Neuronal exosome-derived human tautoxicity on recipient cells V.Tsetlin

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Abstract

Alzheimer's disease (AD) is characterized by deposition of beta-amyloid as amyloid plaques and tau as neurofibrillary tangles. While the distribution of beta-amyloid is diffuse and does not correlate well with disease symptomatology, tau deposition follows progression in a synaptically connected pathway. Such progression is the basis of the Braack staging for the pathological diagnosis of AD, and correlate with the severity of patient symptoms. The disease progression suggests spreading of pathology from one area to another in the brain. Recently published work suggest that propagation of toxic protein tau can be mediated by exosomes. Exosomes belong to extracellular vesicles (EVs), which are released by the cells through the late endosomal pathway. We hypothesized that exosomes contain cargos which could mediate propagation of toxic proteins. We isolated exosomes derived from neuronally-differentiated, human induced pluripotent stem cells that expressed the repeat domain of tau P301L and V337M mutations (NiPSCEs) and injected them into the wild-type mouse brain. We observed pathological changes including hyperphosphorylated tau, cell loss and blebbing of the dendrites in the recipient mouse neurons in vivo. The pathological tau also spread to other cortical and subcortical regions in both hemispheres. These results suggest that exosomes may regulate propagation of neurodegeneration, which may have implications for diagnostic and therapeutic potential. Progressive accumulation of aggregation-prone proteins, amyloid-β (Aβ) and hyperphosphorylated tau (p-tau), are the defining hallmarks of Alzheimer's disease (AD). The mechanisms by which Aβ and p-tau are transmitted throughout the diseased brain are not yet completely understood. Interest in exosome research has grown dramatically over the past few years, specifically due to their potential role as biomarkers for staging of neurodegenerative diseases, including AD. Despite their diagnostic utility, the pathogenic potential of exosomes has yet to be fully elucidated. In this study, we use a series of recombinant tau antibodies to characterize a new model of human tau in vivo. Exosome suspensions derived from neuronally-differentiated, human induced pluripotent stem cells that express the repeat domain of tau P301L and V337M mutations (NiPSCEs) were injected into the wild-type mouse brain and pathological changes were characterized by immunostaining at one- (1 m) and two-month (2 m) post-injection. We found that tau inclusions were present throughout the brain at 2 m post-injection, which were detectable using antibodies raised against full-length tau (K9JA) and misfolded tau (MC1). Furthermore, we found that phosphorylated tau immunoreactivity was elevated 1 m post-injection, which was surprisingly normalized after 2 m. Finally, we observed extensive degeneration of neuronal dendrites in both ipsilateral and contralateral hippocampi in NiPSCE treated mice. In summary, we demonstrate that exosomes are sufficient to cause long-distance propagation of tau pathology and neurodegeneration in vivo. These novel findings support an active role of exosomes in AD pathogenesis. Irresistible confusions Alzheimer's infection (AD) is portrayed by testimony of beta-amyloid as amyloid plaques and tau as neurofibrillary tangles. While the dispersion of beta-amyloid is diffuse and doesn't relate well with sickness symptomatology, tau testimony follows movement in a synaptically associated pathway. Such movement is the premise of the Braack organizing for the obsessive determination of AD, and relate with the seriousness of patient manifestations. The infection movement recommends spreading of pathology starting with one zone then onto the next in the cerebrum. As of late distributed work propose that engendering of poisonous protein tau can be interceded by exosomes. Exosomes have a place with extracellular vesicles (EVs), which are delivered by the cells through the late endosomal pathway. We guessed that exosomes contain loads which could intercede spread of poisonous proteins. We disconnected exosomes got from neuronally-separated, human instigated pluripotent undifferentiated cells that communicated the recurrent space of tau P301L and V337M transformations (NiPSCEs) and infused them into the wild-type mouse mind. We noticed neurotic changes including hyperphosphorylated tau, cell misfortune and blebbing of the dendrites in the beneficiary mouse neurons in vivo. The neurotic tau additionally spread to other cortical and subcortical locales in the two halves of the globe. These outcomes propose that exosomes may direct engendering of neurodegeneration, which may have suggestions for indicative and restorative potential. Despite the fact that the specific capacity of exosomes in the mind isn't completely perceived, plainly these little EVs can intercede cell correspondence at the focal sensory system level and assume significant parts in keeping up typical cerebrum physiology. Neurons—oligodendrocytes correspondence is such a case of the exosomes—interceded connection, significant for myelination and axons endurance (Frühbeis, Fröhlich, Kuo, Amphornrat, et al., 2013; Frühbeis, Fröhlich, Kuo, and Krämer-Albers, 2013; Krämer-Albers et al., 2007). The arrival of glutamate can animate exosome emission from oligodendrocytes, and these nanovesicles would then be able to be endocytosed by neurons. Besides, expansion of oligodendrocytes-inferred exosomes to refined neurons could expand their practicality, under pressure conditions, applying a neuroprotective job (Frühbeis, Fröhlich, Kuo, Amphornrat, et al., 2013). It was likewise discovered that glutamatergic movement Neuronal exosome-derived human tau toxicity on recipient cells Shauna H. Yuan University of California, USA can manage exosome discharge from somato-dendritic compartments. Exosomes delivery could be a potential component for receptor disposal since these nanovesicles could convey AMPA receptors, controlling their number and possibly tweaking synaptic transmission and versatility (Lachenal et al., 2011). It was later detailed that exosomes emitted from cortical neurons upon synaptic glutamatergic incitement were specifically bound and endocytosed by different neurons (Chivet et al., 2014). Upon neurons depolarization a subset of miRNA and proteins were found advanced in exosomes, among them is the microtubule-related protein 1b (MAP1b), a synaptic pliancy related protein, which fortifies the part of exosomes in the synaptic versatility (Goldie et al., 2014). Exosomes show up similarly to assume a significant function in synaptic associations end, a cycle known as synaptic pruning and interceded by glial cells, which immerse the neurites that declined. It was seen that microglia disguise of exosomes, discharged after PC12 cells depolarization, lead to up-controlled articulation of the favorable to phagocytic microglial segment 3 and animated microglia phagocytic movement (Bahrini, Song, Diez, and Hanayama, 2015). Different jobs additionally ascribed to exosomes were guideline of neurogenesis and alleviation of irritation after awful injury (Zhang et al., 2015) and association in neuronal energy digestion through the exchange of compounds that take an interest in glycolysis and unsaturated fats union (Drago et al., 2017). Taken together, the information reinforce the significance of these nanovesicles in the cerebrum and that dysregulation of EVs biogenesis and discharge can affect neurodegeneration, adding to a few neuropathologies, including Alzheimer's illness (AD). 1.3 | Alzheimer's illness trademarks and atomic determination AD is the most widely recognized type of dementia worldwide and it is assessed that the quantity of people influenced by this neurodegenerative sickness will increment dramatically in the following many years. Promotion is described by cognitive decline, reformist psychological decrease and ruining of the day by day exercises until the people totally lose their independence (DeTure and Dickson, 2019). The two significant sickness histopathological trademarks depicted are the presence of feeble plaques (SPs) and of neurofibrillary tangles (NFTs) in AD minds.

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