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REVIEW ARTICLE

The role of estrogen deficiency in skin ageing and wound healing

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Abstract The links between hormonal signalling and lifespan have been well documented in a range of model organisms. For example, in *C. elegans* or *D. melanogaster*, lifespan can be modulated by ablating germline cells, or manipulating reproductive history or pregnenolone signalling. In mammalian systems, however, hormonal contribution to longevity is less well understood. With increasing age human steroid hormone profiles change substantially, particularly following menopause in women. This article reviews recent links between steroid sex hormones and ageing, with special emphasis on the skin and wound repair. Estrogen, which substantially decreases with advancing age in both males and females, protects against multiple aspects of cellular ageing in rodent models, including oxidative damage, telomere shortening and cellular senescence. Estrogen's effects are particularly pronounced in the skin where cutaneous changes post-menopause are well documented, and can be partially reversed by classical Hormone Replacement Therapy (HRT). Our research shows that while chronological ageing has clear effects on skin wound healing, falling estrogen levels are the principle mediator of these effects. Thus, both HRT and topical estrogen replacement substantially accelerate healing in elderly humans, but are associated with unwanted deleterious effects, particularly cancer promotion. In fact, much current research effort is being invested in exploring the therapeutic potential of estrogen signalling manipulation to reverse age-associated pathology in peripheral tissues. In the case of the skin the differential targeting of estrogen receptors to promote healing in aged subjects is a real therapeutic possibility.

Keywords Estrogen · Ageing · Skin · Wound healing

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Evolutionary conservation

The links between hormones and ageing, principally identified through the study of model organisms, are numerous. The most prominent example would be the correlation between lifespan and insulin signalling, which is conserved across numerous species. Indeed, the importance of endocrine signalling in lower animal species was initially demonstrated for nematode (*Caenorhabditis elegans*) DAF-2, a homologue of the mammalian insulin and insulin-like growth factor (IGF) receptors, mutations in which lengthened lifespan (Kimura et al. 1997; Kenyon et al. 1993; Larsen et al. 1995). Mutations in numerous genes in the insulin and IGF signalling pathway have also been shown to prolong the lifespan of *Drosophila melanogaster* (Tatar et al. 2001). Mice and higher

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vertebrates, unlike worms and flies, have separate insulin and IGF receptors. Interestingly, mice heterozygous for IGF-1 receptor live ~30% longer than wild-type mice (Holzenberger et al. 2003), while mice null for the downstream mediators, insulin receptor substrate (IRS)-1 and -2, also have extended lifespan (Selman et al. 2008; Taguchi et al. 2007). Such extensive cross-species conservation confirms the importance of this pathway in regulating lifespan (Liang et al. 2003). In fact, decreasing insulin/IGF signalling remains one of the few interventions that does robustly extend murine longevity.

Reproductive state and reproductive system signals can also influence lifespan. For example, germline precursor cell ablation in *C. elegans* and *D. melanogaster* extends lifespan by ~60% (Hsin and Kenyon 1999; Flatt et al. 2008; Arantes-Oliveira et al. 2002), a process thought to be regulated via DAF-2 (Hsin and Kenyon 1999), DAF-9 [a homologue of mammalian cytochrome P450] (Gerisch et al. 2001; Gerisch and Antebi 2004; Jia et al. 2002) and DAF-12 (Broue et al. 2007), amongst others (Fig. 1a). The hormone repertoire of model organisms most commonly used for ageing research, such as *C. elegans* and *D. melanogaster*, is limited, yet they do express hormone precursors present in higher animals, such as pregnenolone and essential enzymes necessary for conversion, such as cytochrome P450 (aromatase) (Broue et al. 2007; Motola et al. 2006). Signalling via such precursors extends lifespan in *C. elegans* (Yamawaki et al. 2010; Broue et al. 2007; Mak and Ruvkun 2004) and *D. melanogaster* (Yamawaki et al. 2010; Simon et al. 2003). For example, pregnenolone extends lifespan in nematodes, via DAF-9 (Broue et al. 2007) (Fig. 1b). Surprisingly, the relevance of steroid precursors, such as pregnenolone, in mammalian longevity is largely unknown. Interestingly, aged ovariectomised (Ovx) mice transplanted with the ovaries of young mice exhibit significantly increased life expectancy (Mason et al. 2009; Cargill et al. 2003), an effect potentially mediated through the estrogen receptors and/or the IGF-1R (Fig. 1c).

