Dental pulp stem cells as new tool for studying neurodegenerative diseases

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The identification of adequate and reliable model systems is essential for every Research field, including the medical one. At this regard, study of central nervous system diseases is traditionally hampered by the intrinsic characteristics of neuronal cells and by the consequent difficulty in finding an appropriate cell model. Primary cell cultures were widely used to study cellular and molecular aspects, but their utilize is now restricted because of their inherent heterogeneity, the incapability of cells to divide and the contamination with non-neuronal elements. Some limitations can be considerably overcome by clonal cell lines. For example, neuroblastoma cell lines (NB) are frequently employed as an *in vitro* neuronal model. NB are transformed, neural crest derived cells, characterized by the ability to proliferate indefinitely *in vitro* and differentiate into neuronal cell types under specific treatment. However, such transformed cells often display morphological, developmental, and signaling characteristics that are significantly different from the parental cell type. Consequently, the response of NB cells to drugs/molecules exposure may differ from that of neurons. Based on this assumption, the identification of a cell model as closely as possible to a neuron is compelling. On this regard, we purpose dental pulp stem cells (DPSCs) as an innovative *in vitro* neural model. In fact, among all the exploitable stem/progenitor cells, they appear one of the best choice thanks to peculiar properties, such as easy accessibility, clonogenicity, self-renewal and potency. Indeed, due to their neural crest origin, DPSCs show high plasticity and are particularly able to differentiate towards neural lineage *in vitro* (as we demonstrated by the expression of some typical markers, e.g. GFAP, PSA-NCAM, nestin, NeuN, TUBB3, NSE). Here, we employed this innovative approach to clarify some molecular mechanisms underlying Alzheimer's disease (AD). AD is a neurodegenerative pathology characterized by extracellular deposits of amyloid-β (Aβ) and intracellular inclusions of hyperphosphorylated tau (neurofibrillary tangles). Moreover, several publications have suggested a link between lipid peroxidation and AD. Indeed, the brain is particularly vulnerable to oxidative stress, which is responsible for the formation of cholesterol oxidation products (oxysterols), and highly reactive aldehydes, among which the most relevant to brain pathophysiology seems to be 4-hydroxynonenal (HNE). HNE production in the brain is stimulated by Aβ and, conversely, Aβ production is up-regulated by this aldehyde. In addition, in the brain, cholesterol is primarily converted into 24-hydroxycholesterol (24-OH) which has been shown to enhance Aβ neurotoxicity in human differentiated NB cell lines, as well as increasing ROS production. In our work, we observed the ability of HNE and 24-OH to potentiate Aβ cytotoxicity as determined *in vitro* using neuron-like cells derived from DPSCs. Cell pre-incubation with the aldehyde or the oxysterol strongly enhanced Aβ uptake and intracellular accumulation, by up-regulating a cluster of membrane receptors, composed by CD36, β1-integrin and CD47. Consequently, the two lipid peroxidation products markedly potentiate Aβ neurotoxicity, in terms of necrosis. These data confirm the hypothesis already seen in other cell models that there is a primary involvement of altered brain lipid metabolism in AD demonstrating the fine value of DPSCs as neural model. In conclusion, stem cell technology has been considered not only as a therapeutic instrument but also as a valid and useful research tool since it may offer some advantages over transformed cell lines.