PhD in Chemical Sciences
Department of Chemistry "Ugo Schiff"
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PhD Seminar

"Brain vascular dysfunction in Alzheimer's disease: molecular targets and novel therapeutic strategies."

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Abstract

Cerebral endothelial cell (cEC) and neurovascular stress induced by vascular amyloid β (Aβ) and tau deposits are early contributors to cerebrovascular damage, blood-brain barrier (BBB) dysfunction and clearance impairment, precipitating neurodegeneration and neuroinflammation processes in cerebral amyloid angiopathy (CAA), Alzheimer's disease (AD) and dementias. However, the cellular and molecular mechanisms through which Aβ and tau drive cEC and BBB dysfunction remain to be fully clarified, and possible therapeutic strategies are sorely needed. Our lab aims to understand the effects of aggregated Aβ and tau on the cerebral vessels and is testing novel potential therapeutic strategies against cerebrovascular dysfunction and neurovascular stress in the AD and CAA brain.

We revealed mitochondrial and metabolic insights into the detrimental effects of both amyloid and tau on cECs, which are directly and causally linked to EC inflammatory activation, BBB dysfunction, and associated to activation of the pro-apoptotic cascade. We discovered that these toxic mitochondrial and apoptotic mechanisms are rescued by CA inhibition. Using human cECs and AD animal models, we tested the potential protective effects of carbonic anhydrase inhibitors or of the genetic deletion of a mitochondrial CA enzyme on cerebrovascular dysfunction. CAIs are also proving effective against the cardiac consequences of AD pathology *in vitro* and *in vivo*.

These findings improve the understanding of the vascular contributions to AD and dementia, while unveiling novel molecular targets with high therapeutic potential.