The Triangle of Death in Alzheimer's Disease Brain: The Aberrant Cross-Talk among Energy Metabolism, Mammalian Target of Rapamycin Signaling, and Protein Homeostasis Revealed by Redox Proteomics

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Significance: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder and represents one of the most disabling conditions. AD shares many features in common with systemic insulin resistance diseases, suggesting that it can be considered as a metabolic disease, characterized by reduced insulin-stimulated growth and survival signaling, increased oxidative stress (OS), proinflammatory cytokine activation, mitochondrial dysfunction, impaired energy metabolism, and altered protein homeostasis. Recent Advances: Reduced glucose utilization and energy metabolism in AD have been associated with the buildup of amyloid-? peptide and hyperphosphorylated tau, increased OS, and the accumulation of unfolded/misfolded proteins. Mammalian target of rapamycin (mTOR), which is aberrantly activated in AD since early stages, plays a key role during AD neurodegeneration by, on one side, inhibiting insulin signaling as a negative feedback mechanism and, on the other side, regulating protein homeostasis (synthesis/clearance). Critical Issues: It is likely that the concomitant and mutual alterations of energy metabolism-mTOR signaling-protein homeostasis might represent a self-sustaining triangle of harmful events that trigger the degeneration and death of neurons and the development and progression of AD. Intriguingly, the altered cross-talk between the components of such a triangle of death, beyond altering the redox homeostasis of the neuron, is further exacerbated by increased levels of OS that target and impair key components of the pathways involved. Redox proteomic studies in human samples and animal models of AD-like dementia led to identification of oxidatively modified components of the pathways composing the triangle of death, therefore revealing the crucial role of OS in fueling this aberrant

vicious cycle. Future Directions: The identification of compounds able to restore the function of the pathways targeted by oxidative damage might represent a valuable therapeutic approach to slow or delay AD.

Alzheimer disease

energy metabolism

mTOR

protein degradation

amyloid beta protein

insulin

mammalian target of rapamycin

proteasome

ubiquitin

insulin

proteasome

target of rapamycin kinase

ubiquitin

Alzheimer disease

autophagy

degenerative disease

energy metabolism

glucose utilization

human

negative feedback

nonhuman

priority journal

protein homeostasis

protein phosphorylation

protein synthesis

proteomics

Review

signal transduction

unfolded protein response

Alzheimer disease

animal

brain

case control study

homeostasis

metabolism

nerve cell

oxidation reduction reaction

oxidative stress

pathology

procedures

proteomics

Alzheimer Disease

Animals

Autophagy

Brain

Case-Control Studies

Energy Metabolism

Homeostasis

Humans

Insulin

Neurons

Oxidation-Reduction

Oxidative Stress

Proteasome Endopeptidase Complex

Proteomics

Signal Transduction

TOR Serine-Threonine Kinases

Ubiquitin

Unfolded Protein Response