SMGroup

SM Gerontology and Geriatric Research

Review Article

Aging of the Skin

Robert L*, Labat-Robert J and Robert AM

Hôtel Dieu Hospital, Université Paris 5, France

Abstract

We present a short review of human skin aging with a complete list of our previous publications as well as on fibroblasts and their aging process. Age-dependent skin loss was measured on biopsy samples from a relatively large number of Caucasian Europeans, males and females, showing a loss with age of about 7% of the "original" (0 age) skin thickness every 10 years. The age-dependent loss of two major constituents of the skin extracellular matrix, collagen and elastin and their age-dependent modifications are described in some detail. We insisted on the age-dependent loss of hyaluronan, the most important reason of loss of hydration and wrinkling.

Article Information

Received date: Jul 25, 2017
Accepted date: Jul 30, 2017
Published date: Aug 02, 2017

***Corresponding author**

Robert L, Hôtel Dieu Hospital, Université Paris 5, France,
Email: lrobert5@orange.fr

Keywords Skin; Aging; Collagen elastin; Fibroblasts; Collagenases; Elastases; Proteoglycans; Glycosaminoglycans; Hyaluronan; UV-radiation

Article DOI 10.36876/smggr.1003

Introduction

Aging is a universal phenomenon affecting from living cells to organisms by a variety of mechanisms. Few biological parameters are variable between such large limits as life expectancy of different organisms shown on Table I. The following reflections will concern essentially humans. There is however among humans also a large variety of life expectancies as known since ancient times and confirmed by recent studies [1,2].

An important variety of aging, at least for humans, is photo aging (Figure 1). The most exposed tissue of the body is in this respect the human skin which varies also according to the pigmentation of the body as well as its protection by clothing and by procedures as sun-creams, hats or other devices as umbrellas etc. In this short review we shall concentrate on human skin aging, more precisely on "caucasian skin". The more strongly pigmented human skins, as those of the african inborn populations, efficient sun-protection is provided by skin melanocytes. Some essential aspects of skin aging will also be succinctly presented. More details can be found in our previous publications listed separately from other references in the bibliography. For a number of years skin aging was one of the important subjects of our laboratory as shown also by these citations.

The Human Skin

Skin [3,4] is the largest tissue of the body, representing 16 to 18% of its weight. Skin tissue uses up about 2% of inspired oxygen, is irrigated by blood and lymphatic capillaries. Skin assumes largely the thermoregulation of the body by evaporating water. It also plays an important role in the

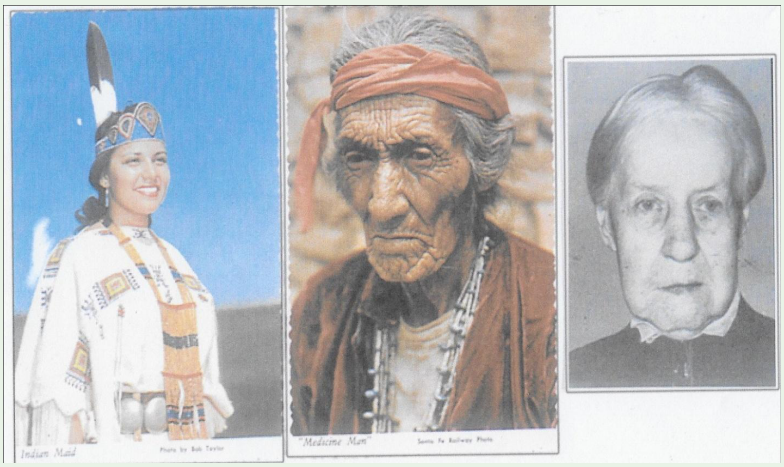

Figure 1: Photo-aging.
Left: a young woman from an Indian tribe in North America, with her face-skin not yet sun burn ed.
Middle: the "medicine man" of an Indian tribe of North America of about 40-50 years. The skin of his face is a good example of photo-aging.
Right: a hundred years old Hungarian women, photo from a collection of Prof. Haranghy: Gerontological studies on Hungarian centenarians (Akademiai Kiado, Budapest, 1965), a time women did not expose to sunshine (with permission).

