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REVIEW ARTICLE

The impact of perceived stress on skin ageing

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Abstract

Skin ageing can be divided according to phenotypical features into *intrinsic* (by the passage of time) and *extrinsic* (with the addition of the effects of environmental factors). Photoageing is by far the most researched factor of extrinsic ageing but the additional impact of other factors such as cigarette smoking and exposure to air pollution ought to be taken into account. One of the least researched topics in relation to extrinsic skin ageing is the impact of psychological stress. A contemporary review of response of human skin to stress describes the molecular mechanisms of extrinsic skin ageing, but has fallen short of explaining resilience to stress exhibited by people. Mechanisms to regulate gene expression, define cellular identity and promote functionality are responsible for the adaptive response to stressful events. Conversely, maladaptive response of human tissues to chronic stress appears to have an impact on gene regulation. Epigenetics is the study of heritable changes in organisms due to modifications in gene activity and expression, as opposed to the genetic code (DNA genome). Chronic stress appears to be an important factor in determining an individual's vulnerability to ageing and age-related comorbidities via epigenetic modifications. Forerunners in epigenetic research recognized the necessity of a reliable biomarker in order to develop a better understanding of the role of epigenomics in ageing. Genomic DNA methylation patterns (DNAm) appear to be valuable in age prediction but variability in specificity exists across species of mammals, human races and tissues. Neuroscience research appears to be leading the way in epigenomics whilst the lack of a valid and reliable DNAm-associated age predictor compatible with human skin tissue hinders research endeavours for the epigenetics of skin ageing.

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Introduction

Ageing is the time-dependent process of physiological decline of an organ's functionality, characterized by the progressive reduction in function, mechanical properties and morphological changes.[1] Skin ageing can be categorized into intrinsic – due entirely to the passage of time – and extrinsic, under the influence of environmental factors. Extrinsic skin ageing is defined as an enhanced process of degradation of skin structural integrity and functionality upon exposure to environmental factors (coarse wrinkles, dyspigmentation and uneven skin tone)[2] and is phenotypically distinct from intrinsic ageing. Studies investigating the impact of psychological stress on skin ageing is challenging *in vivo* owing to confounding factors of extrinsic ageing such as chronic sun exposure, cigarette smoking, air pollution and diet. For instance in practice, individuals may experience psychological stress due to day-to-day life events whilst also being subjected to other lifestyle factors such as living in urban areas with air pollution, cigarette smoking and unhealthy diet including high sugar and salt intakes[3] which may further impact on the rate of ageing.

Psychological stress and skin

Psychological stress is known to have a negative impact on physical well-being.[4] Furthermore, it is a well-recognized factor in the exacerbation of inflammatory skin diseases including psoriasis and atopic eczema, where a temporal link between stressful

stimuli and disease flares has been established in observational studies.[5,6] A 'brain-skin' link is backed by *in vivo* evidence of increased circulating cutaneous inflammatory cells, as well as stress-related alterations in cutaneous neuropeptide expression, to form the basis of research into the skin's response to psychosocial stress in an intersection of inflammatory cell-mediated and neuroendocrine pathways[6,7] (Fig. 1).

Neuroendocrine aspects of skin's responses to stress: acute versus chronic

Stress may be defined as any disturbance to homeostasis.[8] An evolutionary response to stress to protect and restore a balanced system in human body takes place via several known neuroendocrine pathways (Fig. 1).[9,10] Stress has a differential effect on skin's response depending on duration: from acute over minutes to hours, to chronic stress that persists beyond hours to weeks or months (Table 1).[11]

Epigenetics of ageing

Genetic material within the nucleus of eukaryotic cells is constantly under threat of damage and mutations by oxidative stress. Oxidative stress can be generated endogenously through mitochondrial production of free radicals and reactive oxygen species (ROS) in cellular metabolism and inflammation, or by exposure to exogenous factors including ultraviolet radiation (UVR), air pollution, cigarette smoking, chronic inflammation and psychological stress.[12] The regulation of gene expression is ubiquitous in all living cells to maintain homeostasis in cellular

