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Review

Molecular aspects of skin ageing

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ABSTRACT

Ageing of human skin may result from both the passage of time (intrinsic ageing) and from cumulative exposure to external influences (extrinsic ageing) such as ultraviolet radiation (UVR) which promote wrinkle formation and loss of tissue elasticity. Whilst both ageing processes are associated with phenotypic changes in cutaneous cells, the major functional manifestations of ageing occur as a consequence of structural and compositional remodeling of normally long-lived dermal extracellular matrix proteins. This review briefly considers the effects of ageing on dermal collagens and proteoglycans before focusing on the mechanisms, functional consequences and treatment of elastic fibre remodeling in ageing skin.

The early stages of photoageing are characterised by the differential degradation of elastic fibre proteins and whilst the activity of extracellular matrix proteases is increased in photoexposed skin, the substrate specificity of these enzymes is low. We have recently shown however, that isolated fibrillin microfibrils are susceptible to direct degradation by physiologically attainable doses of UV-B radiation and that elastic fibre proteins as a group are highly enriched in UV-absorbing amino acid residues. Functionally, elastic fibre remodeling events may adversely impact on: the mechanical properties of tissues, the recruitment and activation of immune cells, the expression of matrix metalloproteinases and cytokine signaling (by perturbing fibrillin microfibril sequestration of TGFβ). Finally, newly developed topical interventions appear to be capable of regenerating elements of the elastic fibre system in ageing skin, whilst systemic treatments may potentially prevent the pathological tissue remodeling events which occur in response to elastic fibre degradation.

Contents

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1. Introduction

The appearance and mechanical function of human skin undergo profound changes with both increasing chronological age and crucially with cumulative exposure to external factors such as ultraviolet radiation (UVR) and smoking (for recent reviews see [1,2]). The fine wrinkles [3] and reduced elasticity (both compliance and ability to recoil) which characterize intrinsically aged skin are exaggerated in photoaged skin, where exposure to UVR is associated with the development of both deep wrinkles and a marked loss of elasticity [4,5]. Whilst both the intrinsic and extrinsic ageing processes are associated with phenotypic changes in cutaneous cells, major structural and functional changes occur in the dermal extracellular matrix (ECM) where fibrillar collagens, elastic fibres and proteoglycans are required to confer tensile strength, resilience (recoil) and hydration, respectively. The extreme longevity of these biomolecules [6,7], compared with intracellular proteins [8] exposes these assemblies to accumulated damage, which in turn impacts on their ability to both confer mechanical properties and to mediate tissue homeostasis [9,10]. This review briefly summarises the current state of knowledge regarding age-related remodeling of dermal collagens, proteoglycans and, in particular, elastic fibre components before considering: (i) the cellular and acellular mechanisms which may drive differential ECM remodeling, (ii) recent progress made in understanding the central biochemical role played by elastic fibres in maintaining tissue homeostasis and (iii) the potential for interventions to prevent or reverse age-related changes in ECM composition and architecture.

2. Structure and molecular composition of young skin

Skin function is mediated primarily by the structure of the epidermal and dermal layers. The highly cellular, yet avascular, epidermis forms a barrier which both prevents water and heat loss and the entry of pathogenic organisms. In contrast, the dermis is both vascularised and relatively acellular. The two layers are joined by a compositionally complex undulating dermal–epidermal junction (DEJ) in which basal epidermal keratinocytes are secured to a type IV collagen-rich basement membrane by hemidesmosomes and the dermis is anchored by collagen VII fibrils and fibrillin-rich microfibril bundles (extensions of the elastic fibre system termed oxytalan fibres). Sparsely distributed, dermal fibroblasts are thought to be responsible for synthesising the three major groups of dermal ECM proteins and collectively these ECM assemblies not only dominate the structure and function of the dermis, but via aberrant remodeling, mediate the changing function of ageing skin (Fig. 1).