OPEN ACCESS

ISSN: 2576-5434

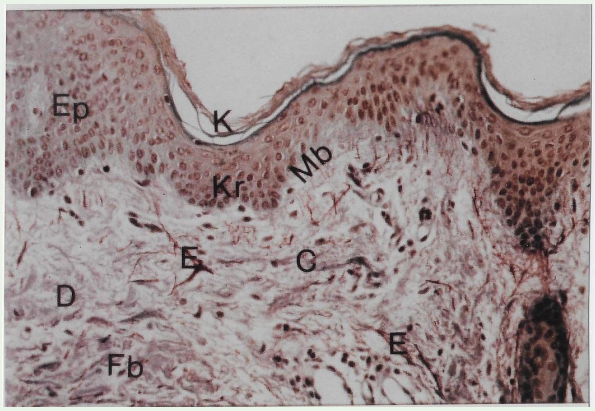

Figure 2: Histological section of a human skin: K= keratin layer; Ep=epidermis; MB= dermo-epidermal basement membrane; D= dermis; E= elastic fibers; Fb= fibroblasts; C= collagen fibers.

elimination of CO_2 by perspiration. As shown on figure 2 its upper layer consists of keratin produced by the keratinocytes, separated from the deeper dermal layers by a basement membrane. The major constituent of the dermis is composed of collagen fibers. About 29 genetically distinct collagen types were described [5], several of them present in the dermal layers of the skin. The majority of skin collagen fibers are composed by types I, III and V collagens, except the basement membranes where collagen type IV is predominant with some type VII. The recent publication of the skin proteome listing about 160 types of proteins [6] will considerably facilitate the study of the large number of skin proteins in order to reach a better understanding of skin structure and function (Figure 2).

Elastic fibers are the second important protein component of the skin. As shown on Figure 3 in a young skin, the dermo-epidermal limit is ondulating, wavy. Elastic fibers of the superficial dermal layer form "candelabre"–shaped bundles, first described by Cotta-Pereira et al, in Rio de Janeiro, Brazil [7]. With aging, these superficial elastic fibers are lysed, replaced in the deeper dermal layers by horizontal fibers, staining as elastin but inelastic, called elastotic fibers.

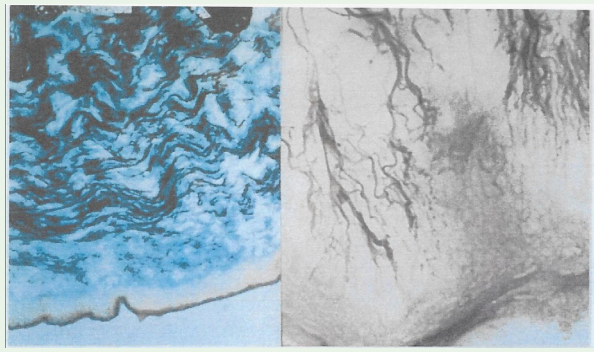

Figure 3: The elastic fiber system of the skin.
Left: the elastic fibers of the superficial dermis in a young skin forming bundle-like structures anchoring in the dermo-epidermal basement membrane. The dermo-epidermal junction is sinuous.
Right: Aging dermis, the bundle-like elatic fibers disappeared by elastolysis, replaced in the deeper dermis by horizontal elastin-staining but non-elastic fibers, called elastotic fibers.

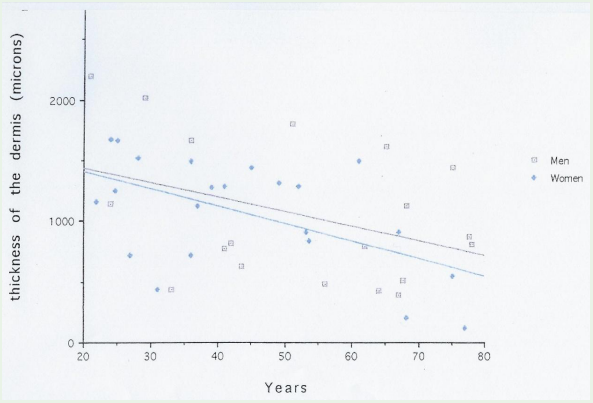

Figure 4: Loss of skin tissue with age: abscissa: years of age. Ordinates: skin thickness in microns. For men: squares, for women: lozenges; Skin thickness measured on biopsies, taken at the interior-superior part of the upper arm (sun-protected). The individual values are quite dispersed, result of the large individual differences in the rate of skin-loss with age. The adjusted evaluations correspond to a skin-loss of about 7% of the original value (extrapolated to 0 age) for 10 years of aging [7].

Among the other constituents of the skin extracellular matrix we should mention hyaluronan (hyaluronic acid), a large, strongly hydrated polysaccharide, largely responsible for skin hydration [8]. Hyaluronan is highly sensitive to attack by Redox Processes **(ROS)** Reactive Oxygen Species among them free radicals [9]. Skin hyaluronan content is decreasing with age, contributing largely to wrinkling of aging skin, mostly by loss of hydration.