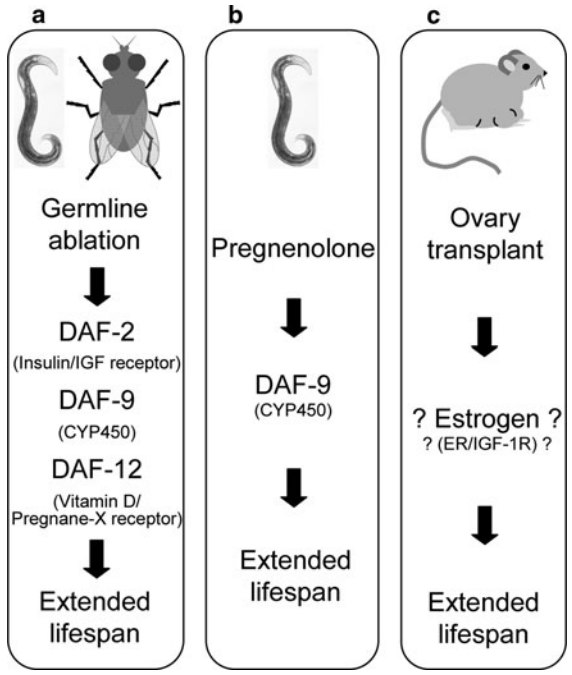

Fig. 1 Association between steroid sex hormones and lifespan. **a** Germline cell ablation in *C. elegans* and *D. melanogaster* extends lifespan via DAF-2, -9 and -12. **b** Pregnenolone signals via DAF-9 and extends lifespan in *C. elegans*. **c** Hormone transfer by ovary transplant from young mice to aged mice extends lifespan, an effect presumably mediated by estrogen and the ERs or IGF-1R

Ageing in humans, the menopause and pathology

With increasing age the human endocrine system undergoes substantial change, particularly with respect to hormones of adrenal origin. The steroid precursor dehydroepiandrosterone (DHEA), its sulphate, DHEA-S, and the precursor androstendione decline substantially in both males and females from age 20 (Labrie et al. 1997). Interestingly, serum concentrations of pregnenolone (discussed above) also decrease with age in both males and females (Havlikova et al. 2002; Labrie et al. 1997). In women levels of sex steroid estrogens begin to fall from approximately 35 years of age and follicle stimulating hormone (FSH) production is increased in an effort to stimulate ovarian function (Chakravarti et al. 1976). While 17β-estradiol, the most potent form of estrogen, decreases with age serum estrone concentrations remain fairly constant (Labrie et al. 1997). The most pronounced changes occur when women enter the menopause, a permanent cessation of menstruation resulting from the loss of ovarian follicular activity, which occurs at an average age of 51 years in the developed world (Stanford et al.

1987). Post-menopause the majority of circulating sex steroids actually originate from circulating adrenally-derived DHEA (Labrie et al. 2011). In aged males estrogen levels also decrease, although not as rapidly as in females. By contrast, testosterone and dihydrotestosterone (DHT) fluctuate but remain fairly constant with age in both sexes (Labrie et al. 1997). Of note, the enzyme 11β-hydroxysteroid hydrogenase (HSD), which is responsible for the conversion of cortisone to cortisol, is markedly increased with age (Vukelic et al. 2011; Tiganescu et al. 2011).

Increasing life expectancy now means that the average woman in the developed world spends one-third of her life in the post-menopausal period (Kligman and Koblenzer 1997). It is widely accepted that decreased systemic hormones in the post-menopausal state is associated with increased risk for a range of age-associated pathologies (Table 1).

Estrogen deficiency as a general mechanism of ageing

Arguably the most profound hormonal change in ageing is the post-menopause reduction in 17β-estradiol. Moreover, a substantial body of literature links estrogen decline to the distinct cellular ageing mechanisms of oxidative damage and cellular senescence.

Oxidative damage

Free radicals are strongly implicated in the cellular damage that accompanies ageing and age-associated disease (Harman 1956; Beckman and Ames 1998), part of the 'mitochondrial theory of ageing' (Miquel et al. 1980). The link between mitochondria and longevity comes from the observation that by reducing mitochondrial peroxidase production lifespan can be extended (Lopez-Torres et al. 1993; Ku et al. 1993). Pertinent to this review is the observation that both peroxidase production and mitochondrial DNA damage are significantly (40–80%) higher in male rats than in age-matched females, and this is directly attributed to differences in estrogen levels (Borras et al. 2003; Pinto and Bartley 1968, 1969). Mitochondrial glutathione, a biological marker of ageing and age-associated damage (Hazelton and Lang 1984; Sastre et al. 2000) is significantly higher in male rats than females (Vina et al. 2005). Conversely, expression of 16S ribosomal RNA, a biological marker of youth (Calleja et al. 1993), is substantially higher in female rats than males (Borras et al. 2003; Vina et al. 2005). Although, Sanz et al. (2007) report no difference in oxidative stress, age-related damage or lifespan between male and female C57Bl6 mice, Ali et al. (2006) show that females, the reported shorter lived gender, exhibit enhanced reactive oxygen species (ROS) production with age.

