β-Amyloid and cell cycle activation in Alzheimer's disease: perspectives for drug development

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Expression of cell cycle proteins and replicative DNA synthesis have been observed in neuronal populations fated to degenerate in the Alzheimer's disease (AD) brain (Herrup et al., 2004). Consequently, cell cycle activation in AD neurons might lead to cognitive deficits that precede neuronal death (Arendt et al. 2010). In cultured neurons, synthetic □-Amyloid (Aß) reproduces the neuronal cell cycle re-entry observed in transgenic AD animals and in the human AD brain (Copani et al., 2006). Inhibition of cell cycle activation represents a new pharmacological strategy to prevent A□-induced neurodegeneration. Cytostatic drugs that act as cyclin-dependent kinase inhibitors, including flavopiridol, are protective in cultured cortical neurons challenged with synthetic A□ and rescue memory deficits induced by the intracerebroventricular injection of Aß1-42 oligomers in CD1 mice (Leggio et al., 2016). An alternative strategy could be the use of drugs able to increase the release of Transforming growth factor β1 (TGF-β1), an anti-inflammatory cytokine that prevents Aβ-induced S phase, via Smad-dependent and Smad-independent signalling pathways (Caraci et al., 2008). Recently we identified the antidepressant, fluoxetine, as a new neuroprotective drug against Aß toxicity, which increases the release of active TGF-β1 from cortical astrocytes (Caraci et al., 2016).

DNA polymerase-□ (DNA pol-□) plays a causal role in the DNA replication process that contributes to generate a death signal in neurons (Copani et al. 2006). In fact, DNA pol-□ inhibitors, such as 5-methoxyflavone, prevent DNA replication and ensuing apoptosis in Aß-treated neurons (Merlo et al. 2015). Analysis of the molecular mechanisms linking DNA replication to neuronal apoptosis might lead to the identification of new pharmacological targets. We are currently examining in pure rat neuronal cultures challenged with synthetic Aß (1-42) oligomers (100nM), the role of claspin, a protein required for the activation of the conserved checkpoint pathway started by DNA replication stress (Lee et al. 2003). Claspin inactivation is known to switch the cellular response from cell cycle arrest to apoptosis in cancer cells. We hypothesized that claspin inactivation can promote the transition from cell cycle arrest to apoptosis in Aß-treated neurons. By performing co-immunoprecipitation experiments on cross-linked nucleoprotein fragments in Aß-treated neurons, we obtained preliminary evidence that claspin co-immunoprecipitates with cell division cycle 45 (Cdc45) at early times (4h) following Aß treatments, and disappears at longer times (16h) when neuronal death occurs (as assessed by cytofluorimetric analysis). Along this line, we found that selective inhibitors of caspase-7, an enzyme known to promote claspin inactivation, hold neurons in S phase and reduce apoptosis. These data suggest that claspin and the downstream checkpoint signaling kinase, Chk1, might constitute the molecular link between DNA replication and apoptosis in Aß-treated neurons, therefore representing a new relevant pharmacological target to prevent apoptosis in AD.

Arendt et al. (2010). Biochim. Biophys. Acta 1772, 413-21.

Caraci et al. (2016). Front Pharmacol 7,389.

Caraci et al. (2008). Neurobiol Dis 30, 234-42.

Copani et al. (2006). J Neurosci 26,10949-57.

Herrup et al. (2004). J Neurosci 24,9232–9239.

Lee et al. (2003). J Mol Cell. 11,329-40.

Leggio et al.(2016). Pharmacol Res 106,10-20.

Merlo et al., (2015). J Nat Prod 78, 2704-11.