Figure 4 shows the loss of skin tissue with age. This was measured in our laboratory on biopsies taken on the sun-protected upper-inner side of the arm from about 60 voluntaries aged from a few months to about 80 years, both males and females as shown on Figure 4. Several important facts can be deduced from these data [10,11]. Both males and females loose skin tissue with age at a comparable rate, just a little faster for women than for men. Approximately 7% of "original" (extrapolated to 0 age). Skin-thickness is lost every decade, with however important individual variations as can be seen on the graph of Figure 4. Some men and women loose a considerable part of their skin tissue, others loose much less during the same period.

We determined on the same biopsies the collagen content of the skin, collagen being quantitatively the most important matrix

Table 1: Longevity.

Every Animal Species has a Different Genome and a Different Life Expectancy	
Arthropods	**4-20 years**
Mice	2-3
Rats	4-5
Dogs	15-20
Elephants	~60
Chimpanzee	~60
Man	100 - 120
Turtle(Galapagos)	~120
Sturgeon	~120

Citation: Robert L, Labat-Robert J and Robert AM. Aging of the Skin. SM Gerontol Geriatr Res. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smggr.1003

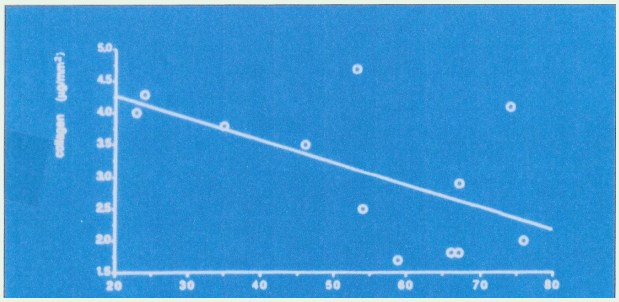

Figure 5: Loss of skin collagen with age (measured by hydroxyproline determination). Abscissa:age in years, ordinates: skin collagen as µg/mm³ adapted from [10].

component of skin tissue, as can be seen of figure 5. Individual values can be quite different at the same age, some having kept most of their skin-collagen up to or over 80 years, some others, even much younger, having lost a large part of skin- collagen fibers (quantified by hydroxyproline determination) [10].

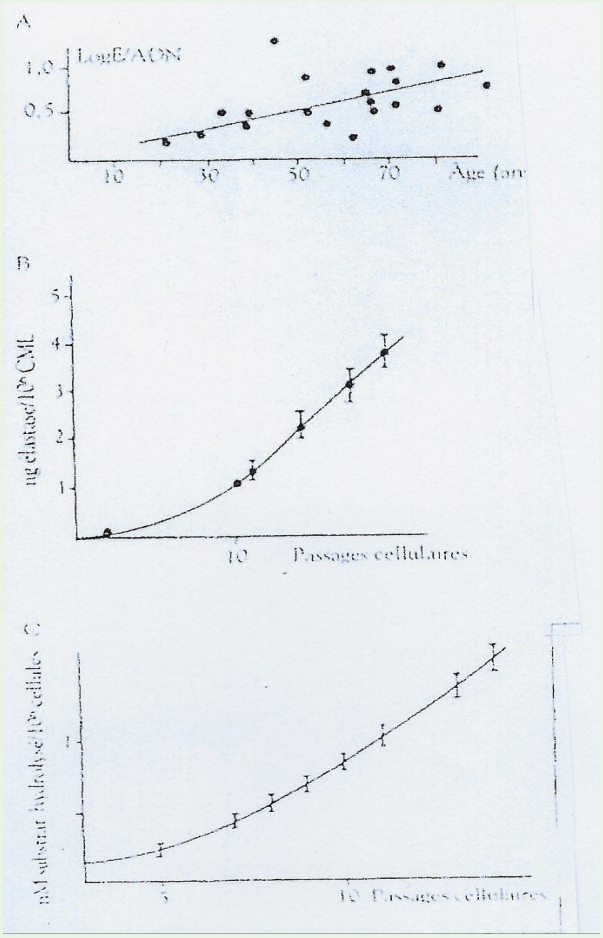

Figure 6: A: exponential increase with age of elastase activity of human aorta wall extracts. Abscissa: age in years, Ordinates: Log elastase activity per cells expressed in DNA. B: exponential increase of elastase activity in vascular smooth muscle cells (CML) cultures with increase in passage numbers. C: same as B for human skin fibroblasts

