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REVIEW ARTICLE

Facial skin ageing: Key concepts and overview of processes

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Abstract

Introduction: The face is a cosmetically sensitive region where the process of ageing is most clearly manifested. With increased focus on anti-ageing and longevity, more anti-senescent treatments are being proposed despite limited evidence. This study outlines the pathways and mechanisms underpinning the biological process of ageing in the face.

Methods: Comprehensive searches of MEDLINE, EMBASE, Cochrane Library and CINAHL from inception to 2020. Inclusion criteria included all empirical human research studies specific to facial ageing features, written in the English language.

Results: A total of 65 papers met inclusion criteria for analysis. Pathways were subdivided into intrinsic and extrinsic senescence mechanisms. Intrinsic pathways included genetics, generation of reactive oxygen species and hormonal changes. Extrinsic pathways included photoageing and damage to skin layers. The combined intrinsic and extrinsic pathway alterations result in wrinkles, higher laxity, slackness and thinning of the skin. Skin functions such as barrier immune function, wound healing, thermoregulation and sensory function are also impaired.

Conclusion: The ageing process is unique to the individual and depends on the interplay between an individual's genetics and external environmental factors. Through understanding the molecular and cellular mechanisms, an appreciation of the consequent structural and functional changes can be achieved. Based on this knowledge, further research can focus on how to slow or impede the ageing process and identify specific targets to develop and evolve new treatment strategies.

KEYWORDS
moisturisation, skin physiology/structure, suncare/UV protection

Résumé

Introduction: Le visage est une zone du corps esthétiquement importante où le processus de vieillissement se manifeste particulièrement clairement. Avec l'attention croissante portée aux soins anti-âge et à la longévité, de plus en plus de traitements anti-sénescent sont proposés malgré des preuves d'efficacité limitées.

Cette étude décrit les voies métaboliques et les mécanismes à la base du processus biologique de vieillissement du visage.

Méthodes: Recherches exhaustives dans les bases de données bibliographiques MEDLINE, EMBASE, Cochrane Library et CINAHL de leur création à 2020. Les critères d'inclusion comprenaient toutes les études empiriques spécifiques aux caractéristiques du vieillissement du visage chez l'Homme, rédigées en langue anglaise.

Résultats: Un total de 65 articles répondait aux critères d'inclusion pour l'analyse. Les voies métaboliques ont été subdivisées en mécanismes de sénescence intrinsèques et extrinsèques. Les voies intrinsèques comprennent la génétique, la génération de dérivés réactifs de l'oxygène et les changements hormonaux. Les voies extrinsèques comprenaient le photovieillissement et les dommages causés aux couches de la peau. Les altérations combinées des voies intrinsèque et extrinsèque entraînent des rides, une laxité plus importante, un relâchement et un amincissement de la peau. Les fonctions cutanées telles que la fonction de barrière immunitaire, la cicatrisation, la thermorégulation et la fonction sensorielle sont également altérées.

Conclusion: Le processus de vieillissement est unique à l'individu et dépend de l'interaction entre la génétique d'un individu et les facteurs environnementaux externes. La compréhension des mécanismes moléculaires et cellulaires permet d'appréhender les changements structurels et fonctionnels qui en découlent. Sur la base de ces connaissances, la recherche peut se concentrer sur les moyens de ralentir ou d'entraver le processus de vieillissement et identifier des cibles spécifiques pour élaborer et développer de nouvelles stratégies de traitement.

INTRODUCTION

Schrödinger famously remarked that organisms are 'feeding on negative entropy' due to the mechanisms that have evolved to defy the laws of thermodynamics, and instead preserve order over time. However, this preservation of order on a cellular level does not continue indefinitely in humans, and due to the complex and interrelated nature of human cells, such processes encounter problems at different stages within different individuals, resulting in differences in natural lifespan. The study of longevity and anti-ageing is rapidly expanding; however, limited work has been done on the process of ageing in the face, particularly within plastic surgery.

Unlike other areas, ageing of the face and skin is visible and of significant cosmetic importance to the individual; therefore, an understanding of the underlying processes governing ageing is fundamental to develop strategies to prevent or slow down such processes. Ageing of the face occurs on both a molecular and cellular level. The skin and underlying bone and cartilage structures, as well as fat tissue and muscles age chronologically and biologically. Ageing is determined by intrinsic and extrinsic factors such as decreased hormone levels, lower deoxyribonucleic acid (DNA) repair capacity, accumulation of DNA mutations caused by free radicals or ultraviolet (UV) radiation and additional environmental factors, such as air pollution, malnutrition and smoking [1]. Among these environmental factors, UV radiation contributes up to 80%. The combined effect of all of these factors and interactions results in macroscopic changes in the face.