Table 1 Chronic pathologies associated with ageing and menopause

Pathology	Age	Menopause
Auditory degeneration	Weinstein and Ventry (1982)	Hederstierna et al. (2010)
		Hederstierna et al. (2007)
Cancer	Yancik et al. (2001)	Trichopoulos et al. (1972)
Heart disease	Lindblad et al. (2001)	Lokkegaard et al. (2006)
	Lye and Donnellan (2000)	Jacobsen et al. (1997)
	Colditz et al. (1987)	Barrett-Connor (1995)
Muscular degeneration	Evans (2010)	Calmels et al. (1995)
Neurodegeneration	Kukull et al. (2002)	Simpkins et al. (2005)
	Suthers et al. (2003)	Morrison et al. (2006)
Optical degeneration	Owsley et al. (2007)	Siesky et al. (2008)
	Carcenac et al. (2009)	Evans et al. (1998)
Osteoporosis	Gates et al. (2009)	Melton et al. (1992)
	Simonen and Mikkola (1991)	
Skin ageing	Lavker (1979)	Brincat et al. (1987)
	Gilchrest et al. (1983)	Sumino et al. (2004)
Urinary incontinence	Williams and Pannill (1982)	Waetjen et al. (2009)

Estrogen deficiency post-menopause is also strongly linked to altered oxidative state, with estrogen a potent direct antioxidant and indirect inducer of antioxidant enzymes. In ovariectomised (Ovx) female rats oxidised glutathione, lipid peroxidation and mitochondrial DNA damage are significantly increased, and can be reversed by estrogen replacement or phytoestrogen treatment (Baeza et al. 2010). In vitro both estradiol and the phytoestrogen genistein reduce the production of hydrogen peroxide in MCF-7 cells (Borras et al. 2005, 2006). Additionally, keratinocytes isolated from aged female rats exhibit increased oxidative stress (lipoperoxides) and apoptosis (caspases 3 and 8), which can be reversed by estrogen treatment (Tresguerres et al. 2008). Finally, it should be noted that while gender-specific effects are common across many species, including man (Gurwitz 2005), marsupials (Humphries and Stevens 2001) and non-human primates (Herndon et al. 1999) this is not the case in all animal species. Some species lack gender difference in lifespan (Sanz et al. 2007; Wich et al. 2004) while in a limited number of species males actually live longer (Asdell and Joshi 1976; McCulloch and Gems 2003).

Senescence

Significant telomere shortening is associated with replicative cell senescence and tissue deterioration (Allsopp et al. 1992; Harley 1991), and prevented by the enzyme telomerase (Morin 1989). The expression of the human telomerase reverse transcriptase (hTERT) gene and telomerase activity (TA) is upregulated in hepatocytes in vitro in response to estradiol, leading to maintained telomere length (Sato et al. 2004). Similarly, estrogen dose-dependently prevents cellular senescence and increases telomerase activity in endothelial progenitor cells (Imanishi et al. 2005b), vascular smooth muscle cells (Ling et al. 2006) and leukocytes (Aviv et al. 2006) in vitro. In endothelial progenitor cells estrogen prevents angiotensin-II-mediated oxidative stress and senescence (Imanishi et al. 2005a). Estrogen deficiency significantly inhibits TERT expression and telomerase activity in the mouse adrenal gland, an effect reversed by estrogen replacement (Bayne et al. 2008). It has thus been speculated that gender specific differences in longevity are, at least in part, due to hormonal regulation of telomere function (Aviv et al. 2005; Stindl 2004). One method of detecting senescent cells in vitro is a modified beta-galactosidase (β-gal) assay (Dimri et al. 1995). Interestingly, the soy-derived phytoestrogen genistein suppresses UVB-induced expression of β-gal in primary human dermal fibroblasts (Wang et al. 2010), while soybean extract protects against cellular senescence in HaCaT cells (Chiu et al. 2009).

