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NF-κB signaling in skin aging

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ABSTRACT

Skin is the largest organ of the body, and is prone to be affected by external environmental factors. Skin aging is caused by both genetic and environmental factors. Furthermore, aging skin tissue is known to create a permissive tissue microenvironment that promotes the initiation, progression and resistance of cancer cells by promoting the senescence-associated secretory phenotype (SASP). Therefore, more attention should be paid to skin aging. In this review, we highlight the common Rel proteins and two activation pathways: the canonical activation pathway and the non-canonical activation pathway. Furthermore, we summarize the role of NF-κB in skin aging. The effects of UV on the skin results from the production of ROS. Excessive free radicals activate the NF-κB signaling pathway and MAPK signaling pathway, contributing to the activation of AP-1 and NF-κB. Then it increased the level of TNF-α and the expression of MMPs, which induce the degradation of ECM and accelerated skin aging. We also summarize some reported natural antioxidants and synthetic antioxidants which are related to NF-κB signals. On the other hand, NF-κB plays a key role in SASP. Upon senescence-inducing signals, ATM and ATR block p62-dependent autophagic degradation of GATA4, contributing to NF-κB activation and SASP induction.

1. Introduction

Skin is the largest organ of the body, covering an area of 1.5–2 m^2 (Richardson, 2003) and is prone to be affected by external environmental factors (ultraviolet radiation, air pollution, smoking and so on) due to the bareness of skin. So skin aging is one of the most important phenotypes of aging, which is caused by both genetic and environmental factors (Kagan et al., 2002). In view of the aging society, people pay more and more attention to appearance, and skincare and anti-aging has become one of the hot spots of national concern. In addition, multiple DNA-damage inducers, comprising UVR and cancer therapies, as well as telomere shortening and activated oncogenes promote cells getting into an aging state and induce to the secretion of the array of cytokines, chemokines, growth factors and proteases known as the senescence-associated secretory phenotype (SASP), which create a permissive tissue microenvironment that promotes the initiation, progression and resistance of cancer cells (Ghosh and Capell, 2016). Above all, skin aging is an important phenotype of aging, which should receive sufficient attention.

2. A brief introduction of NF-κB signaling pathway

NF-κB is an important nuclear transcription factor, which plays a key regulatory role in innate immunity, acquired immunity, inflammatory response and the progression of tumors (Basseres and Baldwin, 2006). NF-κB exists in the form of a dimer, and dimers are members of the Rel protein family. The common feature of Rel family proteins is that there is a conserved sequence of about 300 amino acids at the N-terminal (Rel homology domain, RHD). This conserved sequence is significant for the binding of members of the Rel family to other proteins and DNA. The binding regions of two dimers of NF-κB protein and the region combined to IκB protein are located in the domain of this sequence (Hayden and Ghosh, 2008). Common Rel proteins are p50, p52, Rel A (p65), Rel B and c-Rel. Those 5 Rel family proteins can be divided into two classes, the first one included p50 and p52, which arose from precursor proteins, p105 (NF-κB1) and p100 (NF-

Abbreviations: TNF-α, tumor necrosis factor-alpha; SASP, senescence-associated secretory phenotype; RHD, rel homology domain; AnkR, ankyrin repeats; TADs, transcription transactivation domains; TNFR, 1tumor necrosis factor receptor 1; IL-1R, interleukin 1 receptor; TLR, toll like receptor; TCR, T cell receptor; BCR, B cell receptor; dCK, deoxycytidine kinase; NEMO, the nuclear factor NF-κB essential modulator; NIK, NF-κB inducing kinase; INF-γ, interferon-γ; IL-2, interleukin 2; IL-6, interleukin 6; ROS, reactive oxygen species; MMPs, matrix metalloproteinases; AP-1, activator protein 1; ECM, extracellular matrix; UV, ultraviolet radiation; MLB, magnesium lithospermate B; MAAs, mycosporine-like amino acids; NHEKs, normal human epidermal keratinocytes; DDR, DNA damage response

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κB2). A C-terminal region containing ankyrin repeats (AnkR) is post-translationally cleaved from p50 and p52. The second class includes p65, Rel B, c-Rel, which are synthesized as mature proteins with transcription transactivation domains (TADs) (Smale, 2012). Two paradigmatic dimers (p50:p65 and p52:Rel B) exist most widely in eukaryotic cells and play the most important regulatory role, although other combinations include homodimers p50:p50 and p52:p52or heterodimers p52: Rel A and p50: Rel B with different functions (Adler et al., 2008; Smale, 2012).