BACKGROUND

Genetic alterations

Telomers are the terminal components of chromosomes. In each cell division cycle, telomers are shortened until the cell-cycle arrests and apoptosis commences. Throughout the cellular ageing process, an inclination of the DNA repair capacity occurs and is caused by decreased protein levels [2]. Alterations in DNA stability, mitochondrial function, ubiquitin-induced proteolysis, cellular metabolism and an accumulation of gene mutations also contribute to cellular ageing [3]. Gene

expression and protein synthesis are the main orchestrators of the ageing process. A combination of processes has been described including the transforming growth factor (TGF) pathway with tumour-suppressor activity, apoptotic genes being upregulated due to the downregulation of FOXO1. Furthermore, cytoskeletal proteins, extracellular matrix components, proteins involved in cell-cycle control, disturbed lipid metabolism, and altered insulin and STAT3 signalling have all been implicated in the genetic ageing process [4].

Reactive oxygen species (ROS) and free radicals

Free radicals are oxygen molecules with an unpaired number of electrons that take electrons from other components. Consequently, these molecules are highly reactive and damage cell structures such as cell membranes and DNA, resulting in cell death or mutations and cellular ageing. Antioxidants, such as superoxide dismutase, catalase, alpha-tocopherol, ascorbic acid, ubiquinone,= and glutathione, protect the genetic material against ROS and occur physiologically in the skin and cellular membranes. UV light can inhibit these antioxidants and cause photochemical reactions [5]. Accordingly, ROS-induced ageing of skin can be mitigated by physical filters, such as microparticles of zinc oxide and titanium oxide, and by supplements with antioxidative abilities, including vitamins A, E and C, coenzyme Q10 and alpha-lipoic acid [6].

Hormones

Hormone synthesis and levels of circulating hormones decline with age, which affects cell metabolism and interacts with gene expression and protein synthesis [7]. Sex hormone levels play a key role in the accelerated ageing process, as well as declining levels of melatonin, cortisol, thyroxine, growth hormone, insulin-like growth factor, vitamin D 1–25 dihydroxy and fewer receptors of interleukin and beta adrenalin are involved [3,8,9]. Oestrogen is crucial for skin integrity and stimulates DNA repair. Oestrogen therapy stimulates collagen synthesis, slows its degradation and can consequently reduce skin thinning, helping to maintain skin hydration. In the postmenopausal period, topical oestrogens, phytoestrogens or selective oestrogen receptor modulators may contribute to skin health improvement [10]. When considering the general use of oestrogen for improving skin health, however, the appropriate timepoint for the start of a oestrogen therapies needs to be evaluated carefully to mitigate the associated risks and maximize benefits [10].

These processes are fundamental to understanding the basis of facial and skin ageing. This study further extends this knowledge, through a review of available literature on ageing of the skin, particularly in the face, exploring underlying mechanisms and early studies on treatments.

SKIN AGEING

Skin ageing takes place on different levels in the epidermis, dermis and in the dermo-epidermal junction. The skin provides barrier function, wound healing, thermoregulation, sensory function, immune function and vitamin D metabolism, which decline globally with increased age [2]. Alterations in skin structure result in laxity, wrinkles, slackness and neoplasms of the skin [11]. Structural stability of the epidermis, dermis and hypodermis depends on the integrity of extracellular matrix such as collagen and elastin, a stable cellular proliferation process, intact vascularization and sufficient barrier function with lipids and skin hydration [12]. The biological age of the skin can be analysed by the structure of the skin including thickness, collagen matrix, cell size, as well as a functional analysis with elasticity, torsion extensibility, neuroperception, trans-epidermal water loss (TEWL) and proliferation rate measurements [11].

Extracellular matrix components

Collagen is a major component of the extracellular matrix and contributes to the structural stability of the skin [13]. The different types of collagens fulfil different functions: collagen VII is a component of anchoring fibrils and stabilizes the dermal-epidermal adhesion, while collagen XVII exists in hemidesmosomes, and the extracellular matrix in the dermis contains collagen type I and III in a ratio that changes with ageing [14].