Skin ageing and estrogens

With increasing age a combination of intrinsic and extrinsic factors (primarily UV exposure) lead to skin deterioration. Aged skin has altered structure and reduced function, particularly loss of elasticity, wrinkling, thinning and fragility. While there are differences in the etiology of intrinsic and extrinsic ageing (Tsoureli-Nikita et al. 2006) the majority of resultant changes are similar (Tsoureli-Nikita et al. 2006; Pillai et al. 2005; Ashcroft et al. 1997e; Varani et al. 2001; Lavker 1979). Specifically, intrinsic ageing involves thinning of the epidermis and dermis, reduced epidermal proliferation and turnover and reduced vascularity (Gilchrest et al. 1982b; Lavker 1979). Collagen production is reduced (Shuster et al. 1975) and distribution is altered (Richard et al. 1993), while the production of matrix degrading enzymes (MMPs) is increased with intrinsic ageing (Ashcroft et al. 1997e). Extrinsic ageing or photoageing involves dermal elastosis (Mitchell 1967; Braverman and Fonferko 1982), reduced Langerhans cell numbers, altered melanocyte distribution (Thiers et al. 1984; Gilchrest et al. 1982a) and increased MMP activity (Pillai et al. 2005). With advancing age reduced sebaceous gland secretion leads to skin xerosis, an event that involves corticotropin-releasing hormone (CRH) and coincides with the onset of menopause in women (Pochi et al. 1979; Zouboulis et al. 2002).

The effects of ageing can be readily observed in skin cells in vitro, where dermal fibroblasts and epidermal keratinocytes from aged donors have reduced proliferative capacity and display premature senescence (Stanulis-Praeger and Gilchrest 1989; Gilchrest 1983; Schneider and Mitsui 1976; Mets et al. 1983). In ageing human skin senescent cells accumulate through a combination of growth arrest and increased resistance to apoptosis (Dimri et al.

1994; Wang 1995). In the principal skin cell types (keratinocytes/fibroblasts) telomeres shorten an average of 9 and 11 base pairs per year, respectively, throughout life (Sugimoto et al. 2006; Krunic et al. 2009). Interestingly, telomere shortening is reportedly unchanged in sun-exposed (extrinsically aged) versus sun-protected (intrinsically aged) skin (Sugimoto et al. 2006). Instead, large deletions of the mitochondrial genome are believed to be involved in UV-induced skin photoageing (Schroeder et al. 2008). In vitro, repetitive exposure of human dermal fibroblasts to UVA has been shown to induce deletions of up to 5000 base pairs, causing a partial loss of the mitochondrial genome (Berneburg et al. 1999). Moreover, in a model where mtDNA deletions were induced without irradiation, gene expression mirrored that observed in photoaged skin (Schroeder et al. 2008).

While laboratory animals provide excellent tractable models, some aspects of skin ageing, e.g., changes in epidermal thickness, are contentious and appear species and strain dependent. The majority of mouse studies find that with age epidermal thickness is reduced (Iversen and Schjoelberg 1984; Haratake et al. 1997; Bhattacharyya and Thomas 2004; Argyris 1983) and epidermal keratinocyte proliferation is decreased (Cameron 1972). However, other studies have reported increased epidermal thickness with age (Hill 1988). Epidermal thickness in aged rats has been reported to increase (Bhattacharyya et al. 2005; Thomas 2005), decrease (Morris et al. 1990) or remain unchanged (Giangreco et al. 2008; Monteiro-Riviere et al. 1991). Interestingly, Ishibashi rats (progeny of Wistar and wild rats) reportedly undergo qualitatively similar skin changes to humans. From 12 weeks of age wrinkling of the skin occurs, consistent with a reduction in elastin (Sakuraoka et al. 1996). Calorie restriction (CR), which extends lifespan in numerous model organisms (*S. cerevisiae*, *C. elegans*, *D. melanogaster*) (Lin et al. 2002; Klass 1977; Hosono et al. 1989; Mair et al. 2003; Pletcher et al. 2002) and higher mammals, such as mice and non-human primates (Lane et al. 1995; McCay et al. 1935; Rezzi et al. 2009; Ramsey et al. 2000), prevents age-related skin changes when compared to age-matched ad libitum controls (Thomas 2005; Bhattacharyya et al. 2005). Unfortunately, neither of these studies specifies the sex of the experimental animals.

Historic studies provide the first evidence of estrogen's cutaneous effects: topically applied follicular hormone, now known to be estrogen, was found to locally improve acne and eczema (Loeser 1937). It has also long been known that the symptoms of skin disorders such as psoriasis improve during pregnancy, an observation now directly attributed to increased circulating estrogen (Dunna and Finlay 1989; Boyd et al. 1996) Moreover, the oral contraceptive pill is often prescribed to treat severe acne (Arowojolu et al. 2009). During the menopause, skin undergoes major changes which include reduced epidermal and dermal thickness, a decrease in collagen content (Brincat et al. 1987), reduced elasticity (Sumino et al. 2004), dryness and fragility (Brincat et al. 1985). Crucially, the majority of these changes can be reversed by either topical or systemic hormone replacement therapy (HRT) (Table 2). Not surprisingly, topical estrogen treatment has little effect on young skin (Goldzieher 1949). The effects of estrogen are predominantly mediated through the estrogen receptors (see "Estrogen receptors and SERMs" section). Estrogen also protects against photoageing, with mortality rates from both melanoma (Miller and Mac Neil 1997) and non-melanoma (Weinstock 1994) skin cancer lower in women than men. In experimental animal studies estrogen deprivation enhances sensitivity to UV skin damage and accelerates photoageing, measured as wrinkling, a loss of elasticity and damage to elastic fibres (Tsukahara et al. 2001; Tsukahara et al. 2004), while estrogen treatment increases skin collagen content in rats and guinea pigs (Smith and Allison 1966; Henneman 1968), increases hyaluronic acid synthesis (Sobel et al. 1965) and promotes epidermal thickening in mice (Bullough 1947). A potential link between ageing and estrogen involves IGF-1. Estradiol is known to be able to signal through the IGF-1R in the skin, in a non-genomic manner, strongly implicating it's involvement in the regulation of cutaneous ageing (Makrantonaki et al. 2008; Surazynski et al. 2003).

