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EDITORIAL

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Alzheimer's disease in aging Down syndrome

Down syndrome (DS) is one of the most common causes of intellectual disability, accounting for approximately 15% of all individuals with intellectual disabilities. The incidence of DS is 1:800 live births, with an estimated 7,000 babies born with DS annually in the US (Hook, Cross, & Schreinemachers, 1983). DS has one of the best understood initiating events in Alzheimer's disease (AD)—the overproduction of amyloid-beta (Aβ) protein. In virtually all cases of DS, the condition is associated with three copies of chromosome 21, each containing of copy of the Aβ precursor protein gene ultimately leading to a 1.5-fold increase in Aβ protein (Prasher et al., 1998; Rovelet-Lecrux et al., 2007; Zigman et al., 2008). AD pathology, characterized by the presence of neurofibrillary tangles and neuritic plaques, is seen uniformly in individuals with DS by their fourth decade (Hyman, 1992; Lemere et al., 1996; Wisniewski, Wisniewski, & Wen, 1985). However, most do not show clinical signs of dementia until their sixth decade (Coppus et al., 2006). The life expectancy of individuals with DS has increased over the last several decades (Yang, Rasmussen, & Friedman, 2002); with improved health care for the systemic sequelae of DS, many individuals are surviving into this period of very high AD risk. Beyond the clear fact that the DS population merits special attention for and inclusion in therapeutic trials targeted at AD, the study of AD in DS presents special opportunities. From a scientific perspective, DS can be seen as a setting that presents amplified sensitivity to both risk and protective factors that moderate the relationship between Aβ pathology, neurodegeneration, and clinical dementia. Understanding the factors that moderate the relationship between AD neuropathology, neurodegeneration, and dementia in DS and biomarkers for those factors will be critically important in the design of effective therapeutic trials for AD, not only in DS, but in the general population as well.

In this special issue of *Developmental Neurobiology*, we have brought together the leaders in the fields of AD and DS to discuss the central issues currently facing the field. How can blood and exosomes and neuroimaging biomarkers be used effectively to detect AD pathology in DS? How does mitochondrial dysfunction contribute to neurodegeneration in DS? How do lifestyle factors modify neurodegeneration in DS? Addressing these questions requires a multidisciplinary approach requiring in vitro study, animal models, and clinical neuroimaging. In this special issue, we present reviews and original research across this spectrum.

Hamlett et al. (2019) review current knowledge on exosome biology in individuals with DS and discuss their complex multicellular processes. Exosomes are one type of extracellular vesicles, that have significant potential for the development of new biomarkers, particularly for AD in DS. Exosomes also appear to be critical in the transsynaptic spread of AD pathology. In an original research contribution, D'Acunzo et al. (2019) demonstrate that late endosomes/multivesicular bodies from a DS animal model are larger, more abundant, and contain a higher number of intraluminal vesicles per neuron compared to control mice. These data suggest that the increases in intraluminal vesicles may be a key homeostatic mechanism to alleviate endosomal dysregulation, a known early event in both DS and AD. In another original research study, Kelley et al. (2019) demonstrated that perinatal maternal choline supplementation in a mouse model of DS isassociated with changes in select gene transcripts in the basal forebrain cholinergic neuron projection system, a brain region affected early in AD, providing insight into the effects of maternal choline supplementation at the molecular level in basal forebrain cholinergic neurons.

Additional reviews explore neuroimaging of AD pathology in DS, including tau imaging (Rafii, 2019), imaging of cerebrovascular pathology (Carmona-Iragui et al., 2019), and postmortem correlations of AD pathology to amyloid PET imaging (Abrahamson et al., 2019). Biomarkers are also a central theme of the reviews by Petersen and O'Bryant (2019) who explored the current state on the literature of blood-based biomarkers found in individuals with DS, particularly those with AD or prodromal AD and by Alhajraf, Ness, Hye, & Strydom (2019) who conducted meta-analyses of studies comparing plasma amyloid beta (Aβ) levels between DS individuals and controls, and between DS individuals with and without dementia. Gross et al. (2019) show that using blood-based metabolomics can provide insights into altered cellular metabolism in DS, which may also serve as a biomarker for transition to dementia in future studies.

Finally, an original research study by Mihaila et al. (2019) demonstrated that participation in cognitively stimulating activities is associated with better episodic memory and with less decline in episodic memory from baseline to follow-up. High levels of social and overall leisure activity also moderated the association between increases in brain β-amyloid and decline in episodic memory. These data suggest that participation in cognitively stimulating and social activities

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could potentially protect against the deleterious effects of AD pathology on cognition in DS.

It is clear from the reviews and original research presented in this special issue that the field of AD and DS has progressed substantially. These articles represent a subset of the substantial research efforts to better understand the progression to AD in aging DS. These efforts to detect the pathology of AD in DS early and to identify strategies to treat and potentially prevent AD in this population will be critical as life expectancy in DS increases into the age of significant AD risk.

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