 2: Localisation of steroidogenic enzymes in the skin. Underlined text denotes sites of high enzymatic activity.

Table 1: Cutaneous distribution of the steroidogenic enzymes involved in androgen formation. (See Figure 2 for abbreviations).

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Distribution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid Sulphatase</td>
<td>KC, F, SeG</td>
<td>5-7</td>
</tr>
<tr>
<td>3β-HSD</td>
<td>SeG</td>
<td>4, 9-10</td>
</tr>
<tr>
<td>17β-HSD</td>
<td>SeG, KC, HF</td>
<td>4, 11</td>
</tr>
<tr>
<td>5α-R type 1</td>
<td>SeG, SwG, HF, KC, F, EC</td>
<td>14-15</td>
</tr>
<tr>
<td>5α-R type 2</td>
<td>HF, A, SG, KC</td>
<td>14-15</td>
</tr>
<tr>
<td>Aromatase</td>
<td>DPC, F, KC, SeG, HF</td>
<td>10, 25-26</td>
</tr>
</tbody>
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Cutaneous androgen formation
Skin components express all the enzymes required to convert DHEA to DHT and the cutaneous distribution of these enzymes is summarised in Table 1 and Figure 2. Androgen-sensitive skin components include the hair follicles, sebaceous glands, sweat glands, epidermis and dermis, which all express 3β-HSD, 17β-HSD and 5α-R (4). High levels of 3β-HSD expression are
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found only in the sebaceous glands, whilst 17β-HSD activity is mainly localised to the hair follicles, sebaceous glands and epidermal keratinocytes (3, 7-8).

Sex steroids produced in skin most likely have an intracrine mechanism of action (3). DHT is the most potent naturally occurring androgen and is synthesised in tissues as required (9). The enzyme 5α-R catalyses the irreversible conversion of T to DHT. There are two isoforms of 5α-R both of which are expressed in normal skin. Type 1 5α-R shows high levels of activity in the hair follicles, sebaceous glands, epidermis and sweat glands, whilst type 2 5α-R is found almost exclusively in hair follicles with epidermal keratinocytes and subcutaneous adipocytes exhibiting significant levels of expression (3, 10). No qualitative differences in the expression of 5α-R have been observed between male and female skin (10). However, the activities of 5α-R and 17β-HSD have been shown to be significantly higher in sebaceous glands from males than females (11).

5α-R activity, which is low before puberty and in hypogonadal males and increases with androgen secretion and androgen therapy, has been shown to be induced by various factors including DHT, IGF-1, TGF-β1 and TGF-β2 (12-13). A decrease in the levels of T and DHT in male pubic but not scrotal or thigh skin has been observed with age, as has a reduction in foreskin fibroblast 5α-R activity (14-15). Disruption of 5α-R activity has been implicated in various medical conditions e.g. acne vulgaris, hirsutism and androgenic alopecia (16-18).

4-DIONE and T are irreversibly converted to E1 and E2 respectively by aromatisation reactions catalysed by enzyme complexes known as aromatases. The enzyme aromatase has been localised by immunostaining to the hair follicles and sebaceous glands with no qualitative sex difference, indicating that the skin is able to synthesise estrogens (7).

Androgen signaling

Androgens such as T and DHT act via androgen receptors, steroid hormone receptors located in the cell cytoplasm which, in their inactive, unbound state, are complexed to heat shock proteins. After diffusing into cells through the cell membrane lipid bilayer, androgens bind to and activate the androgen receptors (reviewed in 19-20). Steroid binding results in a conformational change that enables the receptors to translocate to the nucleus.

Ligand-activated androgen receptors represent DNA-binding transcription factors that bind as dimers to consensus androgen response element sequences in target genes and recruit other cofactors to regulate gene expression (19-20). Androgens also act at G-protein-coupled receptors located in the plasma membrane of various cells including T cells and macrophages. Activation of these receptors results in an increase in intracellular Ca²⁺ levels (21-22).

The classic intracellular human androgen receptor (AR) is a 110-kDa protein with ligand binding, DNA binding, nuclear localisation, dimerisation and transactivation domains (Fig. 3). It is activated by phosphorylation, dimerisation and acetylation following the binding of DHT or T (23-25). Ligand binding results in AR translocation from the cytoplasm to the nucleus in various cell types. However, in unstimulated human foreskin, AR expression has been shown to be higher in the nucleus than in the cytoplasm in keratinocytes, fibroblasts and vascular endothelial cells, suggesting that androgens may also bind to AR after translocation to the nucleus (26).