In reality, the skin is not only an estrogen target, but also a major synthetic organ with the capacity to release and produce a wide range of hormones, including estrogens. Skin cells are able to synthesise locally acting estrogens from the precursors cholesterol and DHEA (Fig. 2) (Simpson et al. 1997; Bulun et al. 1999; Chen et al. 2002; Chen et al. 1998;

Table 2 Cutaneous changes with post-menopausal estrogen replacement

Cutaneous changes	Reference(s)
Increased epidermal thickness	Punnonen (1971), Brincat (2000), Fuchs et al. (2003)
Increased dermal thickness	Son et al. (2005), Shuster et al. (1975), Brincat et al. (1985)
Increased collagen content	Castelo-Branco et al. (1992), Savvas et al. (1993), Shuster et al. (1975), Varila et al. (1995)
Increased elastin content	Punnonen et al. (1987)
Increased skin moisture content	Pierard-Franchimont et al. (1995), Schmidt et al. (1994)
Improved external appearance	Schmidt et al. (1996), Schmidt et al. (1994), Brincat et al. (1985), Creidi et al. (1994)
Fewer wrinkles	Aertgeerts (1974)

Thiboutot et al. 1998; Hughes et al. 1997; Sawaya and Penneys 1992; Dumont et al. 1992; Eicheler et al. 1995; Thiboutot et al. 2000). Additionally, local production of 11β-HSD by epidermal keratinocytes, dermal fibroblasts and hair follicles (Tiganescu et al. 2011) increases cortisol conversion and has been speculated to control the inflammatory response (Vukelic et al. 2011). In aged individuals peripheral hormone production and local hormone signalling are likely to be particularly important, in light of the considerable reduction in systemic hormone production (Longcope 1971). Surprisingly, the effects of ageing on peripheral hormone synthesis/conversion are virtually unknown.

Wound repair with age

Cutaneous wound healing is a complex tightly orchestrated response to injury, carefully regulated at temporal and spatial levels (reviewed in Shaw and Martin 2009). In young individuals the innate

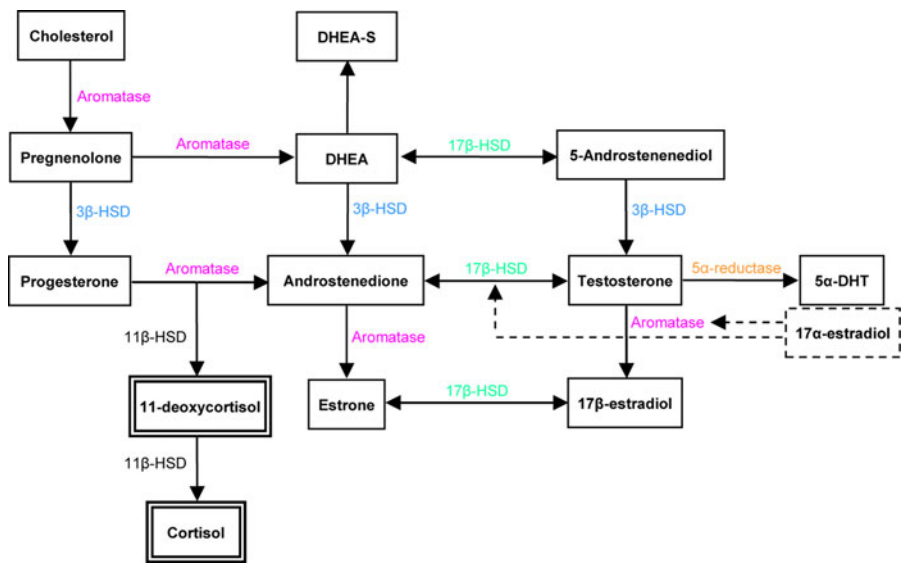

Fig. 2 Skin contains all the components for peripheral steroid hormone synthesis. The precursors cholesterol and dehydroepiandrosterone (*DHEA*) can be converted to steroid hormones by aromatase (the product of the CYP19 gene), 3β-hydroxysteroid dehydrogenase (*3β-HSD*), 17β-hydroxysteroid dehydrogenase (*17β-HSD*) and 5α-reductase. 17α-estradiol has been shown to influence the conversion of testosterone to 17β-estradiol and androstenedione. *Double boxes* represent functionally important non-steroid hormone synthesis