Due to declining numbers of fibroblasts with increasing age, collagen and elastin synthesis are subsequently reduced, and collagen fibres are thinner with reduced density [15,16]. Moreover, collagen and elastic fibre degradation is increased by activation of metalloproteinases (MMPs) through UV radiation and smoking, and calcifications stimulate elastin fibre degeneration [17,18]. Degenerated collagen fibres lose their crosslinking formation which stabilizes the skin structure and accumulates in unorganized bundles, and degenerated collagen subsequently appears basophilic [19]. Due to molecular structural changes of collagen, its integrity and function are impaired, and the strength and resistance of skin are reduced. Vitamin A and moisture have been shown to reduce collagen damage [13,20].

Photoageing

Photoageing interacts with the physiological ageing process and accelerates ageing. However, the mechanism of ageing acceleration through UV radiation has yet to be fully elucidated. UVA penetrates the dermis and damages both the epidermis and dermis, whereas UVB radiation is predominantly epidermally absorbed. UV radiation damages the DNA in keratinocytes and melanocytes and induces production of the soluble epidermal factor (ESF) and proteolytic enzymes. UVB activates MMPs and induces thymidine dimers, which cause an accumulation of mutations, and UVA radiation produces ROS [21].

Non-UV-exposed skin shows alterations caused by ageing in the epidermis and the basal cells [3]. The extracellular matrix is atrophic and cellularity is reduced [12,22,23,24]. UV-exposed skin is thin, finely wrinkled, smooth, dry, sallow and pale, with loss of elasticity [23].

Photoageing of UV-exposed skin depends on the skin type and exhibits different characteristics [25]. In skin of Fitzpatrick type I and II, there is an atrophic epidermis with a high potential of developing skin malignancies. Skin types III–V demonstrate thickening of the skin with high levels of glycosaminoglycans. UV-exposed skin can have wound-like morphological alterations in the dermis. Deep wrinkles, laxity, roughness, sallowness, increased fragility, blister formation, pigmentary changes, telangiectasias, impaired wound healing and benign and malignant growths are important characteristics of UV-exposed skin. Photoaged skin generally demonstrates irregularities in the dermal connective tissue. These alterations of the extracellular matrix cause instability that deepens the wrinkles [26,27]. Histologically, solar elastosis shows as degraded elastic material and collagen, directly accumulated under the epidermis. While elastin fibres are dystrophic, elastin gene transcription is increased, as is desmosin 28,29]. Conversely, expression of fibrillin-1 and collagen I and III is reduced, while the ratio of collagen type III: I is relatively increased [19,22,30,31,32]. Other data suggest that collagen synthesis is stable but enzymatic degradation rate is higher [2,24]. MMPs are usually strictly regulated by their endogenous inhibitors (TIMPs), but due to the effect of UVA and UVB, enzymatic breakdown of connective tissue fibres is stimulated [33-37]. Furthermore, the epidermal xeroderma pigmentosum factor (XPF) is increased and induces epidermal-dermal invagination, representing the beginning of wrinkle formation. Moreover, solar elastosis demonstrates increased amounts of glycosaminoglycans [38]. Under normal conditions, glycosaminoglycans are diffusely spread in the extracellular matrix and are responsible for sufficient skin hydration by binding water. Although glycosaminoglycans and versican, a large chondroitin–sulphate proteoglycan with a hyaluronic acid-binding domain as component of elastin and fibrillin are increased in photoaged skin, they are unable to bind water and function adequately due to altered elastotic material [39].

Epidermis

The epidermis chronologically thins by 10–50% during life. However, sun-exposed skin has a thickened epidermis, especially the stratum corneum, due to continuous UV damage with chronic repair processes [40]. During the ageing process, keratinocytes alter their shape and become smaller and fatter, while corneocytes grow in size due to slower cell turnover. In UV-exposed skin, the differentiation process of keratinocytes is further impaired, and there is an increase in the expression of involucrin, a differentiation marker, expressed by irreversibly differentiated keratinocytes in the stratum corneum [41].

Furthermore, the biophysical properties of the stratum corneum have key implications in maintaining an intact epidermal barrier. This is associated with changes in age and appearance, with increases in pH noted as individuals age [41]. The increase in pH leads to the protective acidic epidermal barrier being weakened and thus increasing the susceptibility to infection and mechanical induced stress, thereby appearing rougher in texture in an older individual [42].