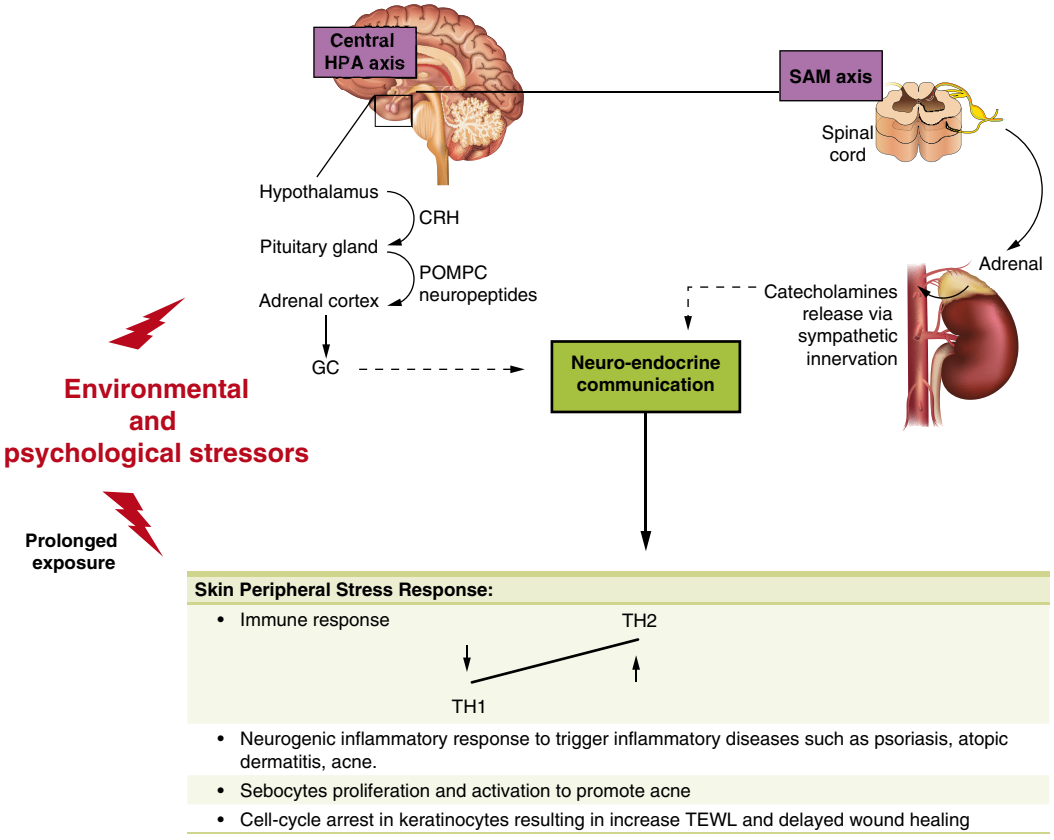

Figure 1 Neuroendocrine aspects of the impact of stress on skin adapted from[7,29]: The sensation of stress primarily triggers a central response via hypothalamus–pituitary–adrenal (HPA) axis, through the release of corticotropin-releasing hormone (CRH) by the hypothalamus to stimulate production of proopiomelanocortin (POMC)-derived neuropeptides in the pituitary gland and glucocorticoids (GC) within adrenal cortex. Stress also induces the release of catecholamines by the adrenal medulla through the Sympathetic adrenomedullary system (SAM) pathway. Recent findings suggest that human skin cells (epidermal and follicular keratinocytes, Langerhans cells, melanocytes and fibroblasts) have receptors for mediators of the HPA system, but also the ability to produce stress mediators such as CRH, POMC, catecholamines and cortisol. Observable effects of chronic stress on skin include delayed wound healing,[30] defective skin barrier function via an increased trans-epidermal water loss (TEWL),[31] immunosuppression[32] and susceptibility to flares of inflammatory skin conditions such as psoriasis, atopic dermatitis (AD) and acne vulgaris.[18,33]

Table 1 Skin tissue's maladaptive response to chronic stress was first observed clinically in wound healing.[34] In acute injury, the body directs blood supply and immune cells to the injury site to facilitate wound healing, a complex process that begins with haemostasis, achieved by clot formation by platelets and an immediate constriction of bleeding vessels by the release of endogenous catecholamines (epinephrine and norepinephrine) through the locus ceruleus–norepinephrine (LC-NE) sympathetic adrenomedullary system (SAM) pathway. This is followed by inflammation driven by T_H-1 cytokines (IL-2, interferon-gamma, TNF) to eliminate cell debris, and support cell proliferation and tissue remodelling. Acute stress results in immune-enhancement not only through the collaborated mechanisms of upregulated release of T_H-1 cytokines and autonomic (LC-NE) nervous system centrally, but also via sensory nerves peripherally to promote mobilization of immune cells. Conversely, chronic stress leads to an immunosuppressive response by a switch to T_H-2 dominated immuno-dysregulation, impaired barrier function and delayed wound healing

