Extracellular Vesicles in the pathogenesis of Alzheimer's disease and related disorders

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Cells release into the extracellular environment diverse types of membrane vesicles of endosomal and membrane origin called exosomes and microvesicles/ectosomes, respectively. The interest towards these extracellular vesicles (EVs) has grown exponentially over the last few years following the discovery that they are involved in intercellular communication by serving as transfer vehicles of proteins, lipids, DNA and RNA between cells. There is increasing evidence that EVs play important roles in numerous aspects of biology: deregulation of EVs secretion may alter signaling activities, leading to severe pathogenesis, in diseases including cancer and neurological disorder. Aggregating proteins associated with neurodegenerative disorders can be released within EVs. In particular, the finding that proteins and peptides associated with Alzheimer's disease (AD) - such as Amyloid Precursor Protein (APP) and its fragments/metabolites, Abeta peptide, tau, presenilins - are released in association with exosomes has shed light on previously unidentified pathways in the processing of APP and provided potential explanation for extracellular amyloid deposition in the brain. Recent evidence indicates that EVs carry on their surface, specific molecules which bind to extracellular Aβ, opening the possibility that EVs may also influence Aβ assembly and synaptotoxicity. On the other side, we hypothesized that during aging, characterized by progressive loss of neurons, EVs could become the key player of neuronal communication: in this view, the fate of neurons could be easily influenced by factors modulating EVs release/composition (Ghidoni et al., 2009). Herein recent investigations on the role of EVs in the pathogenesis of Alzheimer's disease and Frontotemporal lobar degeneration (FTLD) will be presented and discussed. We demonstrated that mutations causing AD alter exosomal levels of cystatin C, a protease inhibitor with neurotrophic function (Ghidoni et al., 2011). Thus, we focused our studies on progranulin, a neurotrophic factor that has gained the attention of the neuroscience community because null mutations in its gene (*GRN*) cause frontotemporal lobar degeneration (FTLD), a common cause of early onset dementia. In human primary fibroblasts we demonstrated that exosomes transport glycosylated progranulin and that exosomal progranulin as well as the total amount of exosomes are strongly reduced in the presence of GRN mutations. Taken together these data support the hypothesis that mutations causing neurodegeneration reduce EVs transport of proteins with neurotrophic function. On the opposite, experimental evidences supporting a toxic role of EVs in neurodegeneration will be also presented and discussed (Joshi P. et al., 2014; Joshi P. et al., 2015). A better understanding of the role of EVs in neurodegeneration is of great therapeutic interest and may have important implications for the fight against AD and other neurodegenerative diseases.

Ghidoni et al. (2008)/ Med Hypotheses/70:1226-7
Ghidoni et al. (2011)/ Neurobiol Aging/32: 1435-42
Joshi et al. (2014)/Cell Death Differ/21: 582-93
Joshi et al. (2015)/Int J Mol Sci/16: 4800-13