Ageing across the life span: time to think again

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Summary

Living organisms are subject to ageing. This natural process has gained greater importance in socially and medically affluent societies. For many, ageing connotes unattractive changes in the appearance of the skin. The gross morphological changes of ageing skin are mirrored by a range of more profound age-associated physiological declines. Thus, skin ageing can be put into other perspectives which lie at the interfaces of molecular biology, cellular biology, oncology and cosmetic dermatology. Genetically programmed replicative senescence and stress-induced premature senescence (SIPS) are two processes that are fundamental to skin ageing. Some iteroparous species can be used as animal models for human ageing.

Undoubtedly, scientific understanding of skin ageing is firmly rooted in the distinction between intrinsic and extrinsic types of ageing. However, seven major types of skin ageing can be distinguished: genetic, chronological, solar, behavioural, endocrinological, catabolic and gravitational types. Preventative measures can target each of these.

Keywords: ageing, cancer, stress-induced premature senescence, telomere, wrinkle

Introduction

The pace of change in the demography of Western countries has never been so rapid as in the past century. In affluent societies, there is an extraordinary shift in the age profile of the population, with older people representing a progressively growing segment. Such a demographic evolution has enormous social and medical implications. Indeed, the ageing process has become one of the darling topics of the media and medical community over the past few years. As a result, any new anti-ageing treatment modality is avidly watched by the population. Middle-aged and even younger subjects show a craze for cosmetic dermatology when their once youthful bodies exhibit the early signs of wear and tear. Indeed, breakthroughs and novel techniques in cosmetology, cosmetic dermatology and cosmetic surgery fulfil much of the promises. In addition to new technological advances, the forefront in the future of cosmetic dermatology relies on a better understanding of the relationships between skin biology and physiology, and the ultimate clinical appearance.

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From global to molecular ageing and back again

Living organisms are subjected to ageing. However, this multifaceted process is not the same in all of them.[1] The limitation to any definition of ageing lies in the diversity of organisms' life histories. Two distinct classifications of life histories are of major importance. The first distinguishes species that have a clear distinction between germ cells and somatic tissues from those that do not. The second classification makes a distinction between the semelparous species reproducing only once in their lifetime, and the iteroparous species, which reproduce repeatedly. The concept of ageing is most clearly defined in iteroparous species which have a distinct soma separate from the germ line. Ageing needs to be considerably qualified when applied to species with

other kinds of life history. It is mistaken, for example, to regard the post-reproductive end of life of semelparous species, which usually occurs in a highly determinate fashion, as being comparable with the more protracted process of senescence in iteroparous species.

Ageing of human being is a physiological process corresponding to a progressive loss in homeostatic capacity of the organism, ultimately increasing vulnerability to environmental threats and to certain disease status. Obviously, the process progresses differently among individuals of the same age. In a given subject, senescence is also heterogeneous among organs, and also among their constituent tissues, cells and subcellular structures. Intracellular and extracellular molecules are also involved differently by ageing. Within each organ system, ageing manifests as a progressive, approximately linear reduction in maximal function and reserve capacity. Some aspects of ageing can be viewed as an in-advance programmed process. In addition, there is concern that many of the age-associated physiological decrements result in part from environmental insults, either acute or chronic, but in some instances there are relatively few supportive data. To add difficulties, physical growth and senescence are both characterized by cumulative progression of interlocking biological events. They are not always separated because at some time in the life of the organism they may proceed as if they were in tandem.

Cellular senescence in perspective

Granted that death is the ultimate failure of the organism to withstand the onslaughts of an inimical environment, what is it in the ageing process itself that brings about the termination of the replicative ability of cells as the individual becomes progressively older? What is it in cells and organisms that weakens their resistance to the hostile exogenous forces? How is it that some cells and organisms are programmed to die even without the assault from adverse environmental threats?

Many *in vitro* studies have demonstrated that the age of the tissue donor is strongly reflected in the behaviour of cultured skin-derived cells.[2] Replicative senescence of human cells is thus related to and perhaps caused by the exhaustion of their proliferative potential. According to the telomere hypothesis, somatic cells lack sufficient amounts of activity of the enzyme telomerase to maintain the telomeric repeats in the face of the end replication problem. With each round of cell division, mortal cells lose some of their telomeric repeats.[2–6] Since telomere length predicts the replicative capacity of cells, it may provide the best biomarker for cellular ageing.

Stress-induced premature senescence (SIPS) occurs after many different sublethal stresses such as those induced by H_2O_2, other oxygen species and a variety of chemicals.[7] Cells in replicative senescence share common features with cells in SIPS, including morphology, senescence-associated β-galactosidase activity, cell cycle regulation, gene expression and telomere shortening.[7] Telomere shortening is then attributed to the accumulation of DNA single-strand breaks induced by oxidative stress. Thus, SIPS could be a mechanism of the *in vivo* accumulation of senescent-like cells in the skin, and DNA damage plays a key role in skin ageing and photoageing.[8] According to the thermodynamic theory of ageing, the exposure of cells to sublethal stresses of various natures can trigger SIPS, with possible modulations of this process by bioenergetics.