Acute response to stress	Chronic response to stress
Blood supply is redirected to site of injury to promote mobilization of immune cells[35,36]	Enhanced oxidative stress upon prolonged exposure of cellular and extracellular matrix (ECM) components to catecholamines[34]
Activation of SAM pathway to promote immediate haemostasis[29]	Downregulation of differentiation by epidermal keratinocytes, reducing skin barrier integrity[31,37]
A pro-inflammatory effect to promote wound healing, to eliminate cell debris, granulation tissue in proliferation phase and subsequent remodelling[38]	Long-term corticosteroid-induced immunosuppressive effect on skin tissue[32,39]

function in a carefully orchestrated (adaptive) response to stress – from cellular function to evolutionary adaptation to 'changing' stressful environments – epigenetic changes have been the key to cell survival. Several mechanisms have been studied, including transcription factor binding, histone marks, DNA methylation and nucleosome positioning.[13] Changes in histone marks and transcription factor binding are prerequisites for age-dependent differential DNA methylation,[14] which may explain the location of DNA hypermethylation being at CpG islands, where a cytosine (C) nucleobase is followed by a guanine (G) nucleobase, in proximity to transcription factor binding sites.[15]

DNA methylation and ageing

DNA methylation (DNAm) is a stable, enzyme-induced modification of gene expression without changing DNA sequences. It creates a 'memory' within the genome that generally results in downregulation of gene expression at the specific genetic locus. DNA methylation occurs on cytosine of unique dinucleotides, where a cytosine base is followed by a guanine base (hence the term CpG islands).[15] Epigenetic patterns of DNA methylation are unique to age and it has been suggested that age-dependent DNA methylation in specific genetic loci can be biological markers for chronological age (for age prediction; DNA methylation-predicted age) – a total of 353 CpG islands have been located within gene promoter loci that transcribe for cellular growth, differentiation, death as well as survival across the human genome – these CpG islands have been coined 'clock CpGs' because of their close relevance to the cellular ageing process.[16] However, variability in correlation between DNA methylation-predicted age and chronological age exists across the different human tissues, owing to the nature of cultured dermal fibroblasts and keratinocytes being relatively short-lived compared with, for example, neuronal cells and cardiac myocytes, and therefore rendering skin age prediction with DNAm-based biomarkers unreliable.[15]

A study on mice has identified DNA methyltransferases (DNMTs) and ten-eleven translocation enzymes (TETs) as regulators of DNA methylation and demethylation, respectively.[17] Expression of these enzymes appears to be in decline with age, which is manifested in the observation of reduction in age-related cellular proliferation and growth.[17] Moreover, reduced functionality of DNA methylation enzymes undermines gene expression regulation, which can be linked to the loss of the system's resilience to psychological stress, as well as vulnerability to immunopathology and carcinogenesis with age.[18]

Repression of gene expression is associated with DNA methylation in a proportion of CpG islands associated with promoter gene loci and an even smaller number of exceptional gene loci are activated by DNA methylation.[19] Across the human genome, more than half of the CpG islands are methylated; amongst them, two-thirds are related to gene promoter regions important to skin ageing research.[20] Through epigenetics we have begun to understand upstream events that regulate gene expression, functional genomics to study their effects on skin ageing in humans still requires more studies to profile DNA sequences under the influence of age-related regulatory events. Methylated CpG sequences with unmethylated sequences can be characterized by means of DNA methylation analysis[21] (Fig. 2).

The impact of stress perception on DNA Methylation

Epidemiological data related to stress-related disorders such as major depressive disorders (MDD) and post-traumatic stress disorders (PTSD) demonstrate gaps of inheritability of these disorders, with concordance rates in an adult population amongst monozygotic twins being low, in the region of 35–37%.[22,23] The lifetime risk of acquiring stress-related psychiatric disorders must be the product of genetic and environmental factors. One study on an urban African American population (n = 393) found that individuals with high lifetime stress exposure were more likely to age prematurely.[24] Exposure to stress in early life appears to have an influence on vulnerability and resilience of mammalian species to perceived stress in later life.[25] Perception of stress is therefore a subjective measure of an individual's response and varies from one to another.

