

Mechanisms and Pathophysiology of Photoaging and Chronological Skin Aging

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Research conducted during the past 25 years has produced an understanding of the mechanisms that lead to connective tissue damage during chronological aging and as a result of chronic, repetitive exposure to ultraviolet (UV) radiation from the sun. While the etiologies of these two conditions are distinct, they share common pathophysiological mechanisms. In both conditions, upregulation of collagen-degrading matrix metalloproteinases (MMPs) and fragmentation of the major connective tissue elements of the dermis (primarily type I collagen) occurs. For a while, new collagen production keeps up with collagen damage, but eventually the amount of damaged collagen in the skin increases. At that point, the signs of aging and photoaging become evident.

Introduction

Chronologically aged skin has a dry, mottled and saggy appearance. Fine wrinkling is characteristic. It may appear almost translucent to the eye and feel “papery thin” to the touch. Superimposed on the changes that occur as a consequence of the natural aging process are the effects of chronic repetitive exposure to solar radiation (i.e., photo damage). The characteristic clinical feature of photodamaged

skin is the presence of thick, coarse wrinkles. Chronologically aged skin, particularly in areas that are also photodamaged, demonstrates easy bruising. The bruises often do not heal in a timely fashion, and in some cases, go on to form nonhealing ulcers with devastating consequences.

Research conducted over the past 25 years has provided definitive evidence that although both the epidermis and dermis are negatively impacted by chronological aging and solar radiation, damage to the connective tissue is primarily responsible for the attendant cosmetic and medical consequences. [The exception to this rule is skin cancer, which occurs almost entirely in the epidermis.] Research conducted during the same period has produced an understanding of the mechanisms that lead to connective tissue damage in aged/photodamaged skin. While the etiologies of these two conditions are distinct, they share common pathophysiological mechanisms. This chapter summarizes what we currently understand as the mechanistic events that lead to connective tissue damage in chronological aging and photoaging. It should be noted, finally, that damage in the skin, along with the associated cosmetic and medical consequences, is not the inevitable result of living. Quite the contrary, damage to the skin can be prevented or delayed, and accumulated damage can be (at least in part) reversed. Repairing skin damage has both cosmetic and medical benefits.

Histological features of chronologically-aged skin and photodamaged skin

Figure 1.1 compares histological features seen in sun protected skin of a young adult and the changes that occur as a consequence of the chronological aging process. The dermis of sun-protected skin of the healthy young individual is characterized by thick, wavy bundles of collagen with little space in between the bundles. Interstitial cells imbedded in the connective tissue are in intimate contact with collagen fibers and have a flattened or spread appearance. Nuclei tend to be large, oblong and light-staining. In contrast, the collagen fiber bundles are shorter and thinner in the aged skin and have more space between the fiber bundles. The collagen bundles have a disor-

ganized appearance with “tangled” fibers running in all directions. Cells imbedded in the collagen matrix have a rounded appearance and many of the cells appear to be separated from the surrounding collagen altogether.

Skin that is photodamaged has a histological appearance distinct from either healthy skin or chronologically aged skin. Specifically, the histological hallmark of photodamaged skin is the presence of large amounts of elastotic material; i.e., the dense, dark blue amorphous material seen in hematoxylin and eosin-stained sections.

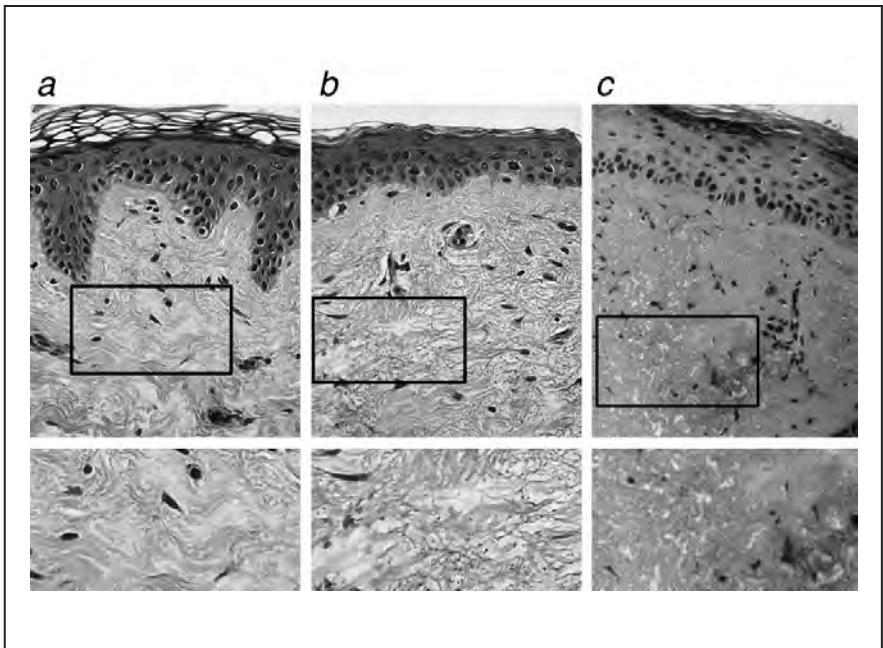


Figure 1.1. Histological features of young skin, old skin and photodamaged skin.

