The Aging Skin: From Basic Mechanisms to Clinical Applications

Societies around the globe are facing dramatic demographic changes with constantly growing elderly populations. These changing demographics are accompanied by the increasing prevalence of aging-associated diseases such as cardiovascular diseases, type 2 diabetes, dementia, cancer, chronic inflammatory, and degenerative processes. Chronic diseases of aging affect almost all organs, including the skin. Demographic changes thus promote multimorbidity that burdens economies, including the health care sectors, as well as societies in general with far-reaching consequences.

The human body comprises a highly complex network of tissues, organs, proteins, and genes whose homeostatic balance deteriorates during aging. Research in simple model organisms such as worms, flies, and mice has allowed the unraveling of key mechanisms underlying many regulatory and metabolic processes in human physiology and disease. The understanding of genetic mechanisms of longevity was initiated by the discovery of *Caenorhabditis elegans* mutants in the insulin-like signaling pathway in the early 1990s (Kenyon, 2010). Consequently, distinct signaling pathways and homeostatic mechanisms, ranging from genome stability to proteostasis, were identified and shown to regulate the aging process in a highly conserved fashion (López-Otín et al., 2013). These signaling mechanisms could ameliorate the onslaught of damage accumulation in which DNA damage has become increasingly recognized as a key driving factor (Niedernhofer et al., 2018). Progeroid syndromes that are caused by mutations in DNA repair genes have been instrumental in understanding the role of DNA damage in the aging process. Here, particularly prominent skin pathologies such as dryness, scaling, inflammation, and atrophy as well as skin cancer are associated with defects in nucleotide excision repair. Moreover, UV-induced DNA damage increases the risk of malignant transformation and promotes photoaging. The role of cellular senescence—an outcome of irreparable DNA damage—and its non–cell-autonomous consequences in skin aging and regeneration is becoming increasingly well-understood and is discussed in several articles in this special issue of the *Journal of Investigative Dermatology*. Declining regenerative capacities and increasing molecular damage that affects both cellular components and extracellular matrix (ECM) are additional characteristic hallmarks of aging skin.

The human skin represents the body's largest organ, and it offers a highly suitable model to study biological pathways and mechanistic underpinnings that are common to many other aging-associated diseases. The skin is the first-line defense of the organism to external injuries, infections, and mechanical or radiation damage. At the same time, the skin also prevents water loss, controls temperature, and acts as a sensory organ. The diverse functions of the skin reflect highly controlled interactions among different cells of epithelial, mesenchymal, neuronal, and immunological origin, which are embedded in a complex ECM structure that is responsible for the biomechanical features of the skin.

Keratinocytes (KCs) in the epidermis are constantly replenished by stem cells (SCs) that reside in the basal layer and rest on the basement membrane (BM). Epidermal homeostasis is dependent on cellular differentiation that involves the regulation of integrins and features the movement of the differentiated cells to the upper layers of the epidermis where they are shed from the skin surface (Driskell and Watt, 2015). Besides the differentiating KCs of the epidermis, the skin also contains structures such as hair follicles (HFs); sebaceous, apocrine, and eccrine glands; and a complex network of immunocompetent cells. The BM zone, a thin but highly complex structure, connects the epidermis to the underlying dermis and subcutis. Here, fibroblasts and vessel-forming cells are embedded into a dense ECM composed of a large number of collagenous and noncollagenous proteins and proteoglycans, which form the skin matrisome (Hynes and Naba, 2012). These different compartments are anatomically and functionally well-connected. Fibroblasts have an important impact on the functions of the KCs, the melanocytes, and the Langerhans cells and also regulate SC reservoirs in the bulge regions of HFs and the interfollicular epidermis.

Currently, the understanding of fibroblast subsets that are characterized by specific

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activities is developing rapidly, and there is growing insight into the roles of these subsets in distinct disease entities (Driskell and Watt, 2015; Hu et al., 2018). All of these cellular and extracellular constituents are modulated in their biophysical and biological activities by intrinsic aging that leads to reductions of elastin fibers and collagen and to loss of tensile strength of the skin. UV irradiation as well as other external environmental factors elicit extrinsic aging with the induction of metalloproteases, release of VEGF, as well as alterations in elastic fibers and the corresponding microfibrillar network (Gilchrest, 2013; Scharffetter-Kochanek et al., 2000). The skin represents a model that is well-suited for studies of principal mechanisms of aging because of its complex tissue composition featuring various distinct cell types and its exposure to the environment, coupled with easy accessibility.

The enormous progress in understanding the fundamental mechanisms affecting the cellular signaling pathways and the interplay among the different cell types operating in skin aging has inspired this special issue of the *Journal of Investigative Dermatology*. Key processes that influence aging include DNA damage, defective repair processes, accumulation of protein aggregates, altered mitochondria functions, and cell membrane defects (Schumacher and Vijg, 2019). Many of these molecular aberrations trigger metabolic changes, cause chronic inflammation, and impair the functioning of the immune system. They are critically involved in the development of common skin diseases in the elderly, including epithelial cancer and autoimmunological diseases, and in alterations in the barrier function. The deepened understanding of the underlying mechanisms, the metabolic pathways, and the role of age-dependent hormonal regulation has already led to the identification of specific target circuits and structures to allow therapeutic modulation (Campisi et al., 2019; Childs et al., 2015).

To comply with the vision and scope of the *Journal of Investigative Dermatology*, we have invited basic scientists and clinicians to explore the different aspects of aging in general and the aging skin specifically and to highlight novel therapeutic concepts to combat aging-associated skin diseases and promote a healthy aging process.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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