inflammatory response is first initiated, followed by a widespread proliferative phase, involving fibroblasts, keratinocytes and endothelial cells. Keratinocyte migration restores the skin's barrier, fibroblast-mediated contraction aids wound closure, while matrix remodelling leads to a mature scar. With the passage of time skin becomes fragile and prone to trauma, while cellular ageing leads to aberrant healing. Platelet function (Boldt et al. 2001; Fukaya et al. 2000) and platelet-derived growth factor (PDGF) expression (Ashcroft et al. 1997d) is altered with age. The inflammatory response becomes disrupted, with excessive neutrophil influx, altered endothelial cell adhesion, prolonged macrophage recruitment and delayed resolution (Ashcroft et al. 1998). This leads to over-production of matrix degrading enzymes, classically elastase and MMPs (Ashcroft et al. 1997e; Ashcroft et al. 1997f; Herrick et al. 1997), and under-expression of tissue inhibitors of metalloproteinases (TIMPs) (Ashcroft et al. 1997b). In vivo, re-epithelialisation is delayed in aged humans and murine models (Ashcroft et al. 1997a). Corroborative in vitro studies show that keratinocytes from young donors proliferate at a faster rate (Stanulis-Praeger and Gilchrest 1986) and exhibit less sensitivity to epidermal growth factor (EGF) and keratinocyte growth factor (KGF) (Gilchrest 1983) than those from old aged donors. Angiogenesis is delayed in aged humans and mice (Ashcroft et al. 1997c; Sadoun and Reed 2003) and collagen deposition is reduced (Lenhardt et al. 2000; Ashcroft et al. 1997c). Ultimately, in elderly subjects scar strength is reduced (Lindstedt and Sandblom 1975; Sandblom et al. 1953; Mendoza et al. 1970), however, scar quality is improved (Ashcroft et al. 1999).

Repair, ageing and hormones

While chronological age is a clear risk factor for poor healing our recent studies suggest that estrogen deprivation is the major factor controlling delayed healing in elderly humans. In our recent microarray study 78% of genes differentially expressed between wounds from young and elderly men were estrogen-regulated, while only 3% were age-associated, strongly implicating reduced estrogen, and not known gerontogenes, as the primary regulator of delayed healing in aged subjects (Hardman and Ashcroft 2008). In post-menopausal women HRT improves healing (Ashcroft et al. 1997a), while topical estrogen treatment improves healing in elderly subjects of either gender (Ashcroft et al. 1999). Estrogen's cellular effects include dampening excessive neutrophil recruitment, preventing disproportionate elastase production, and increasing fibronectin and collagen deposition. Crucially, two independent studies reveal that HRT protects post-menopausal women from developing venous leg ulcers or pressure ulcers (Margolis et al. 2002; Berard et al. 2001).

Animal models have provided key insight into estrogen's role in wound healing (summarised in Fig. 3). Estrogen replacement accelerates cutaneous healing in Ovx female mice and rats (Ashcroft et al.

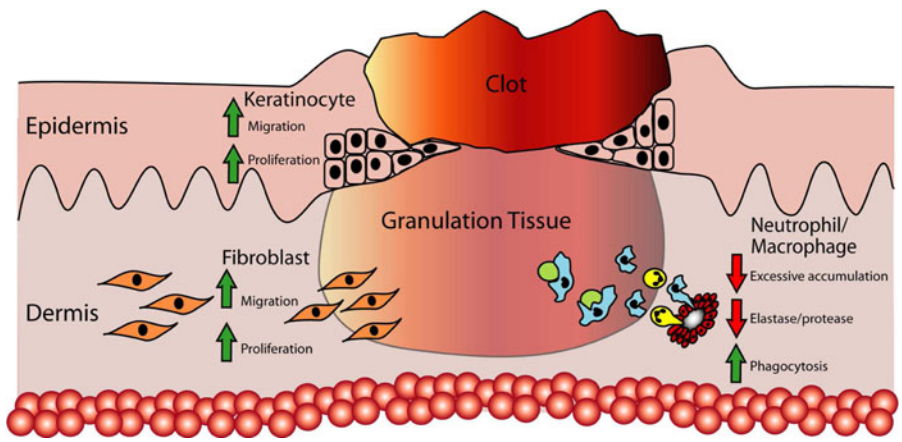

Fig. 3 Mechanism of estrogen activity in older people. Estrogen aids healing through effects on fibroblasts, keratinocytes and inflammatory cells

