Review

Skin ageing: how, why, and what to do

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Medical sciences have made considerable progress in understanding cellular ageing during the past few decades. Skin, being the largest organ in the body, also take part in the sequential series of homeostatic changes taking place in the cellular components, over a period of time, resulting in inevitable biological dysfunction. Organ systems in living organisms maintain structural integrity and functional competence for a varying time span and then begin to show a gradual and progressive impairment of function, increased vulnerability, and a decreased homeostatic capacity. These insidious and inevitable degenerative changes are time-dependant and progressive, but show great variation. They are multi-faceted and multi-step transformations which all living beings are subject to, and is intrinsic or chronological ageing.

The aged appearance of skin is a result of the inevitable intrinsic ageing due to cellular senescence together with the cumulative deleterious effects of exposure to extrinsic agents. Repeated exposure of a living being to these environmental factors will have a variable impact on different individuals. The skin forms the outer covering of the body and the interface between the milieu-interior and the, often adverse, external environment. The major extrinsic environmental factor contributing to the ageing of the skin is solar irradiation[1,2,3] and the combined effect of chronological ageing and aged appearance resulting from sun exposure is termed photoageing.

Intrinsic ageing and photoageing are known to alter the expression of selected genes involved in growth, differentiation, and also immunomodulation, in the skin. The result of these changes lead to the sad and inevitable loss of the smooth, clear, blemish free, beautiful skin one enjoys in early childhood, which of course is the 'ideal' one would cherish to achieve and maintain throughout life.

Cell biology of ageing

Several pathways have been described to account for intrinsic ageing of an organism at the cellular and molecular level. The results of these in vitro studies are also applicable to cutaneous ageing. In 1881, August Weismann proposed the theory of 'immortality of the germ plasm' calling cells of the germline as immortal, and the somatic cells as mortal because of their finite replicative capacity[4]. It was the work of Leonard Hayflick and moorhead, in 1961, with cultured skin fibroblasts, however, that provided a model for the study of cellular senescence[4,5]. They observed a slowing of cell division after a finite number of diploid cell divisions of the cultured fibroblasts. An inverse correlation was seen between the donor age of cells and their proliferative capacity. In addition to this limited, or the finite capacity of the cells to divide, they further observed these cells becoming unresponsive to the proliferative influence of serum growth factors, changes in their morphologic appearances and eventually exiting the cell cycle. This is cellular senescence. Old cells, for reasons as yet poorly elucidated, are relatively insensitive to environmental signals as indicated by thickening of cell membranes, and signal transduction after stimulation is less. Ultimately, this progressive insensitivity to environment leads to cell death[6].

Following the demonstration by Hayflick and Moorhead that somatic cells have a finite replicative capacity, next came the outstanding discovery by Harley, in 1990, of a structural change in the telomeric region of the genome with cellular senescence[7]. The telomere hypothesis provided new insight into DNA damage checkpoint

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mechanisms uncovering the molecular mechanisms regulating cellular ageing. With each cell division the skin fibroblasts lose an average of 50 to 100 base pairs of telomeric repeats until it reaches senescence. He observed this progressive loss of telomeric repeats and proposed a lack of sufficient amount of activity of the enzyme telomerase to maintain telomeric repeats in the face of end replication problem[7].

Imperceptible, yet prepetual, progression from the 'bloom of youth' to the spectrum of features manifested outwardly and accepted as manifestations of aged skin are largely due to changes occurring in the dermis.[1] Extracellular connective tissue matrix constitutes the major part of the dermis, with collagen forming 75% of the dry weight and elastin together with fibrillin contributing another 4%.[8] Hyaluronic acid and dermatin sulphate are the major components of the proteoglycan ground substance. Fibroblasts are the most numerous cellular component and also the most important in regulating the morphogenesis and remodelling of the dermis[8]. Both collagen and elastin are fibrillar proteins synthesised by the fibroblasts. The activity of fibroblasts is regulated by extracellular signals provided by a host of cytokines and hormones. There is a dynamic remodelling of the dermal matrix by the fibroblasts as a result of the synthesis of structural proteins collagen and elastin on the one hand, and the synthesis of a family of protases and protease-inhibitors on the other. The fibroblasts show a 'quiescent' phenotype in its normal maintenance role with a low rate proliferation and a low proteolytic activity, and an 'activated' phenotype in response to various stimuli[4]. Like many ther replicating cells, the fibroblasts also have a finite replicative capacity.

