ISSN 2079-0570, Advances in Gerontology, 2017, Vol. 7, No. 2, pp. 114–119. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © D.A. Gritsenko, O.A. Orlova, N.S. Linkova, V.Kh. Khavinson, 2017, published in Uspekhi Gerontologii, 2017, Vol. 30, No. 1, pp. 10–16.

Transcription Factor p53 and Skin Aging

D. A. Gritsenko[a], O. A. Orlova[b], N. S. Linkova[b, c], and V. Kh. Khavinson[b, d, *]

[a] *Institute of Plant Biology and Biotechnology, Almaty, 050040 Kazakhstan*
[b] *St. Petersburg Institute of Bioregulation and Gerontology, St. Petersburg, 197110 Russia*
[c] *Peter the Great St. Petersburg Polytechnic University, St. Petersburg, 195251 Russia*
[d] *Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, 199034 Russia*
**e-mail: khavinson@gerontology.ru*

Abstract—The review is dedicated to one of the molecular factors of skin aging essential for cosmetic medicine for the elderly. Cell renewal processes slow down with aging, and the proliferation–apoptosis equilibrium shifts towards cell death. One of the pivotal apoptotic markers is transcription factor p53. Its expression in skin keratinocytes increases under the influence of ultraviolet radiation. Mutant forms of p53 have been revealed in 70% of keratinocytes of skin exposed to ultraviolet radiation. On the one hand, suppression of p53 expression decreases apoptosis in skin cells, thereby decelerating senescence. On the other hand, it promotes the development of neoplasms in the skin. Thus, support of the physiological balance of p53 expression in skin cells is important for theoretical and practical gerontocosmetology. In addition, p53 can be used as a marker for skin cell functionality in response to anti-aging cosmetic products and to instrumental cosmetology.

Keywords: *p*53 protein, skin, aging
DOI: 10.1134/S2079057017020072

Skin aging is a complex process, influenced by endogenous and exogenous factors. The former include the accumulation of mutations in cells, telomere shortening, changes in skin cell metabolism, age-related hormonal disorders, etc. The latter are ultraviolet (UV) radiation, ionizing radiation, pollutants, and microorganisms. The numbers and intensities of exogenous and endogenous factors determine the predominance of this or that aging process. Aging includes two major processes: physiological and pathological [5]. The physiological (chronological) process is related to endogenous factors. Its clinical signs are skin dryness and laxity, small lines, and benign neoplasms. The pathological aging process, e.g., photoaging, is induced by exogenous factors. It is characterized by deep furrows, roughness, yellowing, high sensitivity, pigmentation, poor ability to repair wounds, and predisposition to benign and malignant neoplasms.

Studies of skin not exposed to sun show that aging is accompanied by the atrophy of epidermis, which may become 10–50% thinner within the range from 30 to 80 years. Atrophy touches mainly the spinous layer [64]. After the age of 30, the number of melanocytes decreases by 8–20% over each decade and melanocytes become more heterogeneous [22]. Histological studies of epidermis indicate that the basal layer of aging skin experiences profound changes. Keratinocytes of the basal layer become markedly heterogeneous, and the overall volume of a cell increases [10]. These changes are called epidermal dyscrasia. They occur in epidermis damaged by UV radiation [71]. Epidermal dyscrasia is marked by a lower mitosis rate, longer cell cycle, and longer migration of keratinocytes from the basal to the horny layer [18]. In the age range within 25–70 years, the immune function of skin weakens, and the number of white dendritic epidermal cells (Langerhans cells) decreases by 50%. With aging, the total number and activity of T and B lymphocytes in the skin decrease [50]. In elderly people, repair processes in the skin, such as collagen remodeling, cell proliferation, and fibroblast metabolism, slow down [49].

The epidermis is thinned under UV irradiation [16, 21], and the amounts of integrin B1 protein and mRNA in keratinocytes of the basal layer decrease [70]. B1 integrin mediates the attachment of basal layer keratinocytes to each other and to the basal membrane. B1 integrin includes two major protein types: *a*2*b*1 and *a*3*b*1. They interact with extracellular matrix proteins: fibronectin, laminins 1 and 5, and type I and IV collagens. Lower expression of B1 integrin in keratinocytes of aging skin points to lower keratinocyte proliferation and adhesion.

