Modeling aging in a culture dish: towards the development of more sophisticated in vitro models of human skin aging

Abstract

With age, human skin undergoes a progressive decline in essential functions, including barrier protection, immunity, and wound healing capacity, which underlie many age-related skin diseases. Skin aging is not only driven by chronological aging, but also strongly influenced by extrinsic stressors, notably ultraviolet radiation, pollutants, and diet. Thus, understanding the complex interplay between these intrinsic and extrinsic factors is essential for developing strategies to preserve skin health across the lifespan. Given the growing appreciation for the physiologic differences between humans and animal models, more advanced in vitro and ex vivo models are needed to dissect the human-specific mechanisms of skin aging and test emerging therapies. In this review, we summarize the major hallmarks of human skin aging and provide an overview of current in vitro modeling approaches that capture both intrinsic and environmental aging mechanisms. We highlight recent advances in complex 3D in vitro systems - including full-thickness human skin equivalents, organoids, and microphysiological platforms - and discuss how these emerging models can be leveraged to interrogate aging biology and support translational research. Together, these developments pave the way for more predictive and mechanistically informed tools to study skin aging and to accelerate the development of next-generation therapeutic and preventive strategies.