The senescent fibroblast do not show inactivity, as would be expected due to ageing, but instead of a quiescent non-activated state, is locked into a state of activation. This is known as MI activation, and senescence is known as mortality-1 (M1). Early passage young fibroblasts increase expression of collagenase only in response to appropriate cytokines such as serum growth factor, and spends most of the time in the 'quiescent' state. This brings about the desired homeostasis and the maintenance of the normal dermal architecture. In contrast, the senescent fibroblast in its constitutive state of M1 activation inappropriately and constituvely express collagenase without a stimulus. This mechanism of M1 activation is supported by the fact that viral oncoproteins, such as SV40 T antigen, which inactivates p53 and pRb, allow cells to replicate past the M1 limit until they cease to proliferate presumably from a loss of chromosomal integrity. This limit is known as mortality 2 (M2)[4]. Additional evidence to this 'checkpoint' mechanism is provided by the action of DNA damaging agents which lead to arrest of cell proliferation and up-regulation of secreted protases with increased expression of plasminogen activator and collagenase[4]. The senescent cells express less TIMP-1, the naturally occurring inhibitor of collagenase[4].

The senescent fibroblast that underexpress procollagen, overexpress collagenase, and also underexpress collagenase inhibitors would eventually result in loss of integrity of the collagen bundles. The total number of fibroblasts also show a decrease with age. The ensuing result is a reduction in the total structurally intact collagen in the aged skin. Yet, collagen is the structural protein providing the scaffolding to the dermal architecture and is responsible for its tensile strength. With ageing these collagen bundles become tightly coiled, compact, straighter, and also more cross-linked. The elastin fibres also decrease in number and there is damage to the fibres from increased proteolytic activity as manifested by the 'fuzzy' margins. There is also a loss of proteoglycan ground substance. The net result of all these changes is a thin, inelastic, lax, sagging, wrinkled skin with shallow and irregular skin furrows as seen in the aged. The skin becomes less stretchable, less elastic and resilient and easily torn under moderate stress[1].

Dermal thinning that ensues results in turn in a reduction of the interdigitating dermal papillae which in turn leads to a flattening of the dermo-epidermal junction. This causes a decreased cohesion between the dermis and the epidermis which is so vital in maintaining the integrity of the skin as a whole and in withstanding shearing forces. Bullae formation seen in the aged skin is a direct result of this. A relatively high proportion of elderly persons possess anti-basement-membrane-zone antibodies without autoimmune bullous disease. This

might indicate a relationship to ageing phenomenon and may account for the fact that Bullous Phemphigoid commonly affects the elderly[9]. The retraction of the rete-ridges also lead to diminution of the 'proliferative-pool' of basal cells and account for the diminished ability to repair wounds in the elderly. Lack of adequate support to the dermal vasculature leads to commonly observed senile ecchymoses. There is reduced vascularity in the papillary dermis, perhaps partly contributed by the progressive loss of angiogenic stimulus from the decreasing mast cell population. This together with the progressive and linear reduction in number of melanocytes in the epidermis is responsible for the pallor which is a characteristic feature of the ageing skin. The senescent epidermis shows a reduced number of Langerhan cells[5]. This decrease in the immunocompetent cell, and the increased cumulative exposure of the cells of the stratum basale to ultraviolet irradiation would account for the increased incidence of neoplastic and para-neoplastic skin lesion observed in the elderly. The stratum basale in the aged also show an increase in cell heterogenecity in size and morphology[1]. Reduced melanin deposition, with presence of vacuolated and poorly pigmented melanocytes account for greying of hairs. Eventually there is absence of melanocytes in the hair papillae and shafts giving rise to white hairs[4].

Photoageing

Weathering of the skin due to chronic exposure to environmental insults augment features of intrinsic ageing of the skin. Of these elements, ultra-violet irradiation is by far the most important[1]. The ridges and the deep wrinkles of the photoaged skin is influenced by the so-called animation patterns of facial expression, occupational and recreational activities, and the social status[5]. These deep wrinkles do not disappear on stretching. Skin also assume a lemon-yellow hue. There is a variable thickening of the epidermis due to chronic photodamge, but usually not amounting to more than 50-60% of the original thickness. This is contributed by a hyperkeratosis and hypergranulosis with an accompanying increase in the number of melanocytes and an irregularity in the distribution of melanin pigment. Alongside these changes, as the age of the individual increases, there is a decrease in the thickness of the epidermis and a tendency to dysplasia. This produces a complex picture with areas of thining interspersed amidst irregular epidermal thickening[10]. Earliest dermal change occur in the upper dermis where 'fuzzy edged' bands of elastic tissue gets tangled into 'spagetti-like' appearance and still later form globular masses[10]. These changes are known as solar elastotic degenerative changes, and are seen in the upper dermis, but separated from the epidermis by the narrow sub-epidermal Grenz zone. This elastotic material does not have the structure or the properties of the normal elastic fibres. They are aggregates of disorganized and fragmented elastic material, with a reduction in fibrillin which attaches the elastin to the extracellular matrix. This non-functional elastotic material is also responsible for a variety of manifestations of photoageing such as Favre-Racouchot syndrome, cutis rhomboidalis nuchae, and the somewhat pale lemon-yellow colour. The increased telangiectasia is due to lack of adequate support to the dermal vasculature, and the increased incidence of lentigines and freckles are due to the increased population of melanocytes with an irregular distribution of melanin in response to cumulative chronic ultra-violet irradiation.[1].