1997a; Ashcroft et al. 2003; Emmerson et al. 2010; Hardman et al. 2008) and male rats (Rajabi and Rajabi 2007). Systemic treatment with the sex steroid precursor DHEA accelerates wound healing in young Ovx female mice and old male mice, a result attributed to the local conversion of DHEA to estrogen (Mills et al. 2005). Of interest, androgens are detrimental to healing. The testosterone metabolite DHT retards repair (Gilliver et al. 2009), while castration or androgen receptor blockade improves healing in rodents (Gilliver et al. 2003; Gilliver et al. 2006; Ashcroft and Mills 2002).

At the cellular level estrogen down-regulates neutrophil-expressed L-selectin, preventing the excessive neutrophil accumulation and neutrophil-derived elastase production characteristic of aged healing (Ashcroft et al. 1999), and improves neutrophil phagocytic ability (Magnusson and Einarsson 1990). Estrogen dampens expression of numerous pro-inflammatory cytokines, including MIF, TNFα, MCP-1, IL-1β and IL-6 (Kovacs et al. 1996; Hu et al. 1988). The reduction in Macrophage Migration Inhibitory Factor (MIF), in particular, plays a major role in the beneficial effects of estrogen on wound repair (Ashcroft et al. 2003; Hardman et al. 2005; Emmerson et al. 2009). Of interest, plasma MIF levels, which inversely correlate with systemic estrogen (Aloisi et al. 2005), are increased post-menopause and fall following HRT (Hardman et al. 2005). Estrogen is also a keratinocyte mitogen (Verdier-Sevrain et al. 2004), promoting migration across an artificial scratch in vitro (Emmerson et al. 2009; Campbell et al. 2010) and wound re-epithelialisation in Ovx mice (Emmerson et al. 2010; Hardman et al. 2008). Moreover, impaired wound re-epithelialisation post-menopause can be reversed to pre-menopause levels by just 3 months of HRT (Ashcroft et al. 1997a). Estrogen directly stimulates dermal fibroblast migration in vitro (Emmerson et al. 2009; Campbell et al. 2010) and indirectly via stimulating macrophage platelet derived growth factor (PDGF), a key fibroblast mitogen and stimulator of wound contraction (Battegay et al. 1994). The role of estradiol in stimulating angiogenesis is somewhat contentious. PDGF directly stimulates angiogenesis, while estradiol increases endothelial cell capillary-like structure formation upon reconstituted basement membrane (Morales et al. 1995). However, conflicting in vitro studies report either no change or decreased angiogenesis following estrogen treatment (Nyman 1971; Lundgren 1973).

Estrogen receptors and SERMs

Estrogen signals via two nuclear hormone receptors, ERα and ERβ. ERα, the first receptor to be identified and cloned (Walter et al. 1985), predominates in reproductive tissues and is strongly associated with cancer (Zou and Ing 1998; Kuiper et al. 1997; Ali and Coombes 2000). The second receptor, ERβ, identified over a decade later (Kuiper et al. 1996; Ogawa et al. 1998), is more highly expressed in peripheral, non-reproductive tissues (Kuiper et al. 1997; Onoe et al. 1997; Brandenberger et al. 1997; Couse et al. 1997). Both receptors are reportedly expressed in human facial skin (Miller and Mac Neil 1997), scalp (Thornton et al. 2003a, b; Mosselman et al. 1996) and upper arm skin (Reed et al. 2005). Several studies suggest that ERβ predominates in keratinocytes of human scalp skin (Mosselman et al. 1996; Thornton et al. 2003a, b) while others identify both receptors in neonatal foreskin-derived keratinocytes (Verdier-Sevrain et al. 2004). In mouse skin both receptors are widely expressed (Campbell et al. 2010; Cho et al. 2008).

Our recent data indicate that delayed healing in Ovx female mice can be reversed by stimulating signalling through ERβ alone (using the ERβ-specific agonist DiarylPropioNitrile [DPN]) (Campbell et al. 2010). Conversely, signalling through ERα alone (using the ERα agonist Propyl Pyrazole Triol [PPT]) entirely fails to improve healing in Ovx mice. To support this finding, we find that estrogen replacement in Ovx mice lacking functional ERβ (ERβ−/−) actually further delays healing beyond the Ovx wild-type phenotype. Moreover, epidermal specific ERβ null mice (K14-cre/ER$\beta^{L2/L2}$) phenocopy ERβ−/− mice, i.e., estrogen replacement again impairs healing. This would suggest that the beneficial effects of estrogen on cutaneous repair are predominantly mediated via epidermal ERβ (Campbell et al. 2010). Of note, the beneficial effects of 17β-estradiol on outcome in a skin flap necrosis model is reportedly mediated via ERα (Toutain et al. 2009) while Ovx rats treated with PPT exhibit reduced wound tensile strength (Gal et al. 2010). A crucial link between our mouse data and aged human healing is provided by the observation that polymorphisms in the human

ERβ gene are significantly associated with venous ulceration in the Caucasian population (Ashworth et al. 2005, 2008).

