Physiology of skin aging

Physiologie du vieillissement cutané


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Abstract

Skin is the most voluminous organ of the body. It assumes several important physiological functions and represents also a “social interface” between an individual and other members of society. This is the main reason its age-dependent modifications are in the forefront of dermatological research and of the “anti-aging” cosmetic industry. Here we concentrate on some aspects only of skin aging, as far as the cellular and extracellular matrix components of skin are concerned. Most well studied mechanisms of skin aging can be situated at the postgenetic level, both epigenetic and post-translational mechanisms being involved. Some of these mechanisms will be reviewed as well as the capacity of fucose- and rhamnose-rich oligo- and polysaccharides (FROP and RROP) to counteract several of the mechanisms involved in skin aging.

Résumé

La peau est l’organe le plus volumineux du corps et assure plusieurs fonctions physiologiques importantes. Parmi ces fonctions, il y a le rôle de la peau comme interface entre l’individu et la société. C’est la raison essentielle de l’importance qu’a prise la recherche sur le vieillissement cutané au cours des dernières années, aussi bien en dermatologie qu’en dermocosmétologie. Dans cette revue, nous analyserons essentiellement les mécanismes postgénétiques, épigénétiques et post-traductionnels impliqués dans le vieillissement cutané. Nous décrirons aussi des expériences portant sur des oligo- et polysaccharides riches en fucose (FROP) ou en rhamnose (RROP), capables d’inhiber certains des mécanismes impliqués dans le vieillissement cutané.

Keywords: Skin; Aging; Fibroblasts; Keratinocytes; Extracellular matrix; Elastases; Free radicals; Maillard reaction; Receptors

Mots clés: Peau ; Vieillissement ; Fibroblastes ; Kératinocytes ; Matrice extracellulaire ; Radicaux libres ; Réaction de Maillard ; Récepteurs

1. Introduction

It is now largely accepted that aging is not “coded” in the genome although modifications of the coordination of gene functions are certainly involved. The hereditary genetic influences, put to about 25% a few decades ago, are now considered to represent no more than about 3% [1]. Evolution apparently did not care much about aging, perhaps to some extent indirectly since the Paleolithic because of the “grandmother” effect. Most well studied, reproducible mechanisms can be situated at the epigenetic and postsynthetic (post-translational) level [2]. Sirtuins, claimed to produce when stimulated an extension of lifespan, act clearly at the epigenetic level [3,4]. Those mechanisms shown to be involved in skin aging are also driven by epigenetic and post-translational mechanisms. Some of these processes will be described.

2. Mechanisms of skin aging

The most conspicuous process is certainly the progressive loss of skin tissue. Measured by image-analytical techniques on
skin biopsies taken at sun-protected sites (Fig. 1), skin loss amounts on the average to about 7% per decade with however large individual variations [5]. This loss of skin tissue, which underlies most of the easily noticed morphological modifications of the skin, can be attributed to several factors such as loss of cells and loss of extracellular matrix (ECM). Cell loss concerns both the epidermal and dermal layers. Loss of ECM is evident when histological skin sections from young and old individuals are compared. Loss of ECM is the result of cell loss, decreased biosynthetic capacity of remaining cells and to a progressive increase of matrix degrading enzymes.

2.1. Loss of cells

Loss of cells is currently attributed to two distinct processes: slow-down of cell division because of telomere loss and exit of cells from the mitotic pool mediated by some antioncogenes through a “switch mechanism” enabling cells to quit the mitotic pool entering the senescent phenotype, escaping thus from malignancy [6]. This teleological presentation of the observed facts corresponds probably to a stress-mediated process of phenotypic switch. This process might well play an important role in the loss of mitotic cells as shown by our experiments, reproduced on Fig. 2. It is clear that the rate of loss of telomeres is slower than the loss of skin tissue. The difference, of about 3.5 fold in the two slopes shown on Fig. 2, is probably an indication of the importance of other mechanisms, such as the antioncogene mediated switch to the postmitotic phenotype.

More recently, a third mechanism was described by McClintock et al. [7]. These authors showed that progerin accumulates in skin during aging. Progerin is a dominant negative form of lamin A, a nuclear membrane protein which is produced in cells of young individuals affected by the Hutchinson-Gilford syndrome (progeria) and who die young (12–15 years) with cardiovascular symptoms. Ninety percent of these cases carry the LMNA G608G (CGC > CCT) mutation within exon 11 of LMNA. This mutation activates a splice donor site resulting in the production of truncated lamin A designated progerin. The progressive accumulation of this molecular marker of cellular aging was achieved by the use of a specific antibody and immunolabeling of progerin in skin biopsies. Further studies will undoubtedly reveal the importance of this new biomarker of skin aging.

Among the clinical symptoms in children affected by this rare disease is, among others the absence of subcutaneous...
adipose tissue which contributes to the senile appearance of the head and face of these children.

2.2. Increased degradation of skin-ECM

Among the early findings we made during our studies on aging of connective tissues, the most conspicuous was the progressive upregulation of elastase-type endopeptidase activity. This was first demonstrated on human aorta extracts devoid of atherosclerotic lesions [8]. As shown on Fig. 3, the elastase-type activity of aorta extracts increased exponentially with donor age. Similar findings were reported on mouse skin extracts, an exponential increase of elastase-type activity with age, further potentised by UV-radiation [9]. To our surprise, similar upregulation of elastase-type endopeptidase activity was seen when the determinations were carried out on successive passages of arterial smooth muscle cells or on human skin fibroblasts (Fig. 3). Although the mechanism of this intrinsic cellular phenomenon is not yet elucidated, epigenetic modifications increasing the expression of MMP-2 and MMP-9 coding genes are the most plausible\(^1\). There was a strong increase of elastase-type activity of vascular smooth muscle cell cultures in presence of atherogenic lipoproteins, LDL and VLDL. Lipid deposition in the skin, depending at least partially on the quality and quantity of dietary intake, may therefore represent an important factor for the regulation of skin proteolytic activity.

