Cross-Disease Analysis of Alzheimer's Disease and Type-2 Diabetes Highlights the Role of Autophagy in the Pathophysiology of Two Highly Comorbid Diseases

1)Carboni L. 2)Lauria M. 3)Nguyen TP. 4)Rimondini R. 5)Maioli S. 6)Cedazo-minguez A. 7)Sita G. 8)Morroni F. 9)Corsi M. 10)Caberlotto L.

FaBit, Alma Mater Studiorum University of Bologna

The main chronic diseases of aging Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) represent major challenges for public health, since there are currently 11 million with dementia and 60 million people with diabetes in the EU and these numbers are expected to increase. AD and T2DM have been historically separated, although evidence is accumulating that they share several common mechanisms, such as insulin resistance, and that T2DM is a major risk factor for the development of AD (Biessels et al., 2006). The concept that AD is fundamentally a metabolic disease resulting in progressive impairment in brain capacity to utilize glucose and respond to insulin stimulation has recently gained support (Moreira, 2012).

This study aimed at increasing the knowledge of the common mechanisms for disease-specific pathophysiology and co-morbidities in AD and T2DM by applying systems biology approaches to discover novel targets for therapeutic intervention. To meet this objective, we analysed transcriptomic data of post-mortem AD and T2DM human brains to obtain disease signatures of AD and T2DM and availed of protein-protein interaction information to construct two disease-specific networks. The overlapping AD/T2DM network proteins were then used to extract the most representative Gene Ontology biological process terms. The expression of genes belonging to relevant pathways was compared by quantitative PCR in two animal models of disease, the 3xTg mice (Oddo et al., 2003) and the ApoE3/ApoE4 targeted replacement mice challenged with a carbohydrate enriched diet (Maioli et al., 2012).

The systems biology analysis revealed a principal role for autophagy in the molecular basis of both AD and T2DM. Autophagy, a cellular catabolic process that degrades the unnecessary or dysfunctional cell components, is activated by nutrient deprivation as a protective mechanism. In addition, AMP-activated kinase, a core signalling pathway in cellular homeostasis and crucial regulator of energy metabolism, was identified as a central dys-regulated process in AD and T2DM, in line with previous studies (Caberlotto et al., 2013). Quantitative PCR analysis confirmed the role of autophagy-related genes in both AD animal models in baseline conditions and after the diet challenge. Among the modulated genes, Cyclin-Dependent Kinase Inhibitor 1B (Cdkn1b), Autophagy Related 16-Like 2 (Atg16l2) and insulin were highlighted.

The present systems biology investigation revealed the autophagy pathway as the central dys-regulated pathway in two highly comorbid diseases of aging such as AD and T2DM. In addition, this study allowed the identification of specific genes potentially involved in the pathophysiology of the diseases which could be considered as novel targets for therapeutic intervention.

Biessels et al. Lancet Neurol 5: 64–74.

Caberlotto et al. (2013) PLoS One 8:e78919.

Maioli et al. (2012) J Alzheimers Dis 32:341-55.

Moreira (2012) J Alzheimers Dis 30 Suppl 2: S199–215.

Oddo et al., (2003) Neuron 39: 409–421.