New technologies for the diagnosis of neurodegenerative disorders

Fasolino Ines[1]

[1] Institute of Polymers, Composites and Biomaterials – National Research Council (IPCB-CNR), Viale Kennedy 54, Mostra d'Oltremare pad. 20, 80125, Naples, Italy

Neurodegenerative disorders (NDDs) involve a heterogeneous group of diseases characterized by progressive loss of neuronal structure and function, leading to cognitive, motor, and behavioral impairments. NDDs comprise Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease (HD) [1]. Although each condition exhibits distinct clinical features, they share common pathogenic mechanisms such as protein misfolding and aggregation (p-TDP43, β-amyloid, tau, α-synuclein), oxidative stress, mitochondrial dysfunction, and neuroinflammation. Etiology is multifactorial, involving interactions between genetic factors and environmental influences (neurotoxin exposure, diet, microbiota), [1]. Current therapies are mainly symptomatic and fail to alter disease progression; therfore, there is an urgent need for new therapeutic and diagnostic approaches. Indeed, the rising incidence of NDDs, driven by population aging, underscores the need for multimodal strategies for early diagnosis, neuroprotection, and prevention, integrating biomarkers, advanced imaging, and personalized medicine [2]. Specifically, among these NDDs, ALS is the most incurable adult-onset neurodegenerative disease and no efficient diagnostic and therapeutic approaches exist. Studies demonstrated cutaneous nerve degeneration can mirror neurodegenerative mechanisms acting at the central nervous system [3]. Additionally, emerging evidence suggests that NOD-like receptor pyrin domain containing protein 3 (NLRP-3) inflammasome plays a key role in ALS pathogenesis [4] and has been recently linked to TAR DNA-binding protein 43 (TDP-43) aggregates associated with motoneuron degeneration in the central nervous system (CNS). Although skin biopsy is widely used in clinical practice, it involves removing patient tissue and applying local anesthesia. To overcome these limitations, a three-dimensional artificial skin model was developed using 3D printing technology. This model was then colonized with fibroblasts isolated from skin biopsies of ALS patients and characterized from chemical, physical, and morphological perspectives. The biological features of the 3D model were defined based on inflammasome biomarkers detected in skin biopsies and serum of ALS patients and controls [including NLRP-3, associated cytokine levels (transforming growth factor β1 - TGF-β1, interleukin 18 - IL-18, and interleukin 6 - IL-6), oxidative stress markers, and CD8+ or CD4+ lymphocyte infiltration assessed through western blot, ELISA, and fluorescence analyses]. Morphological analysis confirmed that the 3D artificial skin has porosity suitable for cell colonization. Biological findings revealed increased levels of p-TDP-43, NLRP-3, and NEK-7 and their related cytokines in skin biopsies and serum of ALS patients, suggesting activation of the inflammasome cascade linked to neurodegenerative marker accumulation. Finally, these results were validated by analyses performed on fibroblasts isolated from skin biopsies and cultured on the 3D artificial skin model, highlighting the critical role of microglial NLRP-3 inflammasome-mediated activation in ALS disease activity. This important achievement has the potential to accelerate ALS drug development and biomarker discovery in the near future.

Keywords: inflammasome, nerve degeneration, skin biopsy, 3D printed artificial skin.

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