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Multiscale genomic approach and big data analysis support a shared etiology between type 2 diabetes and Alzheimer's disease

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The convergence of several unique features of Alzheimer's disease (AD) [e.g., heterogeneity, complex polygenic etiology, and prolonged asymptomatic phase] indicates the need for large cohorts of well-characterized populations from diverse backgrounds volunteers for: 1) Longitudinal epidemiological studies to discover/validate putative risk factors, and 2) clinical studies for prospective validation of potential preventive interventions. In addition, many epidemiological studies indicate that people with diabetes are at higher risk of eventually developing AD. A longitudinal database involving at-risk populations is essential to address the future needs of a prevention initiative. Along with 'Big-Data', the field of therapy development will require novel computational capabilities to not only sort out the complex interactions between type 2 diabetes (T2D) and cognitive deterioration in AD, but also to discover-validate technologies for early and accurate detection. We used data from public genome-wide association studies (GWAS) to explore the association single-nucleotide polymorphisms (SNPs) between T2D and AD. We then integrated pathway data with gene ontology data, expressional quantitative trait loci (eQTL), and co-expression networks to explore the function of the shared SNPs. We found a significant overlap (p=4.9E-19) between SNPs of T2D and AD. 927 SNPs were associated with both AD and T2D, and we found that they influence 190 genes in brain tissue and 416 in T2D-relevant peripheral tissues. Interestingly, we found that certain mitochondria and innate immune response pathways are particularly enriched. Collectively, we found that T2D and AD share common genetic risk factors, which may partially explain the epidemiological observation of the disease incidence correlation.

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Modulation of calcium-induced cell death in human neural stem cells by the novel peptidylarginine deiminase– AIF pathway

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PADs (peptidylarginine deiminases) are calcium-dependent enzymes that change protein-bound arginine to citrulline (citrullination/ deimination) affecting protein conformation and function. PAD up-regulation following chick spinal cord injury has been linked to extensive tissue damage and loss of regenerative capability. Having found that human neural stem cells (hNSCs) expressed PAD2 and PAD3, we studied PAD function in these cells and investigated PAD3 as a potential target for neuroprotection by mimicking calcium-induced secondary injury responses. We show that PAD3, rather than PAD2 is a modulator of cell growth/ death and that PAD activity is not associated with caspase-3-dependent cell death, but is required for AIF (apoptosis inducing factor)-mediated apoptosis. PAD inhibition prevents association of PAD3 with AIF and AIF cleavage required for its translocation to the nucleus. Finally, PAD inhibition also hinders calcium-induced cytoskeleton disassembly and association of PAD3 with vimentin that we show to be associated also with AIF; together this suggests that PAD-dependent cytoskeleton disassembly may play a role in AIF translocation to the nucleus. This is the first study highlighting a role of PAD activity in balancing hNSC survival/death, identifying PAD3 as an important upstream regulator of calcium-induced apoptosis, which could be targeted to reduce neural loss, and shedding light on the mechanisms involved.

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