Permanent exposure of skin to UV radiation also damages the dermoepidermal junction. In upper layers of dermis constantly undergoing UV irradiation, the expression of fibrillin 1 and type VII collagen decreases. The latter forms anchoring fibrils in the dermoepidermal junction [23]. Light-induced skin senescence is accompanied by the accumulation of

atypical elastic fibers in the middle and lower layers of dermis. These degenerative changes are known as solar elastosis [32]. The elastic fibers accumulated with photoaging can replace normal matrix components. In addition, collagen composition changes with skin photoaging. The amount of type I collagen decreases with aging, whereas its expression does not. This effect is caused by faster type I collagen degradation [32, 60]. Experiments in vitro and in vivo show that UVA and UVB intensify collagen degradation by matrix metalloproteinases and proteases [4, 26, 68]. The most characteristic sign of light-induced skin senescence is the overexpression of p53 protein [6]. It has been found that the expression of active p53 species increases with physiological aging as well. This fact is related to the accumulation of mutations in keratinocytes and telomere shortening.

Thus, p53 is essential for the regulation of apoptosis in skin and other tissues. Aberrations in its expression, including those induced by UV radiation, may cause the formation of tumor cells. These processes are determined by molecular cascades involving p53. These cascades are common for different cell types, and their detailed consideration is beyond the scope of our review. We provide but brief outline of p53 metabolism and its involvement in the regulation of various groups of genes in a cell, so long as it is important for the understanding of the role of p53 in cell aging, including the skin.

p53: Intracellular Metabolism and Regulation of Various Gene Groups

The action of p53 on skin aging is diverse. It touches, as mentioned, dermis and epidermis thickness, hair growth rate, and wound repair. In addition, p53 affects the secretory function of skin sebaceous glands and decreases the amount of subcutaneous fat [27].

The influence of p53 on the secretory activity of sebaceous glands and subcutaneous fat reduction was studied in mice with two phosphomimetic mutations. After DNA damage, p53 is activated by phosphorylation at amino acid residues 21 and 23 to prevent its interaction with Mdm2 and MdmX followed by degradation. Replacements of Thr21 and Ser23 in wild-type p53 by aspartate mimic the phosphorylated state of the protein [34]. The levels of postnatal stem cells in various organs in mutant $p53^{21/23}$ mice are lowered, which causes early senescence. The skin of mutant $p53^{21/23}$ mice shows no change in the expression of apoptosis markers Puma, Noxa, or Bim. However, such mice show higher expression of aging-related markers p16, p21, p27, and PAI1 and lower expression of the proliferation marker Ki67. Protein p53 inhibits mTORC1 and reduces the volume of adipose tissue in the mutant animals. In addition, the mutant mice have lower levels of phosphorylated ribosomal protein kinase S6, which is an mTOR effector.

Study of sebocytes in mutant mice revealed activation of peroxisome proliferator-activated receptor gamma (PPARg). It is involved in the differentiation of adipocytes and skin sebocytes. The activation of PPARg in mice with the $p53^{21/23}$ mutation arrested Blimp1 synthesis in sebocyte precursors in sebaceous glands and the epidermis. Administration of a PPARg antagonist renewed Blimp1 synthesis. It was also noted that sebaceous glands were nearly absent from the adipose tissue of aged $p53^{21/23}$ mice. A decrease in the amount of adipose tissue and PPARg activation were recorded in aged mice with wild-type p53. Thus, the senescence signs observed in the skin of $p53^{21/23}$ mice correlated with signs of natural skin aging [27].

Transgenic mice with inactivated Mdm2 protein and overexpressed p53 showed epidermis thinning and a decrease in the population of hair follicle stem cells [27]. This change, together with changes in the functionality of epidermal stem cells in such mice retarded wound repair and hair growth [17]. Activation of p53-induced senescence of epidermal stem cells was also observed in mice whose cells had shortened telomeres. Inactivation of Mdm2 followed by accumulation of active p53 species was recorded in the skin of young (below 10 months) mice, although it was not accompanied by changes in the regulation of p53-activated genes. Then, epidermis thinning and hair fall-off were observed. In addition to epidermis thinning and hair fall-off, transgenic mice with truncated p53 showed changes in the dermis characteristic of natural skin aging. The dermis of aged (24 months) mice heterozygous for p53+/m, which carried the *m* allele, encoding a truncated p53 variant, was thinner than in wild-type animals [61].