According to different activation pathways, NF-κB signal can be divided into the canonical activation pathway and the non-canonical activation pathway. The canonical pathway dominates and is activated by many factors, including inflammatory factors, pathogen-associated molecular pattern and activation signals in acquired immunity. Among them, the research on TNFR1 (tumor necrosis factor receptor 1), IL-1R (interleukin 1 receptor), TLR (Toll like receptor), TCR (T cell receptor) and BCR (B cell receptor) mediated activation pathway was more comprehensive and thorough. In general, the activation of NF-κB can be summarized as stimulation signal transferring from ligand, receptor, adapter protein, dCK (deoxycytidine kinase) complex to NF-κB. Then the phosphorylation of the transcription factor NF-κB and the transcription of the target gene is initiated by the nuclear entry of NF-κB (Hayden and Ghosh, 2004).

In the resting state, NF-κB bound to IκB and exists in the cytoplasm in the form of an inactive complex. IκB is a specific inhibitor of NF-κB. It blocks the nuclear localization signal by binding to the RHD region of NF-κB, thus preventing NF-κB from entering the nucleus to perform its function. IκB protein mainly includes IκBα, IκBβ and IκBγ (Meffert and Baltimore, 2005). The canonical signaling pathway involves releasing the dimer of NF-κB by degrading the IκB kinase complex and the activation process is rapid. The most common form of the complex is a trimer composed of catalytic subunit IκBα, IκBβ and regulatory subunit IκBγ (NEMO, the nuclear factor NF-κB essential modulator). After activation of the IKK kinase complex activated by inflammatory factors and oxygen free radicals, this complex catalyzes the phosphorylation of serine residues in specific parts of the IκB (the phosphorylation sites of IκBα are Ser32 and Ser36). The phosphorylated IκB binds to several ubiquitin molecules (the polyubiquitination sites of IκBα are Lys 21 and Lys22) and gets degraded by ATP-dependent 26S proteasome (Mattson and Meffert, 2006). Then NF-κB can be activated and freed from p50/p65/ IκB heterotrimeric trimer, translocated into the nucleus through nuclear pore complex, and bound to specific DNA sites, regulates the transcription of target genes, leading to the production and release of inflammatory cytokines such as TNF-α, IL-2, IL-6 and INF-γ. In turn, released cytokines can reactivate NF-κB and thus can mediate the inflammatory damage of tissue through cascade reaction (Hayden and Ghosh, 2011; Schmitz et al., 2001; Wang and Baldwin, 1998). The non-canonical NF-κB activation pathway is mediated by transcription factor p100/Rel B, which is mainly relevant in immune cells. The activation of the non-canonical pathway of NF-κB signaling pathway mainly depends on IκBα, rather than IκBβ and IκBγ (Kaltschmidt et al., 2005). In the resting state, the N-terminal of p100 displays self-inhibition, blocking the transcriptional activity of p100/Rel B. Ligand stimulation (such as CD40 L binding to CD40) can eliminate the K48 ubiquitination of the key protein NIK (NF-κB inducing kinase) and terminate the degradation of NIK by the proteasome. The stable NIK activates p100, resulting in phosphorylation and ubiquitination of p100, which is recognized by the proteasome and partially degraded into p52. Finally, the nuclear translocation of p52 and Rel B initiates transcription (Vallabhapurapu and Karin, 2009).

