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EDITORIAL

Aging imaging: the future demand of health management

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Aging is a ubiquitous biological process that is accompanied by a progressive functional decline of various tissues and organs. This deterioration is the major risk for multiple chronic disorders such as neurodegenerative diseases, cardiovascular diseases, diabetes and cancers [1]. In recent years, aging has become an increasingly attractive field of research, in which accumulating studies have greatly enriched our understanding of the aging processes. In 2023, a comprehensive review titled "Hallmarks of aging: An expending universe" was published in *Cell* [2], which further proposed twelve distinct hallmarks of aging, including genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis. These hallmarks collectively represent a wide range of molecular, cellular, and systematic mechanisms that are interconnected to the aging processes, as well as to the health states. Characterization of these aging hallmarks holds significant potential in informing preventive and therapeutic interventions, which would greatly contribute for a better human health management during lifetime.

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Over the years, various approaches have been used to characterize aging hallmarks and aging processes, such as histopathology, medical imaging, artificial intelligence (AI), and "omics" technologies (e.g., genomics, proteomics, metabolomics, and transcriptomics). These approaches provide diverse avenues for understanding the aging processes across macro-, meso-, and, micro-scales. Among these, medical imaging (e.g., computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, optical imaging, and positron emission tomography (PET)), plays a critical role in monitoring the aging processes since it can provide structural, functional, and molecular information [3]. Indeed, imaging and visualization tools have been recognized as one of the major fields in characterizing senescence [4]. Of which, PET molecular imaging is an advanced imaging technique that facilitates noninvasive visualization, characterization, and quantification of biological processes (e.g., biochemical changes, gene expression, receptor function, and metabolic activity) at the cellular and molecular levels [5, 6]. Through the utilization of diverse radiolabeled probes, PET molecular imaging has found widespread application in the diagnosis, management, and treatment of aging and age-related diseases.

^{18}F-fluorodeoxyglucose ([^{18}F]-FDG) is the most widely used radiotracer in PET imaging, which has been used to study brain aging since it can reflect cerebral neural and synaptic activity by assessing glucose metabolism. Several recent longitudinal and cross-sectional studies have provided evidence that a declined uptake of [^{18}F]-FDG was observed in several brain regions during normal aging and neurodegenerative diseases, such as Alzheimer's disease (AD) [7, 8]. Apart from glucose metabolism, aging has been reported to be closely related to genomic and epigenetic instability. ^{18}F-FluorThanatrace ([^{18}F]-FTT) or [^{18}F]-PARPi PET imaging enables the visualization of PARP1 (a recognized biomarker of DNA damage) activity, thereby facilitating the evaluation of the genomic instability in cancer [9, 10]. Similarly, [^{11}C]-Martinostat PET imaging reveals a decrease in the expression of HDAC I (an epigenetic enzyme), in the brains of patients with AD [11]. The specific binding of [^{18}F]-florbetapir and [^{18}F]-AV1451 to Aβ plaques and tau aggregates, respectively, has been widely validated and applied in AD [12–14]. [^{18}F]-F0502B, a new PET tracer with high binding affinity for α-synuclein, but not for Aβ or tau fibrils has been recently reported, which had a great promising lead compound for imaging aggregated α-synuclein in Parkinson's disease or synucleinopathies [15]. Moreover, numerous radiolabeled molecular probes have been developed for tracking age-related pathophysiological changes, such as chronic inflammation, mitochondrial dysfunction, and atherosclerotic plaques, which exhibited great potential in aging and age-related diseases [16–18].

Although PET molecular imaging provides a powerful tool for studying the pathophysiologic changes in aging and age-related diseases, the combined use of different methods is necessarily required for obtaining full-scale information of the aging processes. Recent years have seen progress in novel research methods, contributing to the further investigation of aging and age-related diseases. Especially, the advances of "omics" technologies have now enabled high-throughput and fine-scaled exploration and validation of aging processes in various tissues of different species. Besides, there has been increasing attention on the systematicness of aging. A number of aging studies now have been focused on two-organ cross-talk (e.g., gut-brain axis) and multi-organ functional network regulation mechanisms [19, 20]. It is also noted that the large quantity of phenome-level data is the natural complement to genome-level data, help identifying the important traits altered with aging, as well as screening aging-related genes and molecules more efficiently [21, 22]. Of course, analyzing the next-generation biomedical data (e.g., biomarker identification and drug discovery) and establishing data-derived models (e.g., aging clocks) relies more on AI technologies [23]. Advances of these methods could contribute to the discovery of new aging hallmarks, and novel targets for imaging and treatment of aging processes.