Protein p53 is rapidly degraded in cells not exposed to stress factors owing to the interaction with ubiquitin ligase E3–Mdm2. This protein inhibits p53 activity in two ways. It binds to transactivating domains, thereby suppressing the transcription activity of p53 [39, 44] or attaches ubiquitin molecules to p53 to drive the protein to 26S proteosomes for degradation [20, 24, 30]. Conformational changes of p53 mediated by phosphorylation, acetylation, methylation, and sumoylation can stabilize p53 and activate its transcriptional potential. The phosphorylation is conducted by ATM, ATR, DNA-PK, Chk1, and Chk2 kinases. Phosphorylation of Thr81 is observed only after the action of UV and hydrogen peroxide. It is mediated by JNK kinase, which stabilizes and activates p53 [46]. It is conjectured that the phosphorylation of serines in p53 prevents its binding to inhibitor proteins Mdm2 and MdmX and favors p53 stabilization.

Protein p53 takes part in DNA repair. It acts as an adapter protein, cofactor in protein complexes, but its chief role is the regulation of gene transcription [3, 47]. It governs the transcription of genes encoding p21;

MDM2; protein 3, which binds insulin-like growth factor (IGFBP3); and TP53I3 [38]. Genes controlled by p53 can have more than one p53-binding element to enhance their response to regulation. The promoter region of p21 has one binding element highly affine to p53 and several elements with weaker affinities. Binding elements can occur in the promoter region, in introns, and far from the transcription start site [25].

Genes whose transcription involves p53 can be divided into four groups. The first group includes genes participating in cell cycle arrest. Protein p53 directly participates in the expression of the $p21^{WAF1/CIP1}$ protein, an inhibitor of cyclin-dependent kinases and a cell senescence marker. Protein p21 inhibits the passage of the G_1-S and G2-M checkpoints of the cell cycle. This group also includes the *Reprimo* gene, which is involved in cell cycle arrest in the G_2 phase [64]. The second group includes genes responsible for apoptosis. There are two major pathways to induce apoptosis. Their goal is to activate initiating caspases 8 and 9, which activate effector caspases 2, 3, and 7. The first, extrinsic pathway is triggered by death receptors. The second pathway is intrinsic, or mitochondrial. It is mediated by cytochrome C release from mitochondria. The mitochondrial pathway involves proapoptotic genes *Bax, NOXA, P53AIP1*, and *PUMA*. Their transcription is triggered by p53 [42, 43]. The *Bax* gene encodes a protein that increases mitochondrial membrane permeability and releases cytochrome C. Its regulatory region contains p53-binding elements. The gene is directly activated by p53 in some groups of human cells [65]. The third group includes genes maintaining cell stability. Genes whose products act in DNA repair belong to this group. Although they do not immediately control cell proliferation or apoptosis, their mutations and inactivation cause DNA damage. The fourth group of genes regulated by p53 inhibits angiogenesis. The formation of new blood vessels favors rapid tumor growth, as observed at later cancer stages. The group of p53-controlled genes preventing angiogenesis includes *GD-AIF* [63], *BAI1* [13], gelatinase *MMP2* [45], *MASPIN* [13], inhibitors of invasion and metastasis *KAI1*, and plasminogen activator inhibitor *PAI-1* [48].

Major Associations of p53 with Skin Aging and Cancer

The chief function of p53 is the support of genome stability and genetic uniformity of cells. Genome stability is maintained by p53 activation and relevant responses to stress signals: DNA damage, oncogene activation, hypoxia, nutrient shortage, and telomere shortening [9, 14, 15, 19, 31]. The stress signals mediated by p53 can be responded by cell cycle arrest, apoptosis, DNA repair, differentiation, or cell senescence.

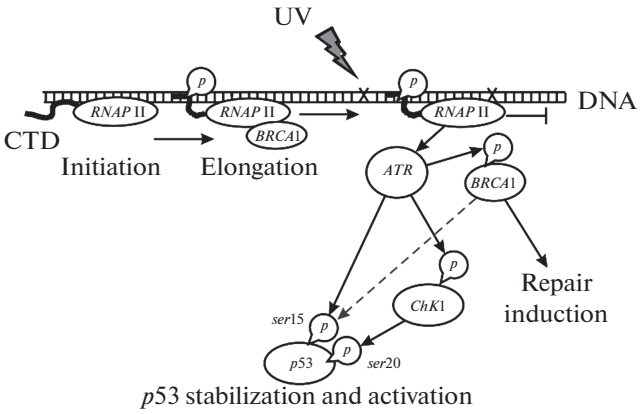

Fig. 1. Influence of UV radiation on the activation of p53 protein [2]. *CTD, carboxy terminal domain.