Most pathological states in the elderly involve a single ER isoform, for example in cancers of the reproductive system ERα predominates (Herynk and Fuqua 2004; Yang et al. 2008; Cai et al. 2003), while in colon cancers ERβ predominates (Arai et al. 2000; Fiorelli et al. 1999; Foley et al. 2000; Qiu et al. 2002). The clear differential roles of the two estrogen receptors in cutaneous repair (Campbell et al. 2010; Gal et al. 2010; Toutain et al. 2009) suggest that pharmacological manipulation may be a viable therapeutic option. Compounds termed Selective Estrogen Receptor Modulator (SERMs) are being developed to treat pathologies such as osteoporosis and breast cancer by exploiting natural estrogen signalling to confer tissue specific estrogenic or anti-estrogenic effects.

SERMs have been developed to provide estrogen-like beneficial effects, to treat disorders such as osteoporosis, an approach that should bypass systemic estrogen risks, including breast cancer (Matsumoto 2006). Arguably, the best characterised and commonly used SERMs are tamoxifen and raloxifene. Both are considered ER antagonists in the breast, but have the potential to act as ER agonists in other tissues (Frasor et al. 2004). The dietary phytoestrogen genistein, is also becoming increasingly popular for the treatment of post-menopausal pathology (Atteritano et al. 2008; D'Anna et al. 2007). Despite use of SERMs in age- and menopause-associated pathologies (reviewed in Pickar et al. 2010) knowledge of SERM activity in the skin is severely lacking. In vitro both tamoxifen and raloxifene stimulate fibroblast proliferation, but fail to promote fibroblast migration (Stevenson et al. 2009). Preliminary studies in post-menopausal skin indicate increased elasticity and collagen content following raloxifene treatment (Sumino et al. 2009) and improved dermal vascularisation and increased epidermal thickness following genistein treatment (Moraes et al. 2009). Topical tamoxifen reportedly improves the appearance of keloid scars in acute burns patients, through dampening of fibroblast proliferation and collagen synthesis (Mousavi et al. 2010; Gragnani et al. 2009). Our recent studies indicate that the SERMs tamoxifen, raloxifene and genistein all substantially benefit healing in the estrogen-deprived Ovx mouse, promoting re-epithelialisation and contraction, and reducing inflammation, an effect that is most likely mediated via ERβ (Emmerson et al. 2010; Hardman et al. 2008), while a separate study provides evidence that genistein accelerates murine healing by modulating TGFβ1 (Marini et al. 2010). Tamoxifen, raloxifene and genistein are anti-inflammatory in other pathologies, including systemic lupus erythematosus (SLE) (Sthoeger et al. 2003), stroke (Tian et al. 2009), UV-associated cutaneous damage (Brand and Jendrzejewski 2008; Shyong et al. 2002; Widyarini et al. 2001), colitis (Seibel et al. 2009), ileitis (Sadowska-Krowicka et al. 1998) and multiple sclerosis (MS) (De Paula et al. 2008). An important and on-going goal of our research is to evaluate cutaneous healing in post-menopausal women prescribed topical SERM treatment.

Conclusions and further perspectives

Despite links between estrogen and ageing being suggested many years ago, only over the last decade has estrogen emerged as a key determinant of ageing in peripheral non-reproductive tissues, particularly bone, skin and brain. Indeed, the endocrine theory of ageing, underpinned by germline cell ablation experiments in model organisms, states that chronological changes in hormones levels accelerate the cellular effects of ageing. In skin particularly, it is only over the last few years that we have begun to understand the relative contributions of hormones and ageing to pathological healing. Indeed, although our knowledge of estrogen's beneficial effects on wound repair has greatly expanded over recent years there is still much that is not understood. The prospect of manipulating estrogen signalling to alleviate poor healing in the elderly is an exciting one, but we have yet to fully understand how such ER-mediated signalling changes with normal ageing and how this impacts upon cutaneous pathology post-menopause. Importantly, how do the protective effects of estrogen on cellular ageing (i.e., prevention of telomere shortening and oxidative stress) directly contribute to improved healing? A clearer detailed mechanistic understanding will be of relevance to a range of peripheral estrogen-target tissues and aid the

development of targeted hormone-based therapies, to promote cutaneous repair in the elderly.

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