EPIDERMAL MOLECULAR CHANGES IN ALZHEIMER'S DISEASE PATIENTS

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Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder that targets mainly, although not exclusively, the CNS. The common ontogenic origin of epidermis and brain cells suggests that the skin could be a model for studying systemic manifestations of the disease that may ultimately correlate with brain dysfunction.

Aims: To explore peripheral molecular changes and their usefulness as disease biomarkers in skin biopsies from AD patients.

Methods: By confocal immunomicroscopy, we studied in postmortem skin biopsies from AD patients and controls the molecular expression of

i) neural-phenotype markers (neuregulin, neurofilaments, tau, MAP2, NSE) and

ii) several key players in APP processing (APP, Aβ peptides, BACE1, TACE, ADAM10).

Results: In the epidermis of AD patients and controls, neural-phenotype markers are expressed mainly in basal keratinocytes, melanocytes, Langerhan's cells and nervous fibers. Interestingly, in basal keratinocytes these markers appear to decline with age and disease onset, suggesting that proliferating keratinocytes suffer partial dedifferentiation. Surprisingly, tau protein was observed in keratinocyte nucleus. Analysis of APP processing indicated that both amyloidogenic and non-amyloidogenic pathways are active in epidermal cells. Remarkably, AD patients show an altered balance of these routes in epidermis that correlates with lower Aβ immunoreactivity in melanocytes and Langerhan's cells. Moreover, the expression of Aβ40 and Aβ42, both in AD and controls, seem to have complementary distributions in keratinocytes, suggesting that changes in APP processing by the gamma-secretase complex are related to keratinocyte maturation.

Conclusions: Altogether, these preliminary results indicate that AD patients manifest molecular alterations that are clearly detectable in skin biopsies.