Expression of p53 in epidermis is detected as early as 30 min after the beginning of UV irradiation [2, 9, 29, 36] (Fig. 1). Ultraviolet radiation produces linkages formed by thymine dimers, which hamper the action of RNA polymerases. It is known that RNA polymerase II performs repair combined with transcription. Inhibition of RNA polymerase II sliding by linkages produced by UV at the elongation stage results in the accumulation of the p53 species phosphorylated at Ser15 and Lys382 [2]. The consequence of the inhibition of RNA polymerase II is the activation of kinase ATR, able to mediate the phosphorylation of p53 at Ser15 and activate kinase Chk1. Kinases Chk1 and Chk2 can phosphorylate Ser20 of p53. In addition to ATR kinase activation by arrest of RNA polymerase II, repair enzymes can be recruited via BRCA1 protein phosphorylation. This protein is associated with RNA polymerase II at the elongation stage. With transcription arrest, it is phosphorylated and removed from the transcription complex [35].

The action of long-wave radiation (UVA) induces intense p53 expression in the basal epidermis layer, whereas shorter wavelengths (UVB) do it in cells of all epidermis layers [53, 62]. Immunohistochemical p53 detection can be applied to visualize keratinocytes and clusters of epidermal $p53^+$ clones scattered in the epidermis [54]. Clusters of $p53^+$ cells occur in permanently insolated epidermis, among cells adjacent to nonmelanoma skin cancer keratinocytes. It has been found that 70% of such clones bear mutant p53 species [37, 66].

Mutations altering the function of p53 are the cause of malignant tumors in 50% of cancer types [12]. Only 5% of these mutations occur in the regulatory domain of p53, and 95%, in the central region controlling specific p53 binding to DNA [67]. In some cancer types, exemplified by colon tumors, mutant p53 species are observed at advanced malignancy stages, whereas in skin cancer, mutant p53 appears at early neoplasia stages [51].

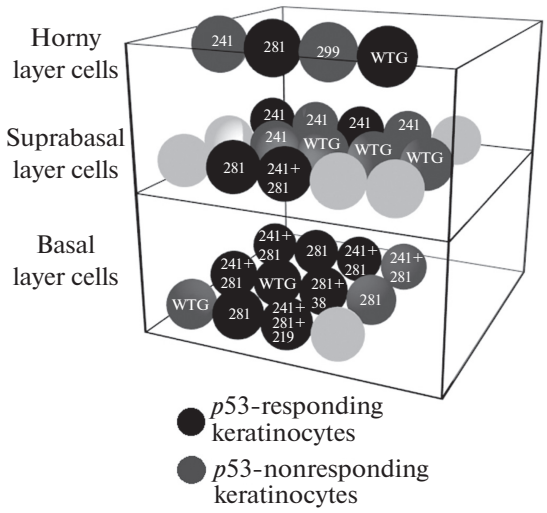

Fig. 2. Location of p53 mutants in skin cells [33]. WTG, wild-type gene; 241, 281, 299, 38, and 219, codons in which mutations were detected.

Nonmelanoma skin cancer is the most widespread cancer form in humans [57]. Mutant variants of the *p53* gene are its characteristic trait [9]. Mutations in p53 occur in 60% of patients with actinic keratosis [42, 51, 53, 57] and 69%, with squamous cell carcinoma [7, 50, 56]. Typical mutations produced in the skin by UV radiation are tandem substitutions CC–>TT [55]. The main mechanism activating p53 in response to UV is shown in Fig. 1 [2].

UVA can induce DNA lesions indirectly. DNA damage can be mediated by the accumulation of UV-sensitive molecules: riboflavin, pterin, and porphyrin [8].

High p53 levels are observed in both naturally aging and cultivated skin cells. Aged cultures of human skin fibroblasts showed high levels of active p53 species [11, 28]. Fibroblast aging in vitro is also accompanied by elevated expression of caspase 3 and lower expression of Ki67. Caspase 3 and Ki67 are commonly used as markers of apoptosis and skin cell proliferation, respectively. Caspase 3 is a marker of apoptosis, and its expression is proven at stages preceding apoptosis. Protein Ki67 is produced in cells at the G1, G2, S, and M phases of the cell cycle. Experiments with rat skin fibroblasts showed that a decrease in caspase 3 production and increase in Ki67 could be achieved with peptides AEDG, KED, KE, and AED, designed at the St. Petersburg Institute of Bioregulation and Gerontology [1].

