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Review

Oxidation events and skin aging

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ABSTRACT

The rate of skin aging, or that of tissue in general, is determined by a variable predominance of tissue degeneration over tissue regeneration. This review discusses the role of oxidative events of tissue degeneration and aging in general, and for the skin in particular. The mechanisms involved in intrinsic and extrinsic (photo-) aging are described. Since photoaging is recognized as an important extrinsic aging factor, we put special emphasize on the effects of UV exposure on aging, and its variable influence according to global location and skin type. We here summarise direct photochemical effects of UV on DNA, RNA, proteins and vitamin D, the factors contributing to UV-induced immunosuppression, which may delay aging, the nature and origin of reactive oxygen species (ROS) and reactive nitrogen species (RNS) as indirect contributors for aging, and the consequences of oxidative events for extracellular matrix (ECM) degradation, such as that of collagen. We conclude that conflicting data on studies investigating the validity of the free radical damage theory of aging may reflect variations in the level of ROS induction which is difficult to quantify in vivo, and the lack of targeting of experimental ROS to the relevant cellular compartment. Also mitohormesis, an adaptive response, may arise in vivo to moderate ROS levels, further complicating interpretation of in vivo results. We here describes how skin aging is mediated both directly and indirectly by oxidative degeneration.This review indicates that skin aging events are initiated and often propagated by oxidation events, despite recently recognized adaptive responses to oxidative stress.

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1. Introduction

1.1. Skin aging

In the twenty-first century, the average age of the population all over the world is still rising, especially in the industrialized countries (World Population Ageing: 1950–2050, United Nations Population Division). The consequences of human aging are predominantly visible in the skin, as increased wrinkling, sagging, and increased laxity of the skin (Jenkins, 2002). Often considered as undesirable for cosmetic reasons, skin aging is also associated with physical disorders of the skin as discussed in this review. There has always been a fascination for conserving youth. People invest much time and money in rejuvenation procedures, of which many lack proven efficacy (Zouboulis and Makrantonaki, 2011).

It has been suggested that aged skin has a disturbed barrier function, resulting in a dry appearance of the skin and an enhanced risk on skin disorders (Hashizume, 2004). Another health drawback is the enhanced risk on malignancies (Goukassian and Gilchrest, 2004). Knowledge about the mechanisms of skin aging is important to develop better skin care products that slow down skin aging and reduce the hazardous effects of aging (Farage et al., 2008; Elsner et al., 2011).

Aging of the skin is induced by both intrinsic, and extrinsic factors (Farage et al., 2008; Landau, 2007), all leading to reduced structural integrity and loss of physiological function (Landau, 2007). Typical extrinsic factors for skin aging are UV-exposure and smoking (Farage et al., 2008; Bernhard et al., 2007). This review describes the central role of oxidative processes in the initiating – and often prolonged – events of aging. Most other aging-contributing events, such as mitochondrial dysfunction, altered intracellular communication, genomic instability, cellular senescence and breakdown of the extracellular matrix (ECM) are a consequence of these oxidative processes.

1.2. Intrinsic aging

Intrinsic aging affects all skin areas. Intrinsically aged skin is thin, transparent and dry, shows fine wrinkles and irregular hair growth, is unable to sweat sufficiently, and suffers from loss of subcutaneous fat tissue, leading to hollowed cheeks and eye sockets, insufficient perspiration, and thinning of nail plates (Sjerobabski-Masnec and Situm, 2010). These symptoms may vary per body site. It has been observed that the intrinsic aging process differs per ethnic group (Davis and Callender, 2011), probably caused by the degree of pigmentation, and possibly more not yet identified contributing factors. Skin that is aged only by intrinsic factors does actually not exist. Individuals that live strictly indoor all their life, may have a close approximation to that skin status. In general, individuals carry skin that reflects various stages of extrinsic aging, superimposed on the level of intrinsic aging.

Reactive oxygen species (ROS) play an important role in skin aging. In the skin, about 1.5–5% of the consumed oxygen is converted into ROS by intrinsic processes (Poljsak et al., 2012). ROS are continuously produced as side products in the electron transport chain of the aerobic metabolism in the mitochondria, and are regarded as the main cause of intrinsic aging (Farage et al., 2008). Keratinocytes and fibroblasts are the main producers of 'mitochondrial' ROS in the skin. A ROS that is predominantly formed in mitochondria from ground state oxygen, is the reactive superoxide anion radical ($^{\bullet}O_2^-$) by the addition of an electron to each oxygen (O_2) molecule (Fig. 1). Abundant generation of superoxide anions, as ROS-particles, may harm cellular function. Recent experimental evidence however shows that moderate levels of ROS have a useful signaling function, especially when superoxide anions are converted into hydrogen peroxide (Section 5).

Manganese superoxide dismutase (MnSOD) is the primary mitochondrial neutralizer of continuously produced superoxide anions. Other forms of SOD exist outside the mitochondria, but only MnSOD has been shown to be essential for the survival of aerobic life (St Clair and Kasarskis, 2003). Genetic polymorphisms of the human (Mn)SOD gene and the corresponding alterations in the mature enzyme have been identified. The alterations lead to aberrant efficiencies of the Mn-SOD enzyme (St Clair and Kasarskis, 2003). Consequently, these polymorphisms may largely determine the natural ability of the cells to neutralize superoxide anions, and the ability to withstand degeneration of (skin) tissue. The variation in genotypes may partially explain the differences in aging conditions among individuals of the same age. The effect of excess of superoxide anions on aging has been shown in *Tet-mev-1* mice, which have mutations in mitochondrial complex II subunits and overproduction of superoxide anions. These mice show excessive apoptosis, which led to low birth weight, growth retardation, precocious aging and other pathologies (Ishii et al., 2011).

Two other main events associated with intrinsic skin aging are a decrease in replicative ability of cells and increased degradation of the extracellular matrix. The replicative ability of all dividing cells decreases with time. In the skin, this particularly affects keratinocytes, fibroblasts and melanocytes. This process is called cellular senescence. Senescent, non-dividing cells are found in higher levels in aged skin (Dimri et al., 1995). The process of cellular senescence is related to the maximum number of cell divisions that somatic cells can undergo. With each division, a small fragment of the telomere, is lost at the chromosome ends. After 25 to 30 divisions, telomeres become critically short, and the DNA loss during subsequent cell divisions can affect areas of essential genes and lead to loss of somatic cell function. In germ cells, the telomerase enzyme prevents this fate by adding six-nucleotide repeats TTAGGG to the 3′ end of DNA strands to the telomere region of chromosomes upon each cell division.