3. Postsynthetic mechanisms of skin aging

3.1. The Maillard reaction

The importance of glycation for the aging of connective tissues was first convincingly demonstrated by the experiments of Verzar [10]. He showed that the tensile strength of tendons, essentially of collagen fibers, increased exponentially with age (Fig. 4). He correctly attributed this process to increasing crosslinking. Later it was shown that glycation by reducing sugars and related molecules is involved [11]. A great number of studies were published since these early observations on the production of advanced glycation end-products (AGE-products) and on their role in tissue aging [12]. We took up this subject during the last few years showing that in vitro prepared AGE-products could directly kill fibroblasts when added even at low concentrations to cultures [13]. As shown on Table 1, two of the AGE-products tested strongly increased cell death and also cell proliferation. AGE-products were also shown to increase elastase-type endopeptidase expression when added to human skin fibroblasts (Fig. 5). As AGE-products are derived not only from local production in tissues by glycation and glycoxidation but are also absorbed with dietary sources [14]. Their local concentration does certainly increase with time. Their role in the age-dependent increase of elastase-type endopeptidase production might therefore be important.

3.2. Proteolytic production of toxic peptides

This process, progressively uncovered during the last decades, might well play an important role in tissue aging. Let us take as an example fibronectin (FN). We could show that its production is increasing with age [15]. The two chains of FN, composed of relatively compact subunits, are easily degraded by proteolytic enzymes, also shown to be upregulated during aging (Fig. 3). Several of the peptides released by proteases were shown to exhibit harmful effects; potentiation of malignant transformation, pro-inflammatory activity, proper proteolytic activity absent in the parent-molecule. One fragment of FN was shown to upregulate the biosynthesis of fibronectin [16]. Similar processes were shown to be produced by degradation products of other ECM macromolecules such as elastin peptides. Although these mechanisms are rather widespread in tissues, their contribution to age-dependent modifications has still to be quantitatively evaluated.

3.3. Loss and uncoupling of receptors

It was shown convincingly that aging is accompanied by the progressive loss of a number of receptors [17,18]. The loss of important receptors as those mediating several hormone actions and the activity of the autonomous nervous system can be considered as important factors in the age-dependent loss of tissue- and cell homeostatic regulations [19]. We described a related process, the uncoupling of a receptor, the receptor recognizing elastin peptide sequences [20]. The elastin-recognition subunit of this receptor has a second, galactose-recognition lectin site. Therefore, elastin sequences act as agonists and galactose-ending oligo- and polysaccharides act as antagonists. The message-transmission pathway was also described, both in human mononuclear cells and endothelial cells [21–23]. It appeared however that with age, the message transmission pathway became modified. Inhibitors of the first step of the transmission pathway from the receptor to the G-protein such as pertussis toxin which blocks the transmission pathway of the receptor at the level of the Gi-protein. This inhibition works only on cells from “young” individuals (<45 years) but does no more function with cells of “old” individuals (>65 years), sign of the uncoupling of the receptor [20].
blood and body fluids, the elastin receptor is constantly exposed to its agonists producing the above-mentioned harmful effects.

4. Inhibition of age-related harmful effects

Among the substances tested during our experiments, several classes of active principles proved efficient to inhibit one or several of the above-mentioned harmful effects. Inhibitors of the Maillard reaction were recently reviewed by Urios et al. [26]. The antagonists of the elastin receptor such as melibiose were used with success (Fig. 7). During the last years, we mainly studied fucose- and rhamnose-rich oligo- and polysaccharides (FROP and RROP). They proved to be active in inhibiting most of the above-described harmful effects such as cytotoxicity of AGE-products (Table 2), the upregulation of elastase activity (Fig. 6) and stimulating cell proliferation and ECM-biosynthesis, in vitro as well as in vivo. They also were shown to counteract periorbital wrinkle formation [27]. Their mode of action was also studied. A fluorescent-labelled oligosaccharide, FROP-3, was shown to react with cell membrane localised receptors and also, surprisingly, to penetrate massively in the cell nucleus [28–30].

5. Discussion

Aging is a complex process, skin aging is no exception. No single process is adequate to describe and even less to “explain” it. Most well studied and reproducibly modelised processes involved in cell-tissue aging appear to belong to the epigenetic and post-translational mechanisms. This is the case for the production of harmful peptides during proteolytic degradation of finbronectine and of elastin, analysed in some detail above. The Maillard reaction is no exception, there is no life without sugar (glucose) but part of this essential nutrient is deviated from the (genetically “programmed”) metabolic pathway to entertain harmful processes. These processes, AGE-production, is the result of a simple organic reaction, glycosylamine formation followed by more complex reactions, not forseen by the “genetic program”. The conclusion proposed by Jacob [31] is unavoidable. As analysed in detail in a previous monography [32] the bio-logics of aging did not arise as a result of life-saving processes. On the contrary, most life-supporting molecular processes appear to produce harmful by-products. This is the case of oxydative phosphorylation in mitochondria, site of active release of free radicals and also of receptor production and function as illustrated above. There is however a practically exploitable aspect of such post-translational mechanisms. They are much easier to understand and modelised in order to be inhibited or at least slowed down as would be the case for genetically “coded” mechanisms, as for instance the pathologies resulting from gene-modifications, for example progeria. In order to be successful, however, tentatives to slow down or to inhibit age-related harmful processes, the most important requisite is their complete understanding and modeling.

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