Studies of normal human epidermal cells revealed $p53^+$ keratinocytes located in various epidermis layers individually or in clusters. In 70% of cases, they contained mutant p53 forms [40, 58, 60]. Most of the mutations appeared to be caused by UV radiation, first, C → T replacements in dipyrimidine sites. Moreover, a single keratinocyte could have up to three different mutant p53 forms. Examination of cells of an epidermal clone showed that missense mutations in exon 8 (codon 281) and exon 7 (codon 241) were present in all epidermis layers; correspondingly, they might have descended from a single cell (Fig. 2). These mutations touched the p53 domain responsible for specific binding to DNA [33].

Examination of skin keratinocytes not insolated for two months revealed cells with p53 mutations typical of UV, although the number of $p53^+$ cells decreased by 66% [69]. Also, mutant p53 forms were noted. However, these mutations were not associated with cancer development.

CONCLUSIONS

As p53 is multifunctional, the investigation of its signaling pathways and their role in skin aging and tumor formation is an urgent problem in modern gerontocosmetology and molecular biology. On the one hand, low p53 expression reduces apoptosis in skin cells and slows down their senescence. On the other hand, it favors the development of skin neoplasms. Overexpression of p53 lowers the risk of skin cancer, but cells rapidly reach the Hayflick limit and senesce. Thus, the support of the physiological balance in p53 expression is essential for theoretical and applied gerontocosmetology. In addition, p53 can be employed as a marker of the functional state of skin cells in using anti-aging cosmetic products and in machine cosmetology.

REFERENCES

1. Lin'kova, N.S., Drobintseva, A.O., Orlova, O.A., et al., Peptide regulation of functions of skin fibroblasts during their aging in vitro, *Kletochnye Tekhnol. Biol. Med.*, 2016, no. 1, pp. 40–44.
2. Chumakov, P., The p53 protein and its universal functions in the multicellular organism, *Usp. Biol. Khim.,* 2007, vol. 47, pp. 38–52.
3. Adikesavan, A.K., Karmakar, S., Pardo, P., et al., Activation of p53 transcriptional activity by SMRT: a histone deacetylase 3-independent function of a transcriptional co-repressor, *Mol. Cell Biol.,* 2014, vol. 34, no. 7, pp. 1246–1261.
4. Agnez-Lima, L.F., Melo, J.T., Silva, A.E., et al., DNA damage by singlet oxygen and cellular protective mechanisms, *Mutat. Res.,* 2012, vol. 751, no. 1, pp. 15–28.
5. Akase, T., Nagase, T., Huang, L., et al., Aging-like skin changes induced by ultraviolet irradiation in an animal model of metabolic syndrome, *Biol. Res. Nurs.,* 2012, vol. 14, no. 2, pp. 180–187.
6. Ashley, B.W. and Schumacher, B., p53 in the DNA-damage-repair process, *Cold Spring Harbor Perspect. Med.,* 2016, vol. 6, no. 5, pp. 1–16.
7. Bernard, J.J., Lou, Y.R., Peng, Q.Y., et al., Inverse relationship between p53 and phospho-Chk1 (Ser317) protein expression in UVB-induced skin tumors in

SKH-1 mice, *Exp. Mol. Pathol.,* 2014, vol. 96, no. 1, pp. 126–131.