Mechanisms of Skin Tissue Loss with Age

Two important processes have to be considered in order to approach the mechanisms of skin tissue loss with age. One is the age-dependent decrease of the biosynthesis of its components. The other mechanism is the increase with age of their degradation. Besides collagen and elastin, several other macromolecules of the skin extracellular matrix play important roles in skin physiology. These are glycosaminoglycans, proteoglycans and the family of matrix- or structural glycoproteins [12,13]. As mentioned above, hyaluronan, the only glycosaminogly can with no protein component is essential for skin hydration. The other proteoglycans interact with the fibrous proteins – collagens and elastin of dermal tissue, interactions important for the acquisition of their three-dimensional structure and interaction with the other dermal matrix components and cells. During the morphogenetic process there is also a continuous increase of the biosynthesis of matrix degrading enzymes, among them elastase-type endopeptidases and smooth muscle cell proteases (Figure 6). Determination of elastase-type endopeptidase activity showed a logarithmic increase in the vessel wall, in fibroblasts and SMC-cultures with sequential passages as shown on figure 6. We tested also atherogenic (LDL, VLDL) and non atherogenic (HDL) lipoproteins added to SMC and fibroblast cultures. Atherogenic lipoproteins showed a strong activation of elastase production. HDL was only slightly active in this respect (Figure 7).

The Maillard Reaction, an Important Factor of Non-Enzymatic Tissue alteration with Age

The reaction described during the early years of the 20th century by Maillard, a French biochemistry professor, acquired first celebrity as an important mechanism of preserved food alteration [14-17]. It became soon evident that this reaction (Figure 8) is proceeding in the organism without needing a catalyst to produce Advanced Glycation Endproducts (AGE-s) with well characterized harmful effects [14-17]. As this reaction precedes increasingly faster as the concentration of the reducing sugars (glucose and others) increases, it will certainly contribute to the age-dependent increase of tissue toxicity. The age-dependent increase of collagen crosslinking discovered by Verzar [18] could also be attributed to the Maillard reaction (Figure 9). The sometimes intense yellow discoloration of diabetic skin could also been attributed to the Maillard reaction. For all these reasons the Maillard reaction can be considered as an important contributor to skin aging.

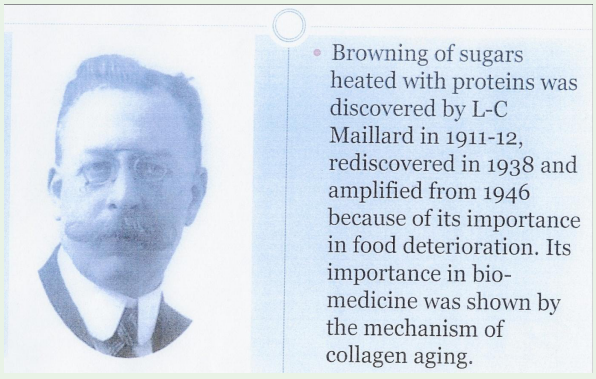

Figure 7: The Maillard reaction.

Citation: Robert L, Labat-Robert J and Robert AM. Aging of the Skin. SM Gerontol Geriatr Res. 2017; 1(1): 1003.
https://dx.doi.org/10.36876/smggr.1003

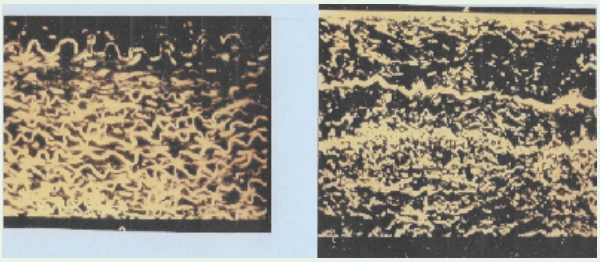

Figure 8: Age-dependent fragmentation of vascular elastic fibers in the human thoracic aorta. Left: from a young (~ 20 years) individual. Right: from an old (~ 70 years) individual (Author's preparations).

Elastin degradation and its contribution to skin aging.

We mentioned already the age-dependent alteration of the special, arborescent elastic fibers of the superficial dermis (Figure 3) [7]. The same process, progressive elastolysis concerns however all elastic fibers in tissues. This is most easily demonstrated in major elastic arteries as the aorta [19]. This age-related elastolysis is the result of the above-described upregulation of elastase-type endopeptidase production. Vascular and also skin elastin degradation are the most important contributors to the production of circulating elastin peptides, we could determine in a large number (over 2000) of human sera [19,20]. Elastin peptides were shown to exhibit several important physico-pharmacological properties, among them stimulation of cell proliferation [19]. This effect may well be important during the atherosclerotic process, especially in the build-up of the plaques containing proliferating SMC-s and fibroblasts. In the skin, loss of elastic fibers with age is an important contributor to wrinkling. Reversible stretchability is exhibited only by elastic fibers among all the constituents of the matrisome [21]. This makes elastin fragmentation a major contributor to skin aging.