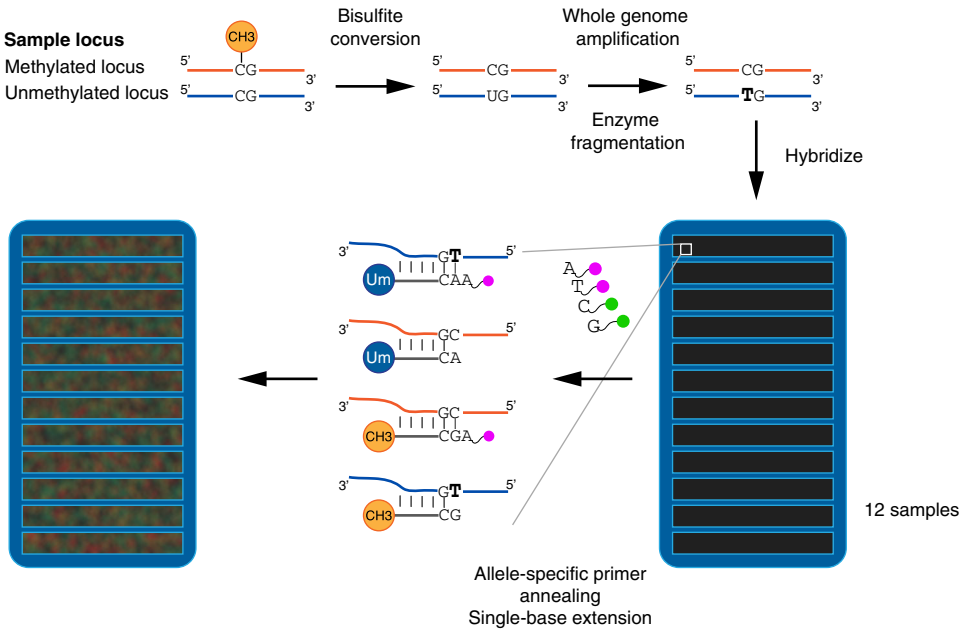

Figure 2 Lu©2009 'Work flow of Infinium I Assay'; a diagrammatic representation of DNA methylation analysis. Hybridized genomic DNA can be analysed on Infinium HumanMethylation450 Beadchip (Illumina UK, Cambridge).[21] It is a three-step process that begins with bisulphite conversion of genomic DNA (The 1000 Genomes Project Consortium 2010) to sort into methylated and unmethylated sequences, which undergo amplification process before enzyme-induced fragmentation and filing of the CpG rich DNA sequences into Beadchip; on the chip, two different bead types to detect CpG methylation are used: CpG target sites are differentially matched with probes via single-base extension to divide into methylated and unmethylated sites, which will then be stained to enable scanning.

Cortisol is a glucocorticoid (GC) in humans that promotes ECM remodelling via interaction with glucocorticoid receptor (GR) to modify gene expression.[26] As an effector molecule of stress responses in humans, it exerts actions on DNA methylation and modifies the epigenetic landscape – in CpG islands that bear functionality of cellular identity and survival, i.e. 'epigenetic clock CpGs'.[15] Evidence of stress perception having an influence on skin ageing via epigenetic modifications has only recently emerged in the most preliminary form.[27] There is an increase in the data afforded by epigenome-wide association studies due to the guidance and quality standards set by the International Human Epigenome Consortium (IHEC) and the advent of Infinium DNA analysis assays.[21,28] The vision of creating comprehensive epigenetic and epigenomic data sets for reference seems within grasp, with the prospect of research into epigenetics of the impact of perceived stress on skin ageing being dependent on it.

In conclusion, DNA methylation (DNAm) is one of several known regulatory epigenetic mechanisms to ensure homeostasis in gene expression. It has been acknowledged that a valid and reliable biomarker of skin ageing is necessary for epigenomics but one that is compatible with all human tissues remains to be identified. Effector gene loci for DNA methylation are located in CpG islands close to transcription factor binding sites, which means that stress-induced differential DNA methylation of human genome demonstrated by Infinium® assay would have an effect on cellular identity. Stress vulnerability and resilience appear to be linked to exposure to stressful stimuli in early life, and the relevant data from neurogenetic studies of a modified epigenomic profile associated with brain activity to the stimuli have to be taken into consideration. Mindfulness has been shown in randomized controlled trials to be positively influential in maintaining good control of cutaneous psoriasis in patients following treatment of psychological well-being[5] and could be considered an area of research in therapeutics of stress-induced skin ageing.

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