3. NF-κB signaling in skin aging

One of the main effects of UV on the skin dermis is to destroy the integrity of connective tissue. In young skin, the level of procollagen is higher than that in aged skin. The other effect of UV on the skin is production of reactive oxygen species (ROS), which disturb the dynamic balance of oxidative stress, contributing to damage to the skin tissue cellular structure by increasing the production of ROS and decreasing the activity of antioxidant enzymes (Chung, 2003; Svobodova et al., 2006). At the same time, excessive free radicals activate the NF-κB signaling pathway, leading to the increase of the level of TNF-α and the expression of matrix metalloproteinases (MMPs) (Chen et al., 2016). MMPs are responsible for the degradation of connective tissue and the transcription of several MMPs is mainly regulated by NF-κB and activator protein 1 (AP-1), which specifically up-regulates MMP1, MMP3, MMP9 (Fisher et al., 1996). MMPs are a superfamily of zinc metalloproteinases with catalytic activity, which can induce the degradation of extracellular matrix(ECM) and accelerate skin aging (Pittayapruek et al., 2016).

Oxidative stress plays a synergistic role in UV-induced skin damage. Ultraviolet radiation (UV) can contribute to the accumulation of reactive oxygen species (ROS) and eventually lead to NO production, skin inflammation and wrinkle formation (Pandel et al., 2013). ROS induces skin inflammation as a potential mechanism, activating NF-κB signal transduction, and is responsible for the expression of various inflammatory cytokines in skin (Bell et al., 2003). Preventing the cascade of NF-κB signals is an important target to inhibit the formation of wrinkles on skin induced by UV. Non-enzymatic antioxidants play an important part in preventing skin aging. We summarize some reported natural antioxidants and synthetic antioxidants which are related to NF-κB signals. In human skin fibroblasts cells, the antioxidant effect of magnesium lithospermate B (MLB) is due to the direct remove reactive oxygen species (ROS) and the inhibitory effects on NF-κB -dependent inflammation genes. MLB inhibited the expression and activities of NF-κB and AP-1-dependent MMPs by regulating ROS production and MAPK signaling pathway. Thus reversing the decrease of skin procollagen levels related to age and UVB. MLB may have a potential role in anti-wrinkle and anti-aging via inhibiting activities of NF-κB and AP-1-dependent MMPs. Besides, MLB significantly decreased the expressions of the COX-2 and iNOS genes (NF-κB dependent genes) (Ri et al., 2014). NF-κB played an important part in the expression of COX-2 and iNOS in mouse skin (Jin-Kyoung et al., 2007) due to the phosphorylation of MAPK, such as ERK and p38 MAP kinase (Feng et al., 2010).

In addition, Mycosporine-like amino acids (MAAs), extracted from Porphyra tenera, inhibit the transcription factor NF-κB and down-regulate the expression of MMP-1, MMP-3 and TNF-α by NF-κB and MAPK signaling pathway. In conclusion, MAAs inhibited the expression of MMPs induced by ultraviolet radiation by blocking the MAPK signaling pathway, thus down-regulating the activity of MMPs in ultraviolet radiation-induced skin photoaging (Rui et al., 2019).

Considering that sustained NF-κB activity is involved in the enforcement of aging (Adler et al., 2007), the down-regulation of NF-κB signal observed in NHEKs (Normal Human Epidermal Keratinocytes) cells with crocin (a carotenoid chemical compound which is found in the flowers crocus and gardenia (Alavizadeh and Hosseinzadeh, 2014)) designated it as a potentially beneficial component for skin aging (Fagot et al., 2018). And MHY384 was synthesized from 2,4-dihydroxybenzaldehyde and l-cysteine, a natural α-amino acid in environmentally friendly reaction medium using ethanol and water and had two chiral carbons, two phenolic hydroxyl groups on the phenyl ring and an α-amino acid functional group (Natarajan et al., 2014). UV exposure significantly increased the concentration of reactive oxygen species (ROS) and Mhy384 may act as an antioxidant to reduce oxidative stress. For Mhy384 treatment can decrease UVB-induced ROS concentration in hairless mice and reduce protein levels of p-p65 (S536), p65 and p50. Therefore, Mhy384 remarkably reversed protein levels of inflammatory mediators including COX2, iNOS, IL-1β, and TNFα. Meanwhile, Mhy384 reversed the increase of MMP-1, MMP-12, MMP-13 and type 1 procollagen in UVA-induced fibroblast damage in a dose-dependent manner to prevent the formation of wrinkles. Overall, MHY 384 can be used to prevent wrinkles via NF-κB signaling to reduce