The grim situation of increasingly aged population calls for a more comprehensive evaluation system of aging, which puts stronger demands on the progress of imaging techniques. The advances of aging imaging concept we proposed here would help solve several key problems in the field of aging: (1) characterization of aging processes; (2) identification of potential internal and external factors on aging; (3) evaluation of aging biology impact on the prevention, diagnosis, and treatment in age-related diseases; (4)

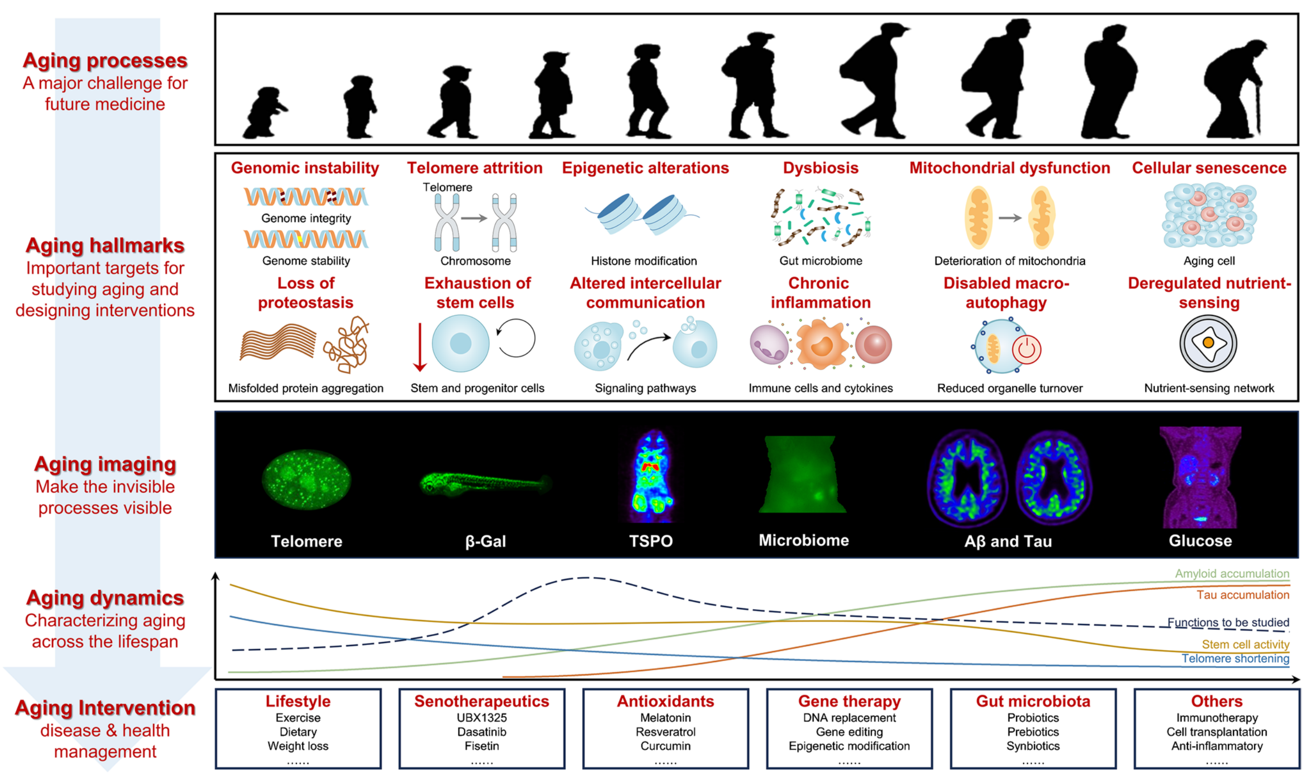

Fig. 1 Aging imaging facilitates future health management. Aging is a major worldwide challenge, and the aging hallmarks constitute important targets for studying aging and designing interventions. Aging imaging is an emerging field to make the invisible aging processes visible, enabling the characterization of aging biology across the life span in vivo. Aging imaging is powerful to connect the mechanism research and the exploration of aging intervention, thus facilitating and optimizing the disease and health management

development of effective intervention methods and assessment of the in vivo efficiency; and (5) assessment of aging status of sub-health and even health people to prevent and reduce burden of age-related diseases.

To address above challenges, we need to overstride the obstruction of disciplines and make more progress in the following three aspects: (1) novel molecular imaging probes. More molecular probes are needed to achieve aging imaging, which not only target hallmarks of age-related diseases but also portray the physiological processes in normal aging. For example, nanobodies and single-domain antibodies showed the incredible advantages of small molecular weight, excellent affinity, specificity, and stability compared with traditional IgG antibodies, so their potential in binding hidden antigen epitopes in molecular imaging field would be further explored in the future [24, 25]. (2) Novel aging imaging approaches. Optimization, development, and integration of aging imaging techniques will greatly contribute to systematically evaluate human beings from unhealthy, sub-healthy to healthy state. For example, total-body PET increased solid angle for detection at any point within the body allows whole-body PET studies to be acquired with unprecedented count density, improving the signal-to-noise ratio of the resulting images [26]; The combination of different molecular imaging multimodalities, such as PET/CT, PET/MRI, and PET/optical coherence tomography (OCT), can provide synergistic advantages over single modality and compensate for the disadvantages of each imaging system [27]. (3) Novel analytical approaches. Advances in algorithms and AI should facilitate the image reconstruction, subtle changes capture and information mining. AI-based image reconstruction or enhancement methods can reduce the required scanning time for patients while maintaining or enhancing the accuracy of quantification and enable attenuation correction. AI could also be used to select the most promising leads to design suitable theranostics for the target in diseases [28].

In summary, aging is a significant challenge for all humanity. Aging imaging is an essential field towards health and diseases management in clinical practice. The advancement of aging imaging will greatly facilitate the establishment of comprehensive aging evaluation system, enhance understanding of pathophysiologic changes in aging processes, and promote the early prevention and treatment of age-related sub-health and age-related diseases (Fig. 1). It is undeniable that there is still a long way to go to promote the development of aging imaging, yet, we firmly believe aging imaging will be the future demand of health management.

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Declarations

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