DHT has higher affinity for AR than does T and the AR-DHT complex is more stable and has greater transcriptional activity than does the T-bound receptor (27). Furthermore, observed differences in the responses to DHT and T may, at least in part, result from an altered ligand-induced conformation, which may in turn determine which cofactors are recruited to the receptor complex (28).

Transactivation by AR is regulated by AR-interacting proteins including AR-associated protein (ARA)₉₀ and Tip60 as well as c-Jun, Ets and the co-repressor SMRT (24, 29-32). cAMP response element-binding protein (CREB)-binding protein (CBP) and the coactivator p300, a functional homologue of CBP, interact with AR during androgen-dependent transactivation, whilst interleukin-6 (IL-6) may transactivate AR-dependent gene expression in the absence of androgens in a process mediated by p300 (33). AR and the TGF-β-activated transcription factor Smad3 have been shown to interact and to regulate each other’s activities (34-35). AR has additional non-genomic effects through activation of mitogen activated protein (MAP) kinases (36).

Expression of the AR has been shown to be regulated (positively or negatively depending upon cell type) by TNF-α, nuclear factor-κB (NF-κB), IL-6 and Sp1 (37-39). Up-regulation of AR expression by 1α, 25-dihydroxyvitamin D₃, and 9-cis retinoic acid has been observed in human prostate cancer cells and down-regulation by all-trans retinoic acid and DHT in human breast cancer cells (40-41). Whilst AR expression is down-regulated by androgens in many tissues, AR up-regulation has been observed in osteoblasts and foreskin fibroblasts.

Figure 3: Functional domain structure of the human androgen receptor. The receptor does not have a modular domain structure and the N-terminal, DNA-binding and Ligand-binding domains have been implicated in several different AR functions. Numbers denote amino acids.
Androgenic effects on normal skin

The male sex organs express high levels of AR whilst the female sex organs and hepatic, thyroid, pancreatic, gastrointestinal, renal, neuronal, bone, and muscular tissues exhibit lower expression (45). In human skin, AR has been immunolocalised to keratinocytes in the epidermis, hair follicles, sebaceous gland sebocytes, apocrine and eccrine sweat glands, dermal papilla cells (DPC), vascular endothelial cells, vascular smooth muscle cells and fibroblasts (26, 44). AR has also been identified on macrophages, B cells, platelets, megakaryocytes and neutrophils (46-48). Moreover, it has recently been reported that during wound healing, AR is expressed by keratinocytes, inflammatory cells and fibroblasts (49).

Androgen-sensitive skin components include the hair follicles, sebaceous glands, sweat glands, epidermis and dermis (50-53). Androgens stimulate normal hair growth in humans by a mechanism that appears to involve regulation of the production by DPC of paracrine factors that act upon other target cells including follicular epithelial cells (54). Androgens also stimulate beard, pubic and axillary hair growth (52). In beard hair follicles, the stimulatory effect of androgens on the growth of outer root sheath cells is mediated by androgen-induced IGF-1 derived from DPC (55). In mice, however, topical treatment with DHT and T inhibits hair growth (56).

T and DHT cause enlargement of sebaceous glands and stimulate sebum production and secretion (57-58). The age-related decline in DHEA-S and androgen levels may contribute to the reduction in sebum production with age, as well as the reduced numbers and function of apocrine sweat glands observed in elderly men (59-60). In addition, androgens promote common dermatological disorders including baldness, hirsutism and acne (16-18).

T must be converted to DHT to act on certain skin components. DHT is more active than T in hair follicles and is required for beard growth (reviewed in 61). In the absence of DHT, hair growth and sebaceous gland activity are reduced (62). T is, however, sufficient for some actions of androgens on the skin such as the stimulation of axillary and pubic hair growth (61).

Roles of androgens in wound healing

Cutaneous wound healing is a complex process involving several overlapping phases. Initially, temporary repair of the wound is achieved by the formation of a fibrin-rich matrix as a result of activation of the coagulation cascade. This is accompanied by an inflammatory response in which large numbers of leukocytes and fibroblasts are recruited to the wound site and activated to release a plethora of growth factors and cytokines that regulate subsequent wound repair processes. Keratinocytes proliferate and migrate over the temporary matrix to restore the epidermal barrier, whilst angiogenesis and fibroblast proliferation result in the formation of a contractile granulation tissue that draws the wound margins together. The provisional matrix is replaced as fibroblasts deposit large amounts of a collagen-rich matrix, resulting in the formation of a connective tissue scar, which is then remodelled over a period of up to two years.

There is a growing body of evidence that sex hormones influence wound repair processes. Elderly males heal wounds more slowly than elderly females and have reduced matrix deposition and an increased inflammatory response (49, 63). In a study on a group of elderly males, increasing testosterone levels were linked to delayed wound healing (49). Additionally, the results of neural network studies indicate that elderly males are more likely to suffer from impaired wound healing conditions than are females (64).