In skin from a young adult (A), thick collagen fiber bundles are present throughout the dermis, extending almost to the epidermis. Interstitial cells imbedded in the collagen have a stretched shape and appear to be in intimate contact with collagen (lower-left, insert). In the skin sample from the old individual (B), healthy collagen bundles have been replaced with thin, short, disorganized fibers. More open space appears in the dermis. Interstitial cells are round or oblong, and some appear to be surrounded by open space. The epidermal layer is thin in old skin and exhibits a loss of rete ridges and rete pegs. Photodamaged skin (C) shows extensive collagen damage (as in old skin) but it is difficult to detect due to the build-up of elastotic material. Upper panels are 5 mm hematoxylin and eosin-stained sections (X160). Lower panels (X240).

While the presence of this material tends to obviate other histological features in the dermis, where the elastotic material is not overwhelming, extensive collagen fragmentation is also present. Collagen damage in photoaged skin is a consequence of events triggered by UV radiation and also reflects the fact that chronological aging has been occurring over the same decades in which solar damage was accumulating.

Direct, biochemical evidence of increased collagen damage in both aged and photodamaged skin abounds. The biochemical data are based on assays that distinguish intact collagen from its fragmented counterpart by virtue of the fact that intact collagen is resistant to digestion by serine proteinases while fragmented collagen can be further degraded to small peptides and single amino acids.¹ We have taken advantage of this to compare chymotrypsin-sensitivity of dermal collagen in healthy young skin versus aged sun-protected skin. The same comparison has been made between photodamaged skin and sun-protected skin. With both comparisons, the amount of fragmented collagen in the damaged skin is increased by approximately four-fold over the amount present in healthy skin.² In the same studies it was shown that total collagen is decreased by 20–30% in the skin of aged (80+ years) individuals as compared to the skin of individuals aged 18–29 years, while total collagen is not significantly different between photodamaged and sun-protected skin in the same individual.

While the focus of this review is on mechanisms of connective tissue (dermal) damage, it should be pointed out that chronological skin aging also produces characteristic changes in the epidermis. Specifically, the epidermis of aged (sun-protected) skin is similar to that of healthy young skin except for the fact that it is thinner and has reduced rete pegs/rete ridges (**Figure 1.1**). In contrast, the epidermis of photodamaged skin is not necessarily thinner than sun-protected skin. In fact, it is often thickened. The major difference is that in the photodamaged epidermis, atypia is common. Epidermal cells with a variety of shapes and sizes are seen, reflecting (at least in part) direct effect of solar UV radiation.

The histological features of chronologically-aged and photo-damaged skin are readily apparent. The question is: how do these histological changes relate to the clinical features that characterize chronological skin aging and photo damage? While acknowledging that correlating histological features with clinical appearance is never absolute, we are confident that the manifestations of aged and photodamaged skin (especially coarse and fine wrinkles) are a reflection of collagen fragmentation and a lack of new collagen to replace the damaged material. In healthy skin, the collagen matrix provides a thick, uniform layer of connective tissue. When this material is fragmented and pulled into clumps (leaving some areas devoid of collagen), the clumps and gaps translate directly into the wrinkled contours. While it may be difficult to prove that this is the case in humans, The fact that formation of a new, thick band of collagen following retinoid treatment occurs in the photo damage mouse model and correlates with a reduction in wrinkling^{3,4} provides good evidence for the relationship between intact connective tissue in the upper dermis and a smooth clinical appearance devoid of wrinkles. Compounding the deficits resulting from fragmented collagen is the overall thinning of the skin (primarily in natural aging) and the buildup in elastotic material during photoaging.

In addition to contributing to skin wrinkling, collagen fragmentation and the overall loss of collagen also contribute to the frequent bruises seen in aged and photodamaged skin in so far as the fragmented matrix provides little support for the microvasculature and results in frequent capillary breakage. Recent studies (reviewed below) suggest that damaged collagen also contributes to the plethora of new blood vessels that are often seen in damaged skin, particularly in aged individuals with a naturally light complexion (skin types I and II). Finally, evidence suggests that the effects of dermal collagen damage extend beyond the dermis itself. Specifically, no data suggests that some of the changes seen in the aged epidermis reflect the presence of collagen damage in the underlying connective tissue rather than intrinsic changes in the keratinocytes, themselves.