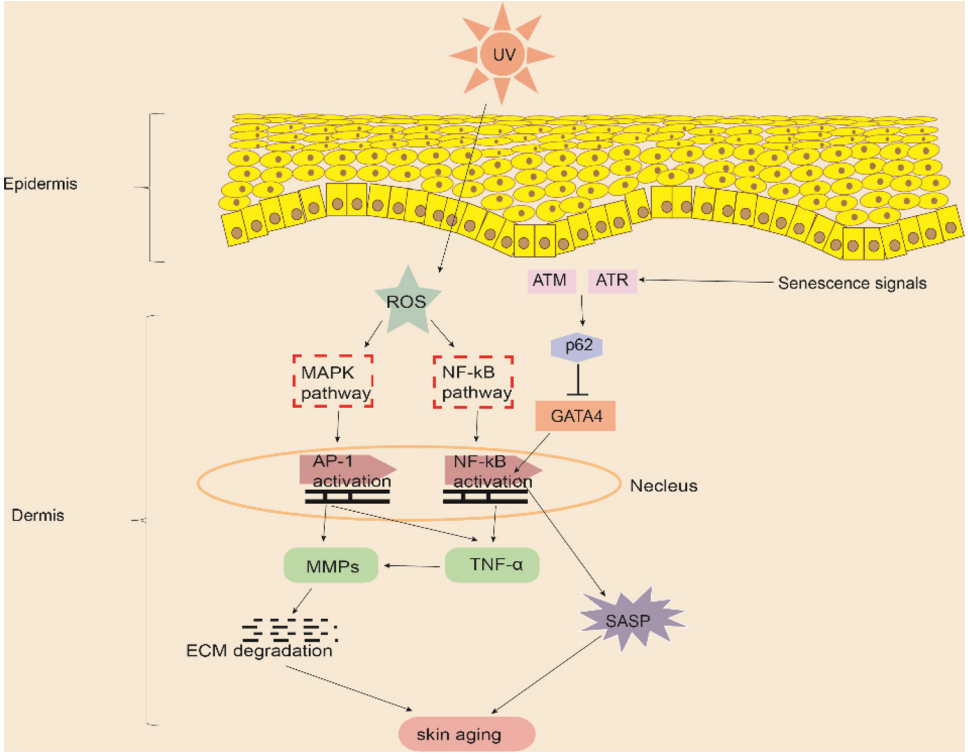

Fig. 1. The effects of UV on the skin is production of ROS, excessive free radicals activated the NF-κB signaling pathway and MAPK signaling pathway, contributing to the activation of AP-1 and NF-κB. As a consequence it increases the level of TNF-α and the expression of MMPs, which induce the degradation of ECM and accelerated skin aging. Upon senescence-inducing signals, ATM and ATR block p62-dependent autophagic degradation of GATA4, contributing to NF-κB activation and SASP induction.

ROS, which may be a new additive for anti-aging cosmetics (Lee et al., 2015).

Oral administration of GTP (5 mg) led to significant decrease in UVB induced skin thickening and modulations in MAPK and NF-κB signaling (Singh et al., 2014). Resveratrol, an antioxidant ingredient from berries, affects the SIRT (Sirtuin gene) by up-regulating its activation, which in turn reduces UV-induced damage by inhibiting NF-κB signaling pathway. The nuclear translocation of NF-κB contributed to the activation of MMPs (Liu et al., 2011). As for curcumin, a well-known antioxidant, it inhibits the phosphorylation of IαBα and its subsequent degradation and hence inhibited the release of NF-κB in the nucleus. This inhibition contributed to the activation of MMPs and subsequent collagen degradation (Thangapazham et al., 2007). In this section, we mainly summarize the effects of exogenous antioxidants (except GTP) acting through NF-κB signaling pathway.