However, the effects of androgens on wound healing are not well characterised. Androgen receptor expression is localised to keratinocytes, inflammatory cells and fibroblasts during wound healing, suggesting that androgens may be involved in the regulation of inflammation and/or repair (49). Recent studies have suggested that, intriguingly, endogenous testosterone inhibits wound healing and promotes inflammation (49). Wound areas are significantly reduced at day 3 and day 7 in mice following castration (Fig. 4). Castrated male mice exhibit accelerated cutaneous wound healing compared to sham-operated controls accompanied by an attenuated inflammatory response, reduced

Figure 4: Day 3 wounds from sham-operated and castrated male mice. Wound areas are greatly reduced in castrated animals compared to sham-operated controls. Arrows demarcate wound margins.
macrophage invasion and increased matrix collagen deposition. Systemic treatment with the androgen receptor antagonist flutamide also significantly accelerates wound healing and reduces inflammation (49).

Another study has shown that, when administered to burn patients, the androgen analogue oxandrolone has anti-catabolic effects and promotes wound healing (65). However, as an anabolic steroid, oxandrolone might be expected to have different effects on wound healing compared with classic androgens such as T and DHT.

**Inflammation**

Androgens are key inflammatory mediators in various pathophysiological processes. They have been shown to possess both pro- and anti-inflammatory actions and to modulate the expression of cytokines including IL-1, IL-2, IL-6, IL-10 and TNF-α in various cell types (49, 66-67). Androgens generally suppress both humoral and cell-mediated immune responses whilst estrogens enhance at least the humoral immune response (68). A more active immune system, higher resistance to infection, faster rejection of skin allografts, a reduced incidence of tumours and a higher occurrence of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and systemic lupus erythematosus in females compared to males may result from higher relative circulating levels of testosterone and estrogen in males and females respectively (69-71).

Androgens have been observed to elicit a variety of responses in cultured inflammatory cells, some of which are summarized in Figure 5. Activation of cultured neutrophils, as assessed by superoxide anion release, is inhibited by T and promoted by flutamide (72-73). Evidence that androgens may regulate macrophage activation comes from the observations that testosterone and DHT respectively stimulate and inhibit superoxide release by rat macrophages whilst testosterone reduces LPS-stimulated release of nitrite from murine macrophages (74-76). Testosterone potentiates LPS-induced IL-1 production in monocytes while testosterone reduces LPS-induced IL-8 expression. These parameters are restored by treatment with testosterone (87). By contrast, in an in vivo study demonstrated that administration of testosterone increased platelet aggregation stimulated by the thromboxane analogue I-BOP (84). This response was accompanied by increased expression of the receptor for thromboxane A₂ (TXA₂), a key promoter of platelet aggregation. Similarly, male rats treated with testosterone exhibited increased platelet and vascular TXA₂ expression and enhanced platelet aggregation in response to I-BOP (85).

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**Angiogenesis**

The results of several studies suggest that androgens are positive regulators of prostate gland angiogenesis. DHT treatment increases expression of the pro-angiogenic factor VEGF in cultured prostatic epithelial cells whilst rats injected with testosterone exhibit greatly increased prostatic VEGF activity (86). Suppression of prostate gland angiogenesis can be achieved through any method that reduces androgen levels. Castration of rats results in reduced ventral prostate endothelial cell proliferation rate and EGF and VEGF expression. These parameters are restored by treatment with testosterone (87). By contrast, in an in vitro model in which human foreskin microvascular endothelium is important in inflammatory and immune responses. Co-treatment with testosterone increases TNF-α-induced expression of the adhesion molecules E-selectin and VCAM-1 in human umbilical vein endothelial cells (HUVEC). These effects are blocked by the AR antagonist cyproterone (80). Acting at the AR, DHT increases surface expression of the adhesion molecule VCAM-1 in TNF-α-activated HUVEC, resulting in increased monocyte adhesion (81). Another study showed that T, but not DHT, attenuates TNF-α-induced VCAM-1 expression in HUVEC. This effect of testosterone was, however, inhibited by the aromatase inhibitor anastrozole and the estrogen receptor antagonist ICI-182,780 and so appears to result from conversion to estradiol (82).

A limited number of studies have provided evidence that androgens influence the clotting process that immediately follows vascular injury. One clinical study has shown that systemic testosterone treatment decreases plasma levels of von Willebrand factor, an adhesion protein to which platelets bind as a crucial, early event in thrombosis (83). Another ex vivo study demonstrated that administration of testosterone increased platelet aggregation stimulated by the thromboxane analogue I-BOP (84). This response was accompanied by increased expression of the receptor for thromboxane A₂ (TXA₂), a key promoter of platelet aggregation. Similarly, male rats treated with testosterone exhibited increased platelet and vascular TXA₂ expression and enhanced platelet aggregation in response to I-BOP (85).

