Age-induced and photoinduced changes in gene expression profiles in facial skin of Caucasian females across 6 decades of age

Alexa B. Kimball, MD, MPH,[a] Maria B. Alora-Palli, MD,[a] Makio Tamura, PhD,[b] Lisa A. Mullins, BS,[b] Chieko Soh, MS,[c] Robert L. Binder, PhD,[b] Neil A. Houston, AB,[a] Emily D. Conley, PhD,[d] Joyce Y. Tung, PhD,[d] Nikki E. Annunziata, BS,[b] Charles C. Bascom, PhD,[b] Robert J. Isfort, PhD,[b] Bradley B. Jarrold, MS,[b] Raghu Kainkaryam, PhD,[b] Heather L. Rocchetta, PhD,[b] Dionne D. Swift, PhD,[b] Jay P. Tiesman, PhD,[b] Kazumi Toyama, BS,[c] Jun Xu, PhD,[b] Xianghong Yan, PhD,[c] and Rosemarie Osborne, PhD[b]
Boston, Massachusetts; Cincinnati, Ohio; Kobe, Japan; and Mountain View, California

Background: Intrinsic and extrinsic factors, including ultraviolet irradiation, lead to visible signs of skin aging.

Objective: We evaluated molecular changes occurring in photoexposed and photoprotected skin of white women 20 to 74 years of age, some of whom appeared substantially younger than their chronologic age.

Methods: Histologic and transcriptomics profiling were conducted on skin biopsy samples of photoexposed (face and dorsal forearm) or photoprotected (buttocks) body sites from 158 women. 23andMe genotyping determined genetic ancestry.

Results: Gene expression and ontologic analysis revealed progressive changes from the 20s to the 70s in pathways related to oxidative stress, energy metabolism, senescence, and epidermal barrier; these changes were accelerated in the 60s and 70s. The gene expression patterns from the subset of women who were younger-appearing were similar to those in women who were actually younger.

Limitations: Broader application of these findings (eg, across races and Fitzpatrick skin types) will require further studies.

Conclusions: This study demonstrates a wide range of molecular processes in skin affected by aging, providing relevant targets for improving the condition of aging skin at different life stages and defining a molecular pattern of epidermal gene expression in women who appear younger than their chronologic age. (J Am Acad Dermatol 2018;78:29-39.)

Key words: aging; facial skin appearance; gene expression; genetics; intrinsic aging; photoaging; photoprotection; pigmentation; transcriptomics.

Visible signs of facial skin aging include fine lines, coarse wrinkling, and pigment irregularities, all of which independently contribute to the perception of age.[1-3] The skin's apparent age and its chronologic age are not always

Abbreviations used:

ECM:	extracellular matrix
LCM:	laser capture microdissection
mRNA:	messenger RNA
UV:	ultraviolet

From Massachusetts General Hospital and Harvard Medical School, Boston[a]; The Procter & Gamble Company, Cincinnati[b]; Procter & Gamble IGK, Kobe[c]; and 23andMe, Inc, Mountain View.[d]

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Correspondence to: Alexa B. Kimball, MD, MPH, Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, 375 Longwood Ave, Boston, MA 02215. E-mail: kimballmdresearch@gmail.com.

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concordant: some individuals appear more youthful than their chronologic age. Rates of intrinsic, or chronologic, aging are at least partially predicted by inherent genetics, including pigmentation and mutations in the melanocortin 1 receptor gene (*MC1R*),[4] and involve biologic processes, including cellular metabolism, DNA transcription, signal transduction, and cell cycle progression.[5-7] Superimposed on these biologic processes, it is well established that extrinsic aging can be induced by environmental factors such as ultraviolet (UV) irradiation and smoking, both of which accelerate changes in appearance.[8,9] Although clinical signs of intrinsic and extrinsic aging are similar, chronologically aged skin tends to be thinner, more evenly pigmented, laxer, and more finely lined than photoexposed skin, which is consistent with different mechanisms being activated through environmental damage.[10]

CAPSULE SUMMARY

- Intrinsic and extrinsic factors affect skin aging.
- Patterns of gene expression accelerated with aging in a group of Caucasian women and differed in a subgroup that appeared exceptionally youthful.
- Patterns of gene expression manifest in appearance. They are partially determined by underlying genetics and might be positively affected by photoprotection.

Although the pathways involved in intrinsic aging and photoaging of skin are not completely understood, accumulation of cellular damage due to excess reactive oxygen species[11-13] and degradation of the extracellular matrix (ECM)[14-16] are thought to play a role in both. In contrast, accumulation of nonfunctional elastin and disorganization of collagen fibrils, known as solar elastosis, is more tightly associated with UV irradiation[17-19] and occurs more profoundly in individuals who lack intrinsic protective pigment.[8]

This study was designed to collect and integrate data at the molecular, cellular, and tissue levels to help produce an overall model of aging skin; this is an integrative systems biology approach. As part of this study, gene expression patterns common in women who were "exceptional agers" and appeared years younger than their chronologic age were identified.

MATERIALS AND METHODS

Subject population

The study was approved by the Partners Human Research Committee Institutional Review Board, and all subjects provided written informed consent before undergoing any study procedures. A total of 158 Caucasian females in good general health with Fitzpatrick types I to III were enrolled at Massachusetts General Hospital in Boston, Massachusetts; the women were within the age ranges of 20 to 24, 30 to 34, 40 to 44, 50 to 54, 60 to 64, and 70 to 74 years (with 25-31 women in each age cohort). Entry criteria included slight-to-moderate photodamage on the skin of the face and dorsal forearms of women in their 20s and 30s, whereas those 40 or older were required to have moderate-to-severe photodamage on these areas.[20] All subjects were required to have areas of buttocks skin with no visual photodamage or history of sun exposure or tanning. Exclusion criteria included smoking; alcohol and drug abuse; use of hormone replacement therapy, anti-inflammatories, or immunosuppressants; skin care treatments such as retinoids (excluded to prevent possible confounding anti-aging effects); and systemic diseases such as diabetes. A survey queried medical history, skin care habits, and attitudes toward sun exposure.

Estimation of genetic ancestry

23andMe, Inc (Mountain View, CA) used a custom genotyping platform to analyze saliva DNA samples and performed subsequent ancestry composition analysis as described in the Supplemental Methods (available at http://www.jaad.org).

Reproductive status

The reproductive status of each subject was determined on the basis of plasma follicle-stimulating hormone level and an internist's evaluation of her medical history.[21]

Age assessment

Standardized photography was obtained with a Visia CR imaging system (Canfield Scientific; Parsippany, NJ). "Appearance age" was determined by applying AgeMash analysis: random pairs of images were evaluated by graders in a crowdsourcing approach to choose which subject had "younger-looking skin." These collective pairwise choices were then used to rank order the entire set of images using a rank aggregation algorithm,[22] with each subject assigned an associated "appearance age" score. Ranking of entities from pairwise choices (eg, overall ranking of chess players from results of pairwise matches) has been used successfully with crowdsourced data in several applications.[22]