8. Bosch, R., Philips, N., Suárez-Pérez, J.A., et al., Mechanisms of photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals, *Antioxidants,* 2015, vol. 4, no. 2, pp. 248–268.
9. Brash, D.E., Cancer. Preprocancer, *Science,* 2015, vol. 348, no. 6237, pp. 867–868.
10. Bregegere, F., Soroka, Y., Bismuth, J., et al., Cellular senescence in human keratinocytes: unchanged proteolytic capacity and increased protein load, *Exp. Gerontol.,* 2003, vol. 38, no. 6, pp. 619–629.
11. Childs, B.G., Durik, M., Baker, D.J., and van Deursen, J.M., Cellular senescence in aging and age-related disease: from mechanisms to therapy, *Nat. Med.,* 2015, vol. 21, no. 12, pp. 1424–1435.
12. Choy, B., Findeis-Hosey, J.J., Li, F., et al., High frequency of coexpression of maspin with p63 and p53 in squamous cell carcinoma but not in adenocarcinoma of the lung, *Int. J. Clin. Exp. Pathol.,* 2013, vol. 6, no. 11, pp. 2542–2547.
13. Duman, J.G., Tu, Y.K., and Tolias, K.F., Emerging roles of BAI adhesion-GPCRs in synapse development and plasticity, *Neural. Plast.,* 2016, vol. 2016, no. 17, pp. 1–9.
14. Emami, S., Interplay between p53-family, their regulators, and PARPs in DNA repair, *Clin. Res. Hepatol. Gastroenterol.,* 2011, vol. 35, no. 2, pp. 98–104.
15. Finzel, A., Grybowski, A., Strasen, J., et al., Hyperactivation of ATM upon DNA-PKcs inhibition modulates p53 dynamics and cell fate in response to DNA damage, *Mol. Biol. Cell,* 2016, vol. 27, no. 15, pp. 1–18.
16. Ganceviciene, R., Liakou, A.I., Theodoridis, A., et al., Skin anti-aging strategies, *Dermatoendocrinology,* 2012, vol. 4, no. 3, pp. 308–319.
17. Gannon, H.S., Donehower, L.A., Lyle, S., and Jones, S.N., Mdm2-p53 signaling regulates epidermal stem cell senescence and premature aging phenotypes in mouse skin, *Dev. Biol.,* 2011, vol. 353, no. 1, pp. 1–9.
18. Grove, G.L. and Kligman, A.M., Age-associated changes in human epidermal cell renewal, *J. Gerontol.,* 1983, vol. 38, no. 2, pp. 137–142.
19. Hasty, P. and Christy, B.A., p53 as an intervention target for cancer and aging, *Pathobiol. Aging Age Relat. Dis.,* 2013, vol. 3, pp. 1–11.
20. Haupt, Y., Maya, R., Kazaz, A., et al., Mdm2 promotes the rapid degradation of p53, *Nature,* 1997, vol. 387, no. 6630, pp. 296–299.
21. Helton, E.S. and Chen, X., P53 modulation of the DNA damage response, *J. Cell Biochem.,* 2007, vol. 100, no. 4, pp. 883–896.
22. Hendi, A., Wada, D.A., Jacobs, M.A., et al., Melanocytes in nonlesional sun-exposed skin: a multicenter comparative study, *J. Am. Acad. Dermatol.,* 2011, vol. 65, no. 6, pp. 1186–1193.
23. Hibbert, S.A., Watson, R.E., Gibbs, N.K., et al., A potential role for endogenous proteins as sacrificial sunscreens and antioxidants in human tissues, *Redox Biol.,* 2015, vol. 5, pp. 101–113.
24. Honda, R., Tanaka, H., and Yasuda, H., Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressorp53, *FEBS Lett.,* 1997, vol. 420, no. 1, pp. 25–27.
