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Conformationally altered p53: a potential biomarker for Alzheimer's Disease
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Alzheimer's disease (AD) cannot be diagnosed until dementia appears, thus the identification of biological markers of AD can improve diagnostic accuracy and therapy follow-up as well as provide information on the pathogenesis of the disease. We found that fibroblasts derived from AD patients expressed an altered conformational status of p53 and were less sensitive to p53-dependent apoptosis compared to non-AD fibroblasts¹⁻². Unfolded p53 found in AD fibroblasts has been demonstrated to be independent from gene mutations, thus suggesting that one of the peripheral events associated to the disease is responsible for generating structural changes in p53². When investigating the mechanism of such alteration, we found that the tertiary structure of p53 and the sensitivity to p53-dependent apoptosis is influenced by low concentrations of soluble beta amyloid (A β)³, not resulting in cytotoxic effects, thus suggesting to consider the unfolded p53 both as an agent participating to the early pathogenesis and as a specific marker of the early stage of AD. We then enrolled more than 150 subjects and tested the content of unfolded p53 in AD, non-AD and subjects affected by other dementias, using a cytofluorimetric approach⁴⁻⁸. We found that peripheral blood cells from AD specifically expressed increased levels of unfolded p53 compared to non-AD subjects. Moreover, we demonstrated that altered p53 is an age-dependent factor. To evaluate the diagnostic performance of unfolded p53 as an AD marker, we worked out sensitivity and specificity within different age intervals, finding a higher significance in subjects up to 70 years of age⁴⁻⁸. This observation is of great importance and could suggest the usefulness of this method especially for younger subjects, thus supporting its putative application for patients with mild cognitive impairment (MCI) and with early onset of AD.

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