"Neurotropic Viruses and Neurodegenerative diseases" by De Chiara G (ORCID: https://orcid.org/0000-0002-2219-6097)

A growing body of epidemiologic and experimental data point to chronic bacterial and viral infections of central nervous system (CNS) as possible risk factors for neurodegenerative diseases, including Alzheimer’s disease (AD), the most common form of dementia in the elderly characterized by a progressive and irreversible decline in cognitive function and memory loss (De Chiara et al, 2012). Despite AD features are well known – including accumulation in the brain of amyloid-β peptides (Aβs) in both oligomeric forms and plaque deposits, hyperphosphorylated forms of tau protein (pTau) resulting in neurofibrillary tangles, high levels of oxidative stress markers and neuroinflammation-), its etiology is still elusive and cures are still missing. Among microbes, increased evidence, including ours, point out herpes simplex virus-1 (HSV-1) as a potential risk factor for AD (Marcocci et al, 2020). HSV-1 is a neurotropic DNA virus that, after primary infection of epithelial cells, is able to establish a life-long latent infection in the human peripheral nervous system and periodically reactivates, giving rise to recurrent clinical or subclinical manifestations throughout life. Following reactivation, HSV-1 may also reach CNS resulting in either a severe, but rare, form of herpetic encephalitis or eventually establishing latency. In collaboration with prof. Palamara’s group at Sapienza University of Rome and prof Grassi’s group at Università Cattolica del Sacro Cuore, Rome, we provided evidence that HSV-1 infection affects excitability and functional properties of cultured neurons (Piacentini et al, 2011 and 2015), induces the amyloidoigenic processing of amyloid precursor protein (APP) and intra- and extra-neuronal accumulation of Aβs and other neurotoxic APP fragments (De Chiara et al, 2010). We also demonstrated that HSV-1 activates intracellular processes leading to neurodegeneration through different mechanisms, most of them driven by APP fragments (Civitelli et al, 2015, De Chiara et al 2016, LI Puma et al 2019 and 2021). However, a causal relationship between HSV-1 and AD has yet to be definitely proved. Hence, we recently set up a mouse model of recurrent HSV-1 infection and provided novel evidence that multiple HSV-1 reactivations trigger in mouse brain accumulation of Aβs, pTau, neuroinflammation and oxidative damages, that are paralleled by increasing cognitive decline (De Chiara et al 2019, Protto et al 2020). Collectively our findings support the view that multiple HSV-1 reactivations, causing mild but repeated viral spreading and replication in CNS, may be a risk factor for AD. In this context, our research lines are currently aimed at:

- further dissecting the molecular mechanisms of neurodegenerative and inflammatory processes driven by HSV-1 infection and reactivations
- identifying novel strategies to limit virus reactivation/spreading to the brain, and evaluate their potential to prevent neurodegenerative damage. These studies are currently extended to respiratory viruses able to reach the CNS (including influenza viruses and coronaviruses)

**Tools:**
- in vitro model of infections: primary culture of cortical and hippocampal neurons; co-cultures of neurons and glial cells; neuronal, epithelial and lymphoid cell lines;
- murine model of recurrent infection resembling an AD-like phenotype

**Team Expertise:** virology (including screening and characterization of antiviral compounds), cellular and molecular biology, biochemistry, neuroscience.

**Collaboration and Networks:** Long-lasting collaboration with Prof Palamara’s team at Sapienza University of Rome (Dept. of Public Health and Infectious Diseases); Prof Grassi’s team at Catholica University of Rome (Dept. of Neuroscience). IFT collaborations: Dr Mollinari (co-author in De Chiara et al 2016), Dr. Marlier (joining in PRIN#20179JHMZ_006)

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