25. Kastan, M.B., Zhan, Q., El-Deiry, W.S., et al., A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia, *Cell,* 1992, vol. 71, no. 4, pp. 587–597.
26. Kim, J.A., Ahn, B.N., Kong, C.S., et al., Antiphotoaging effect of chitooligosaccharides on human dermal fibroblasts, *Photodermatol. Photoimmunol. Photomed.,* 2012, vol. 28, no. 6, pp. 299–306.
27. Kim, J., Nakasaki, M., and Todorova, D., p53 induces skin aging by depleting Blimp1+ sebaceous gland cells, *Cell Death Dis.,* 2014, vol. 5, no. 3, pp. 1–10.
28. Kim, R.H, Kang, M.K., Kim, T., et al., Regulation of p53 during senescence in normal human keratinocytes, *Aging Cell,* 2015, vol. 14, no. 5, pp. 838–846.
29. Kircik, L.H., Histologic improvement in photodamage after 12 months of treatment with tretinoin emollient cream (0.02%), *J. Drugs Dermatol.,* 2012, vol. 11, no. 9, pp. 1036–1040.
30. Kubbutat, M.H., Jones, S.N., and Vousden, K.H., Regulation of p53 stability by Mdm2, *Nature,* 1997, vol. 387, no. 6630, pp. 299– 303.
31. Lane, D.P., Cancer, p53, guardian of the genome, *Nature,* 1992, vol. 358, no. 6381, pp. 15–16.
32. Le, V.H., Lee, S., Kim, B., Yoon, Y., et al., Correlation between polarization sensitive optical coherence tomography and second harmonic generation microscopy in skin, *Biomed. Opt. Express.,* 2015, vol. 6, no. 7, pp. 2542–2551.
33. Ling, G., Persson, A., Berne, B., et al., Persistent p53 mutations in single cells from normal human skin, *Am. J. Pathol.,* 2001, vol. 159, no. 4, pp. 1247–1253.
34. Liu, D., Ou, L., and Clemenson, G.D., Puma is required for p53-induced depletion of adult stem cells, *Nat. Cell Biol.,* 2010, vol. 12, no. 10, pp. 993–998.
35. Ljungman, M. and Lane, D.P., Transcription—guarding the genome by sensing DNA damage, *Nat. Rev. Cancer,* 2004, vol. 4, no. 9, pp. 727–737.
36. Loriaux, M. and Hoffmann, A., A protein turnover signaling motif controls the stimulus-sensitivity of stress response pathways, *PLoS Comput. Biol.,* 2013, vol. 9, no. 2, pp. 1–12.
37. Martincorena, I., Roshan, A., Gerstung, M., et al., Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin, *Science,* 2015, vol. 348, no. 6237, pp. 880–886.
38. Menendez, D., Inga, A., and Resnick, M.A., The expanding universe of p53 targets, *Nat. Rev. Cancer,* 2009, vol. 9, no. 10, pp. 724–737.
39. Momand, J., Zambetti, G.P., Olson, D.C., et al., The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation, *Cell,* 1992, vol. 69, no. 7, pp. 1237–1245.
40. Neto, P.D., Alchorne, M., Michalany, N., et al., Reduced p53 staining in actinic keratosis is associated with squamous cell carcinoma: a preliminary study, *Indian J. Dermatol.,* 2013, vol. 58, no. 4, pp. 325.
41. Nonaka, T., Toda, Y., Hiai, H., et al., Involvement of activation-induced cytidine deaminase in skin cancer