Carcinoma-associated fibroblasts often play a key role in driving carcinogenesis. We mainly discuss the role of NF-κB in skin cancer-related SASP in fibroblasts (Gascard and Tlsty, 2016). The key to SASP transcription is the phosphorylation of transcription factor NF-κB. It has been reported that phosphorylated NF-κB p65/Rel A subunit transferred to the nucleus, where it bound several SASP gene promoters to regulate the induction during aging or DDR (DNA damage response) in human embryonic fibroblasts (Chien et al., 2011). Therefore, NF-κB is often referred as the “main regulator” of SASP, for its activation was vital of SASP expression. Besides, knock out of CCAAT/enhancer binding protein β with shRNA resulted in a decrease in CXCR2 ligand levels, indicating that NF-κB and CCAAT/enhancer binding protein β cooperate in regulating SASP in IMR-90 cells (Acosta et al., 2008).

GATA4, a member of the GATA family, plays a key role in the development and differentiation in eukaryotic cells (Weiss and Orkin, 1995). GATA4 can be degraded by p62-mediated autophagy (Kang and Elledge, 2016). Recent studies on human foreskin fibroblasts have established GATA4 nuclear stabilization as an inducer of IL-1α and upstream activator of NF-κB via the ATM-mediated DDR pathway. The abundance of GATA4 increased in response to senescence-inducing amounts of IR in the skin. It was also reported that NF-κB played a key role in the SASP (Chanhee et al., 2015). In addition, the upregulation of p38MAPK contributed to the increased activation of NF-κB to induce SASP in neonatal skin fibroblasts (Freund et al., 2011).

Human aging is characterized by persistent chronic low-grade inflammation called “inflammaging”, which plays an important part in skin aging. Inflammaging maintains an underlying association between cancer and aging through NF-κB pathways highly affected by specific miRNA (Catana et al., 2015). Overexpression of miR-146a/b in senescent human fibroblasts can significantly reduce the level of IRAK1 and the secretion of IL-6 and IL-8. In addition, the interruption of IL-1R signal transduction prevented the up-regulation of miR-146a/b, which was consistent with the fact that these microRNAs were a part of the NF-κB feedback loop. The study re-emphasized the important role of NF-κB in the positive and negative regulation of SASP (Adam et al., 2010) (Fig. 1).

4. Conclusion

Skin aging is a crucial part of aging, which is caused by both genetic and environmental factors. Furthermore, aging skin tissue is known to create a permissive tissue microenvironment that promotes the initiation, progression and resistance of cancer cells by promoting SASP activation. Therefore, more attention should be paid to skin aging. The NF-κB pathway is of vital importance in skin aging. In Section 2, we briefly introduce the common Rel proteins and two activation pathways: the canonical activation pathway and the non-canonical activation pathway. The canonical activation pathway mainly relies on IκB, a specific inhibitor of NF-κB. In the resting state, NF-κB binds to IκB and exists in the cytoplasm in the form of an inactive complex. Stimulations promote IκB kinase complex degradation and release of the dimer of NF-κB, which translocates into the nucleus and binds to specific DNA sites. There it regulates the transcription of target genes, thus leading to the synthesis and release of inflammatory cytokines. The non-canonical NF-κB activation pathway is mediated by transcription factor p100/Rel B, which is mainly active in immune cells. Then we summarized the role of NF-κB in skin aging in Section 3. The effects of UV on the skin include production of ROS, excessive free radicals, which activate the NF-κB signaling pathway and MAPK signaling pathway, contributing to

the activation of AP-1 and NF-κB. Ultimately the level of TNF-α and the expression of MMPs are increased, which induces the degradation of ECM and accelerates skin aging. UV is not the only cause of extrinsic aging and ROS generation. A long term contact with tobacco smoke and UVA-exposure both independently caused skin aging (Yin et al., 2001). Furthermore both intrinsic and extrinsic skin aging contribute to ROS generation. ROS are continuously produced as side products in the electron transport chain of the aerobic metabolism in the mitochondria, which are regarded as a major cause of intrinsic aging. As for extrinsic aging, both cigarette smoking and UV lead to ROS generation. (Farage et al., 2010) Thus, NF-κB plays a key role in SASP. Upon senescence-inducing signals, ATM and ATR block p62-dependent autophagic degradation of GATA4, contributing to NF-κB activation and SASP induction. In conclusion, this review summarized the role of NF-κB in skin aging, which we should receive more attention. We hope that the research on NF-κB in the field of skin aging will lead to exciting discoveries in the future.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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