Insight: Developing an exosome-based therapeutic strategy coupled with a multiphoton imaging platform to combat age-related neurodegeneration

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ABSTRACT

DNA damage causally contributes to aging, as exemplified by the premature appearance of multiple symptoms of age-related pathologies in a growing family of human syndromes and associated animal models harboring inborn defects in DNA repair [1]. Indeed, the gradual accumulation of irreparable DNA lesions in our genome interferes with vital cellular processes, such as DNA replication and transcription triggering the activation of proinflammatory responses and the premature onset of e.g. rheumatoid arthritis, diabetes, metabolic diseases and neurodegenerative disorders in man.

Recent collaborative work at the IESL and IMBB institutes at FORTH revealed that persistent DNA damage triggers the rapid build-up of single- (ss) and double-stranded (ds)DNA moieties in the cytoplasm of microglia cells in vivo. In turn, cytoplasmic ds/ssDNAs in brain macrophages are recognized by the innate immune system stimulating broad inflammatory and antiviral immune countermeasures [2-3]. The latter perpetuates a vicious cycle of DNA damage accumulation and chronic inflammation leading to progressive neurodegeneration in mice.

Here, we propose to develop a novel therapeutic strategy against age-related neurodegeneration. Specifically, we will exploit the use of a recently established advanced multiphoton imaging platform in order to monitor the use of synthetic anti-inflammatory exosomes on a unique series of DNA repair-deficient, progeroid animal models with documented age-related neurodegeneration. The engineered exosomes have been developed by the participants of this consortium with the ability to selectively target inflamed microglial cells in vivo and remove cytoplasmic ss. or ds. DNA moieties. This interdisciplinary approach is expected to lower neuroinflammation ameliorating the observed neurodegenerative pathological features seen in the preclinical animal models.

REFERENCES

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