Cellular senescence and cancer are closely related by several biological aspects including p53 mutation,[9,10] telomere shortening,[11] vitamin A depletion[12] and defects in intercellular communications.[13] However, wrinkling does not appear to be a marker for increased risk of skin cancer.[14] By contrast, the age-related mottled melanoderma, even at an infraclinical stage, might be a predictive sign for a carcinoma-prone condition.[15–17]

Skin ageing: 1, 2 or 7 mechanisms?

Conceptually, human ageing is one single basic process of physiological decline progressing with age. This basic process exhibits multiple facets affecting differently the subjects and their organs, tissues and cells. This is particularly true in the skin. Over the past decades, understanding of ageing skin has considerably expanded, with a welcome emphasis on differentiating true chronological ageing changes from photoageing (Table 1) resulting from habitual chronic sun exposure.[18–21] The action spectrum of photodamage is not fully characterized. The cumulative effects from repeated exposures to suberythemal doses of UVB and UVA in human skin are involved in these processes. The role of UVB in elastin promoter activation in photoageing is evident. UVA also contributes significantly to long-term actinic damage, and the spectral dependence for cumulative damages does not parallel the erythemal spectrum for acute UV injury in human beings.

Cultures of human keratinocytes derived from donors of different ages and from paired sun-exposed and sun-protected sites of older donors demonstrate that both ageing and photoageing affect gene expression, although in quite distinct manners. Chronological ageing alone strikingly increases the baseline expression of the differentiation-associated gene SPR2 (small proline rich protein) and of the interleukin (IL)-1 receptor

Table 1 Comparison of intrinsic ageing and photoageing.

Feature	Intrinsic ageing	Photoageing
Clinical appearance	Smooth, unblemished surface	Nodular, leathery surface with blotches, yellowing
	Some deepening of skin surface markings	Deep wrinkles
	Some loss of elasticity	Severe loss of elasticity
Epidermis	Thin and viable	Marked acanthosis, cellular atypia
Elastic tissue	Increased, but almost normal	Tremendous increase, degenerates into amorphous mass
Collagen	Bundles thick, disoriented	Marked decrease of bundles and fibres
Glycosaminoglycans	Slightly decreased	Markedly increased
Reticular dermis	Thinner	Thickened, elastosis
	Fibroblasts decreased, inactive	Fibroblasts increased, hyperactive
	Mast cells decreased, no inflammation	Mast cells markedly increased, mixed inflammatory infiltrate
Papillary dermis	No Grenz zone	Solar elastosis with Grenz zone
Microvasculature	Moderate loss	Great loss, abnormal and telangiectatic

Table 2 Types of cutaneous ageing (after Piérard[25]).

Type	Determinant factor
Genetic ageing	Genetic (premature ageing syndromes, phototype-related)
Chronological ageing	Time
Solar ageing	Ultraviolet and infrared irradiation
Behavioural ageing	Diet, tobacco, alcoholic abuse, drug addiction, facial expressions, sleep
Endocrinological ageing	Pregnancy, physiological & hormonal influences (ovaries, testes, thyroid)
Catabolic ageing	Chronic intercurrent debilitating disease (infections, cancers)
Gravitational ageing	Gravity

antagonist gene. By contrast, it has relatively little effect on the UV-inducibility of several other genes, including the proto-oncogenes c-myc and c-fos, the GADD 153, a gene inducible by growth arrest and DNA damage, and the IL-1α and 1L-β genes. Photoageing is different because it increases the UV-inducibility of c-fos, but decreases the baseline expression of the differentiation-associated genes IL-1 ra and SPR2.[22,23] The physiological impact of photodamage occurs at a variable pace in the different skin structures. For instance, skin loosening and solar elastosis show clinical manifestations independently of severity in mottled melanoderma.[24]

This concept based on a duality in skin ageing has been challenged because it may appear as an oversimplification in clinical practice.[25] Thus, another classification of skin ageing into seven distinct types was offered (Table 2). The important variables included the endocrine and overall metabolic status, the past and present life style, and several environmental threats, including cumulative ultraviolet and infrared irradiation, and repeated mechanical solicitations by muscles and external forces such as earth gravity. In this framework, the past history of the subject is emphasized. The global ageing is then considered to be the cumulative or synergistic effects of specific features, each of them being independent of the others. Such a concept allows us to individualize or integrate typical processes, including among others menopausal ageing and smoking effects. Increased awareness of the distinct age-associated physiological changes in the skin may allow for more effective skin care regimens, preventive measures and dermatological treatment strategies in the elderly. The immutability of skin ageing can be challenged.[26] This is one of the endeavours of cosmetic dermatology.

Conclusions

Ageing is apparent at all levels of the physiology and anatomy of the body. Organs, tissues, cells and molecules have their own ageing processes that differ in their clinical relevance. The individual may perceive a global appearance of skin ageing. By contrast, prevention and correction of skin ageing may benefit from specifically targeting some of its underlying biological processes.

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