Difference between photoageing in habitually sun-exposed skin and the innate ageing of the sun-protected skin are clearly apparent, often with abrupt transition at the neckline or the sleeveline. However, these changes show not only an individual variation, but also a marked variation in different skin types. Fair skinned people with skin type I to III display the freckling, lentigenes, guttate hypomelanosis, marked wrinkling, telangiectasia, actinic keratoses, and skin cancers.[11] Darker skinned people with skin types IV and V show a diffuse hyperpigmentation, thickening of the skin, with no telangiectasia, with an extremely low incidence of actinic keratoses and skin cancers. This difference is accounted for by the nature and the distribution of melanasomes in the supra-basal layer of the epidermis[12]. There is a good correlation of skin colour and the degree of melanasome aggregates within the keratinocytes of the epidermis. The larger and more melanised melanasomes of blacks are individually dispersed within the keratinocytes, and they absorb and scatter more energy providing photoprotection. In whites and Orientals the melanasomes are membrane-bound

aggregates, and are 4 times less photoprotective than that of the blacks[13]. Sparse melanin granules absorb very little energy and the photons penetrate deeply with approximately 10% of UVB and 50% of UVA entering the dermis[12]. Intracellular DNA is a major target of these photons leading to changes observed on the skin.

Effects of smoking

There are reports to show that pronounced aged appearance could result with heavy cigarette smoking. Relationship between smoking and wrinkling has been noted as early as 1856, and recent work has shown that smoking causes premature ageing and wrinkling of the face[14]. Women are said to be more susceptible to the wrinkling effect of smoking[15]. When smoking co-exists together with increased sun-exposure the effects on wrinkling becomes, more pronounced. The underlying mechanisms for wrinkling due to smoking are multifactorial. Cigarette smoking has been shown to decrease collagen synthesis and increase neutrophil elastase activity leading to damage to elastin fibres[14]. There is also decreased collagen deposition due to ischaemia. It has been shown that smoking a single cigarette can produce cutaneous vasoconstriction for up to 90 minutes, and that smoking 10 minutes decrease oxygen tension for almost an hour[14]. This is not surprising considering that cigarette smoke contains over 4000 toxic substances.

Inherited disorders

Cutis laxa and elastoderma are two inherited premature ageing syndromes where there are changes similar to those described in intrinsic and photoageing but at a much earlier age leading to premature ageing of the skin. In these disorders there is a lack of homeostasis between elastin biosynthesis and degeneration as a result of increased proteolytic activity[8].

Prospects for rejuvenation

Retinoic acid which down-regulates collagenase activity in skin and up-regulates expression of messenger RNA for procollagen has been shown to have a beneficial effect on skin ageing by a process of biological repair. Topical retinoids decrease epidermal dysplasia, stimulate the production of new dermal connective tissue and incite neoangiogenesis. These regenerative effects have come to be of major biological interest[11]. Vitamin C, in addition to being an anti-oxident, is critical as a co-factor for prolyl hydroxylase, the rate limiting enzyme in the synthesis of collagen. Vitamin E, is an anti-oxident effective in protecting the skin from ultra-violet light.

However, the value of vitamins used topically still remain dubious[16]. By causing controlled necrolysis of the skin, glycolic acid and trichloroacetic acid are used widely for chemical peels to eliminate wrinkles. The effect, however, does not last very long, and often multiple peels may be necessary to bring about a satisfactory result. Skin resurfacing using the ultrapulse carbon dioxide laser has come into vogue in recent times and there are reports of successful outcome in erasing the wrinkles caused by photoageing[17]. In conclusion, the choice of topical applications is between the alpha-hydroxy acids and retinoids. Application of alpha-hydroxy acids has been shown to result in a rapid accumulation of proteoglycans and glycosaminoglycans in the dermis, but the long-term effects on collagen and elastin fibres are unknown[18,19]. Tretinoin and iso-tretinoin have been used in a number of large, well controlled studies and have proved to improve the features of photoageing[20]. The clinical benefit is accompanied by histological evidence of epidermal hyperproliferation, stratum corneum compaction, deposition of glycosaminoglycans in the epidermis, and reduced levels of melanin. It achieves the desired effect of effacement of wrinkles. Collagen levels are restored towards those seen in sun-protected skin[20].

With an anticipated population of over 9.5 million over the age of 65 years by the end of 1996, in the U.K. dermatologists and molecular biologists are actively involved with research into the fascinating field of cutaneous ageing. It is estimated that 8.5% of the population of Sri Lanka will be over the age of 60 years by the year 2000[21]. Aged appearance lowers the self-esteem and contributes significantly towards psychological morbidity. The major contribution towards the 'aged' appearance comes from photodamage. This adds insult to the inevitable intrinsic ageing of the skin, but is preventable and to some degree reversible. The negative impact of sun exposure on physical appearance is convincing. Realization that sun-exposure may lead to disfigurement in

the form of prematurely aged skin may be a message better received by all those who are keen to preserve the 'bloom of youth'.

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