development, *J. Clin. Invest.,* 2016, vol. 126, no. 4, pp. 1367–1382.

42. Oda, E., Ohki, R., Murasawa, H., et al., Noxa, a BH3-only member of the Bcl-2 family and candidate mediator of p53-induced apoptosis, *Science,* 2000, vol. 288, no. 5468, pp. 1053–1058.
43. Oda, K., Arakawa, H., Tanaka, T., et al., P53AIP1, a potential mediator of p53-dependent apoptosis, and its regulation by Ser-46-phosphorylated p53, *Cell,* 2000, vol. 102, no. 6, pp. 849–862.
44. Oliner, J.D., Pietenpol, J.A., Thiagalingam, S., et al., Oncoprotein MDM2 conceals the activation domain of tumor suppressor p53, *Nature,* 1993, vol. 362, no. 6423, pp. 857–860.
45. Pei, J., Park, I.H., Ryu, H.H., et al., Sublethal dose of irradiation enhances invasion of malignant glioma cells through p53-MMP 2 pathway in U87MG mouse brain tumor model, *Radiat. Oncol.,* 2015, vol. 10, no. 1, pp. 1–11.
46. Picco, V. and Pagés, G., Linking JNK activity to the DNA damage response, *Genes Cancer*, 2013, vol. 4, nos. 9–10, pp. 360–368.
47. Pistritto, G., Trisciuoglio, D., Ceci, C., et al., Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies, *Aging* (N.Y.), 2016, vol. 8, no. 4, pp. 603–619.
48. Powell, T., Piwnica-Worms, D., and Piwnica-Worms, H., Contribution of p53 to metastasis, *Cancer Discovery,* 2014, vol. 4, no. 4, pp. 405–414.
49. Quan, T., *Molecular Mechanisms of Skin Aging and Age-Related Diseases,* Boca Raton, FL: CRC, 2016, pp. 51–61.
50. Ratushny, V., Gober, M.D., Hick, R., et al., From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma, *J. Clin. Invest.,* 2012, vol. 122, no. 2, pp. 464–472.
51. Rebel, H.G, Bodmann, C.A, van de Glind, G.C., De Gruij, F.R., UV-induced ablation of the epidermal basal layer inclu ding p53-mutant clones resets UV carcinogenesis showing squamous cell carcinomas to originate from interfollicular epidermis, *Carcinogenesis,* 2012, vol. 33, no. 3, pp. 714–720.
52. Rivlin, N., Brosh, R., Oren, M., and Rotter, V., Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis, *Genes Cancer,* 2011, vol. 2, no. 4, pp. 466–474.
53. Seebode, C., Lehmann, J., and Emmert, S., Photocarcinogenesis and skin cancer prevention strategies, *Anticancer Res.,* 2016, vol. 36, no. 3, pp. 1371–1378.
54. Singh, A., Park, H., Kangsamaksin, T., et al., Keratinocyte stem cells and the targets for nonmelanoma skin cancer, *Photochem. Photobiol.,* 2012, vol. 88, no. 5, pp. 1099–1110.
55. Skinner, A.M. and Turker, M.S., High frequency induction of CC to TT tandem mutations in DNA repair-proficient mammalian cells, *Photochem. Photobiol.,* 2008, vol. 84, no. 1, pp. 222–227.
56. Solus, J.F., Murphy, G.F., and Kraft, S., Cutaneous squamous cell carcinomas of the lower extremities show distinct clinical and pathologic features, *Int. J. Surg. Pathol.,* 2016, vol. 24, no. 1, pp. 29–36.
57. Song, F., Qureshi, A., Giovannucci, E., et al., Risk of a second primary cancer after non-melanoma skin cancer in white men and women: a prospective cohort study, *PLoS Med.,* 2013, vol. 10, no. 4, pp. 1–9.
58. Stahl, P.L., Stranneheim, H., Asplund, A., et al., Sun-induced nonsynonymous p53 mutations are extensively accumulated and tolerated in normal appearing human skin, *J. Invest. Dermatol.,* 2011, vol. 131, no. 2, pp. 504–508.
59. Svobodová, A. R., Galandáková, A., Sianská, J., et al., DNA damage after acute exposure of mice skin to physiological doses of UVB and UVA light, *Arch. Dermatol. Res.*, 2012, vol. 304, no. 5, pp. 407–412.
60. Tsai, K., Lin, J., Yang, S., et al., Curcumin protects against UVB-induced skin cancers in SKH-1 hairless mouse: analysis of early molecular markers in carcinogenesis, *J. Evidence-Based Complementary Altern. Med.*, 2012, vol. 2012, pp. 1–11.
61. Tyner, S.D., Venkatachalam, S., and Choi, J., P53 mutant mice that display early ageing-associated phenotypes, *Nature,* 2002, vol. 415, no. 6867, pp. 45–53.
62. van de Glind, G., Rebel, H., van Kempen, M., et al., Fractionation of a tumor-initiating UV dose introduces DNA damage-retaining cells in hairless mouse skin and renders subsequent TPA-promoted tumors non-regressing, *Oncotarget,* 2016, vol. 7, no. 7, pp. 8067–8077.
63. van Meir, E.G., Polverini, P.J., Chazin, V.R., et al., Release of an inhibitor of angiogenesis upon induction of wild type p53 expression in glioblastoma cells, *Nat. Genet.,* 1994, vol. 8, no. 2, pp. 171–176.
64. Vierkötter, A. and Krutmann, J., Environmental influences on skin aging and ethnic-specific manifestations, *Dermatoendocrinology,* 2012, vol. 4, no. 3, pp. 227–231.
65. Vogelstein, B., Lane, D., and Levine, A.J., Surfing the p53 network, *Nature,* 2000, vol. 408, no. 6810, pp. 307–310.
66. Voskamp, P., Bodmann, C.A., Koehl, G.E., et al., Dietary immunosuppressants do not enhance UV-induced skin carcinogenesis, and reveal discordance between p53-mutant early clones and carcinomas, *Cancer Prev. Res.,* 2013, vol. 6, no. 2, pp. 129–138.
67. Vousden, K.H. and Lu, X., Live or let die: the cell's response to p53, *Nat. Rev. Cancer,* 2002, vol. 2, no. 8, pp. 594–604.
68. Wang, F., Smith, N.R., Tran, B.A., et al., Dermal damage promoted by repeated low-level UV-A1 exposure despite tanning response in human skin, *J.A.M.A. Dermatol.,* 2014, vol. 150, no. 4, pp. 401–406.
69. *Principles and Practice of Photoprotection*, Wang, S.Q. and Lim, H.W., Eds., New York: Springer-Verlag, 2016, pp. 23–38.
70. Watt, F.M. and Fujiwara, H., Cell-extracellular matrix interactions in normal and diseased skin, *Perspect. Biol.,* 2011, vol. 3, no. 4, pp. 1–14.
71. West, M.D. The cellular and molecular biology of skin aging, *Arch. Dermatol.,* 1994, vol. 130, no. 1, pp. 87–95.

Translated by V. Gulevich

SPELL: 1. overexpressed