Major changes in the normal ageing process appear in the basal cell layer [23]. Integrin is a marker for keratinocyte proliferation and adhesion, and its expression is significantly reduced in physiologically aged skin but even more in sun-exposed skin. Integrin β-1 is a transmembrane receptor attaching basal keratinocytes to basal membrane components (such as fibronectin, laminin 1 and 5, and collagen type I and IV) and connects keratinocytes with each other [41]. Fewer Langerhans cells and enzymatically active melanocytes are found in aged epidermis, which causes a change in the immune function of the skin and alteration of skin pigmentation [42,43]. Sebum production is reduced by up to 60% [11], water and lipid content on the skin are also decreased in aged skin [29,44-47]. Moreover, alterations of the amino acid composition reduce the skin's natural moisturizing factor and the epidermal capacity for water binding [29,47].

Dermo-epidermal junction

An intact dermo-epidermal junction is essential for the strength of skin and its ability to resist physical forces such as shear. A large surface area between the two layers ensures the cellular supply of nutrients and oxygen [48].

Collagen VII fibrils serve as anchoring fibrils and are an important component of the junction [49]. As their concentration decreases, the dermo-epidermal bond weakens, which leads to increased vulnerability against mechanical forces and facilitates the formation of wrinkles [50]. Flattening of the dermo-epidermal junction by more than 30% with advanced age of the skin is also a result of flattening of dermal papillae and a reduced interdigitation between layers [48,50–52].

Dermis

Similar to the epidermis, the dermis thins chronologically with age, while vascularity and cellularity also decrease [52,53]. Diminished blood supply, impaired sensory and autonomic innervation of epidermis and dermis, and alterations in cutaneous appendages contribute to an increased vulnerability of the skin. With age, the number of fibroblasts and synthetized products, such as extracellular matrix components, glycosaminoglycans and hyaluronic acid, decrease [48]. By contrast, sun-aged skin shows an accumulation of abnormal dysfunctional elastic fibres and truncated fibrillin, which replaces the normal collagen matrix and leads to an increased dermal thickness [28,54,55]. In turn, decreased integrity of the dermis results in rigidity, reduced elasticity and higher vulnerability [29].

FAT, CARTILAGE, BONE AND MUSCULAR TISSUE

Fat

Fat tissue tends to accumulate with age, and its pattern of distribution also changes [56]. With age, there is a loss of subcutaneous fat tissue in the periorbital, forehead, malar, temporal, mandibular, mental, glabellar and perioral regions. Fat distribution in the sub-mental area, lateral nasolabial fold and labiomental crease, jowls, infraorbital fat pouches and malar fat pad increases due to a redistribution of fat resulting from gravitational forces [2,57,58].

Cartilage and bone

Remodelling of cartilage and bone tissue correlates with a major loss of structural support, visible alterations in facial features and consequently displacement of fat tissue and skin wrinkling in these areas [59]. Facial height is diminished because of a maxillary shrinking, whereas an enlargement in facial width and depth is observed [56,60].

Muscles

Muscle contractions and traction of the skin leads to dynamic wrinkles which chronologically evolve and become permanent under repeated muscular actions, with loss of skin elasticity over time [56]. Therefore, the inhibition of muscle contractions with neuromodulators is a major target in anti-ageing strategies to prevent and smoothen dynamic rhytids [61]. While body muscle mass generally decreases with advanced age [62], Gosain et al. could not find any significant alterations in the substance of mimic muscles in different age groups; muscle length, thickness, volume and fatty infiltration remained the same [58].

CONCLUSIONS

This review provides an overview of each of the biological elements of facial ageing and their various structural changes that occur with age. An understanding and appreciation of each element can guide therapeutic interventions and provide a more tailored and targeted approach to facial rejuvenation. Given the complexities and multifaceted nature of ageing, a key consideration is an elemental type approach based on each of the outlined structures above. The key purpose of this article is to provide a toolkit for clinicians to approach rejuvenation in a more systematic and structured way, paving the way for a paradigm shift in current rejuvenation strategies. These strategies could be shared with prospective patients to further empower them to understand the concert of ageing processes and how to address each in turn. This can be achieved by for example selective liposuction and fat transfer to mitigate the fat changes, or optimizing surface pH to strengthen the integrity of the epidermis and increasing its resistance against mechanical and microbial stresses. Future work could look at creating a framework for facial longevity offering targeted and systematic interventions, increasing safety and personalizing the care patients receive.

CONFLICT OF INTEREST
None.

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