2.1. Collagens

Collagens I and III, which are the most abundant proteins in the dermis, co-polymerise to form extended mechanically stiff fibrils which confer tensile strength to the tissue [9,11,12]. Although widely distributed throughout young dermis, there is evidence for their differential deposition in the papillary and deep reticular dermis [13]. The architecture of these fibrils appears disorganised when compared with highly ordered tissues such as the cornea [14], but in skin, they are usually composed into bundles which in turn are often oriented parallel to the DEJ or organised into basket-weave arrangements [15]. In addition to the fibrillar collagens, collagen VII is localised to perpendicularly oriented [16] anchoring fibrils which play a key role in securing the dermis to the DEJ [17]. In turn, this specialised basement membrane is composed of laminins-1 and -5, nidogen and the network forming collagen IV [18]. Finally, whilst collagen VI microfibrils are widely distributed throughout most connective tissues, their role in skin remains unclear. It appears, however, that these ubiquitous assemblies mediate cell-matrix signaling [19] whilst mutations in collagen VI are associated with the development of muscle wasting and weakness [20,21].

2.2. Elastic fibres

In addition to possessing mechanical strength, skin is required to be both compliant (readily deformable) and resilient (able to recoil). Confusingly, these disparate properties are often referred to in the literature as constituting a single parameter: skin elasticity [22]. Whilst the anisotropic nature of skin structure undoubtedly complicates the task of assigning specific mechanical properties to individual components [23,24], the elastic fibre system is thought to be fundamental in mediating tissue resilience [25]. Elastic fibres may be composed of multiple components, including cross-linked elastin, fibrillin-rich microfibrils, microfibril-associated glycoproteins (MAGPs), fibulins and latent transforming growth factor β-binding proteins (LTBPs) (for reviews see [26–28]). In young skin, the elastic fibre system adopts a characteristic highly ordered architecture, in which perpendicularly oriented fibrillin-rich microfibrils (oxytalan fibres) at the DEJ merge with large diameter elastic fibres in the reticular dermis which are composed primarily of elastin [29,30].

2.3. Proteoglycans and oligosaccharides

The dermal ECM is not wholly composed of fibrous proteins; carbohydrates, both in isolation and in conjunction with proteins, also play an important role in skin biology. Whilst these ECM components are often referred to as ground substance or glycosaminoglycans (GAGs), such terminology fails to distinguish between the three distinct forms of oligosaccharides which are present in human connective tissues. Many ECM proteins, including the fibrillins and fibrillar collagens are glycoproteins which have undergone post-translational modification with numerous, relatively short, yet branched, oligosaccharides [31,32]. In contrast, proteoglycans are glycoproteins in which at least one of the oligosaccharide side chains is an un-branched, and usually long, glycosaminoglycan (GAG). Dermal proteoglycans range in size from the single GAG chain small leucine-rich proteoglycan (SLRP) decorin, which is thought to play a central role in controlling collagen fibril fusion [33,34], to the large proteoglycan aggrecan which may be comprised of over 100 individuals GAGs. Collectively, these hydrophilic glycoproteins and proteoglycans in conjunction with the abundant, polymeric hyaluronic acid are distributed throughout the dermis where they perform a key role in maintaining skin hydration [35].

3. ECM remodeling in ageing skin: structural and functional consequences

In contrast with most internal organs, skin is subject to both an intrinsic ageing process (due to the passage of time) and to an extrinsic ageing processes (principally as a result of exposure to ultraviolet radiation [UVR]). Whilst clinically both intrinsically and extrinsically aged skin become wrinkled, stiffened and less able to recoil, the severity, age of onset and rate of these pathological changes is exacerbated by exposure to UVR [3,5,36,37] (for reviews see [38] and [2]). Furthermore, although structural re-organization of the dermal ECM is evident in both UV-protected and UV-exposed aged skin, the tissues are characterised by profoundly different remodeling events.

In intrinsically aged skin, there is evidence not only for the degradation of fibrous ECM components including elastin, fibrillin-containing oxytalan fibres [39] and the collagens I, III and IV [13]