Discussion

The above-presented succinct review of skin aging leads to several important conclusions. One of them is the recognition of the multifaceted processes involved in skin aging. The above-summarized mechanisms can be divided in (at least) two major classes, one concerns cell replications and cell aging; the other concerns the age-related modifications of the interacting skin-matrix components. The extracellular matrix of the skin is composed of a large number of macromolecules, synthetized mostly by skin fibroblasts and some other cell types as SMC-s and vascular endothelial cells. The age-related modifications of these cell-components are complicated and still insufficiently explored. There is still necessity to explore in great detail the age-dependent modifications of cell-matrix interactions taking in account the skin-matrisome and their interactions between macromolecules and cells mediated by receptors and between matrix macromolecules.

References

1. Riley JC. Rising Life Expectancy: A Global History. Cambridge University Press. 2001; 243.
2. Ward P, Kirschvink J. A new history of life. Bloomsbury Pub, London. 2015.
3. Millington PF, Wilkinson R. Skin. Cambridge University Press. 1983.
4. Lowell A, Goldsmith MD. Biochemistry and physiology of the skin. Oxford University Press. 1983.
5. Nimni EM. Collagen. Biochemistry. CRC Press, Boca Raton. 1988.
6. Parkinson E, Skipp P, Aleksic M, Garrow A, Dadd T, Hughes M, et al. Proteomic Analysis of the Human Skin Proteome after In Vivo Treatment with Sodium Dodecyl Sulfate. PLoS ONE. 2014; 9: e97772.
7. Cotta-Pereira G, Rodrigo FG, David-Fereira JF. The Elastic System Fibers. Adv Exp Med Biol. 1977; 79: 19-30.
8. Ciba Foundation Symposium 143 - The Biology of Hyaluronan. John Wiley & Sons. 1989.
9. Endre A balazs, Istvan Hargittai, Magdolna Hargittai Eds In: Hyaluronan, Endre A Balazs, general editor. History of Hyaluronan Science From Basic Science to Clinical Applications, PubMatrix (Edgewater, NJ). 2011.
10. Branchet MC, Boisnic S, Frances C, Robert AM, Robert L. Skin thickness changes in normal aging skin. Gerontology. 1990; 52: 28-35.
11. Gilchrest BA. Skin and Aging Processes. CRC Press, Boca Raton, Florida. 1984.
12. Ciba Foundation Symposium 124 Functions of the Proteoglycans. John Wiley & Sons. 1986.
13. Robert L, Robert B. Structural glycoproteins of connective tissue: their role in morphogenesis and immunopathology. In: Connective tissues, biochemistry and pathophysiology. Fricke R and Hartmann F Eds. Springer Verlag, Berlin. 1974; 240.
14. Robert L, Robert AM, Labat-Robert J. The Maillard reaction – Illicite (bio) chemistry in tissues and food. Pathol Biol. 2011; 59: 321-328.
15. Robert L, Labat-Robert J, Robert AM. The Maillard Reaction. From nutritional problems to preventive medicine. Pathol Biol. 2010; 58: 200-206.
16. Robert L. Maillard centenary Meeting in Nancy. Hundred years of Maillard reaction. Médecine & longévité. 2012; 4: 131-135.
17. Robert L, Labat-Robert J. Role of the Maillard Reaction in Aging and Age-relatedDiseases. Studies at the cellular-molecular level. Clin Chem Lab Med. 2013; 13:1-6.
18. Robert L. Fritz Verzar was born 120 years ago: His contribution to experimental gerontology through the collagen research as assessed after half a century. Arch Gerontol Geriatr. 2006; 43: 13-43.
19. Fülöp T, Wei SM, Robert L, Jacob MP. Determination of elastin peptides in normal and atherosclerotic human sera by ELISA. Clin Physiol Biochem. 1990; 8: 273-282.
20. Bizbiz L, Alperovitch A, Robert L and the EVA Group. Aging of the vascular wall. Serum concentration of elastin peptides and elastase-Inhibitors in relation with cardiovascular risk factor. The EVA study. Atherosclerosis. 1997; 131: 73-78.
21. Naba A, Clauser KR, Ding H, Whittaker CA, Carr SA, Hynes RO. The Extracellular Matrix: Tools and Insights for the "Omics" Era. Matrix Biol. 2016; 49: 10-24.

Citation: Robert L, Labat-Robert J and Robert AM. Aging of the Skin. SM Gerontol Geriatr Res. 2017; 1(1): 1003. https://dx.doi.org/10.36876/smggr.1003