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Lial cells are cultured on top of a human fibrin matrix in the presence of the pro-angiogenic factors FGF-2 and TNF-α, testosterone inhibits the formation of capillary-like tubular structures (88). This effect, which is mediated by AR, is paralleled by a decrease in the expression of u-PA, which is important in regulating the initial steps of angiogenesis, and reversed by administration of u-PA to the culture.

In one study, DHT stimulated [3H]-thymidine incorporation in cultured HUVECs and had a biphasic effect on [3H]-thymidine incorporation in cultured vascular smooth muscle cells, being stimulatory at lower concentrations and inhibitory at higher doses. All these effects were blocked by flutamide (89). However, another study found that physiological concentrations of testosterone inhibited [3H]-thymidine incorporation in HUVEC and enhanced endothelial cell apoptosis (90). In a third study, testosterone inhibited the proliferation of male, but not female, rat lung endothelial cells (91). These findings suggest that androgens may influence the angiogenic response that follows cutaneous injury in a dose-dependent fashion.

**Re-epithelialisation**
Immunostaining has shown that keratinocytes express AR during wound healing, which suggests that androgens may regulate wound epithelial cell physiology (49). In one study, testosterone was found to inhibit the proliferation of keratinocytes co-cultured with DPC, but had no effect on keratinocytes alone. This effect was reversed by the anti-androgen RU58841 but conditioned media from the co-culture had a similar effect as testosterone, suggesting that testosterone-induced factors in the conditioned media were responsible for the growth inhibition (92). However, DHT has been shown to stimulate the proliferation of cultured human prostate keratinocytes (93). Furthermore, castrated rats display a reduced rate of epidermal keratinocyte proliferation that is restored by treatment with testosterone (51). These findings suggest that androgens may be positive regulators of re-epithelialisation.

**Fibroplasia**
During wound healing, the provisional matrix laid down after injury is turned over by matrix metalloproteinases (MMPs) and replaced by a matrix rich in type I collagen. Type I collagen matrix deposition is increased in the wounds of castrated mice (49). This effect may be a consequence of the dampened inflammatory response, which would be expected to reduce the rate of matrix protein degradation. Up-regulation of MMP-2 expression by the synthetic androgen R1881 has recently been observed in human prostate cancer LNCaP cells (94). By contrast, androgens have been shown to down-regulate the expression of MMP-1, MMP-3 and MMP-7 in LNCaP cells. The down-regulation of MMP-1 expression by ligand-activated AR is achieved by binding to Ets family transcription factors and negatively-regulating their normal ability to activate transcription from the MMP-1 promoter (32). The role of MMP regulation by androgens during in vivo wound healing is yet to be elucidated.

Keloid scarring is a fibrotic disorder of cutaneous wound healing in which androgens may contribute to pathogenesis. Indeed, studies have shown greatly increased androgen binding in keloid tissue compared to normal skin and scar tissue (95). Other evidence for pro-fibrotic effects of androgens comes from the observation that testosterone-treated male rat kidney transplant recipients exhibit increased tubulointerstitial fibrosis compared with vehicle-treated controls (96). Women receiving androgen treatment for osteoporosis exhibit an increase in total skin collagen content (53). Taken together, these studies suggest that androgens may be important regulators of matrix protein deposition during wound healing.

**Conclusion**
Rapid repair of any damage sustained by the skin is essential to protect the body against excessive fluid loss and infection. The roles of sex steroids in these repair processes, suggested by the observation that wound healing is delayed in elderly males compared to females, are now being elucidated. Estrogens have been shown to accelerate wound repair in both human and animal models. They reduce local inflammation, accelerate wound closure and promote matrix deposition. Although the effects of androgens on wound healing are less well characterised, there is growing evidence that endogenous testosterone inhibits wound repair and promotes inflammation. Castration of male mice results in accelerated cutaneous wound healing accompanied by an attenuated inflammatory response and increased matrix deposition. Studies determining the direct effects of androgens on various aspects of wound repair suggest that androgens promote inflammation and regulate matrix deposition and may also influence re-epithelialisation and angiogenesis during wound healing. Future studies are required to determine whether androgens have similar effects on wound healing in human subjects to those observed in rodents. In addition, the downstream mediators of testosterone activities, including cross-talk between the AR and other signaling pathways, require further evaluation. Future studies will help to elucidate the precise roles of androgens in regulating human wound repair.
References