Lipids and lipid transporters

Chapter 9

Reflection on scientific impact

According to the WHO around 55 million people in the world are suffering from dementia. It is estimated that 1 in 5 people will experience it in their lifetime. Alzheimer's disease (AD), the most common form of dementia, is a life-threatening disease of the aged population for which there is no cure. AD is a devastating, progressive neurodegenerative disorder that has an enormous personal and financial impact on individuals, families and society. Currently, over 40 million people suffer from AD worldwide, and the number is expected to increase to more than 100 million by 2050, threatening to grossly overburdening the healthcare systems and the socio-economic sectors of western countries [1].

In the brain of an AD patient, it is possible to identify diverse molecular events that lead the neurodegenerative process. Among them, beside accumulation of proteins and inflammatory events, there is a disbalance of lipid levels.

The brain is largely composed of lipids which play fundamental roles in the biochemical, structural and physiological regulation of the central nervous systems (CNS) such as energy storage, insulation, cellular communication and protection [2].

Professor Thudicum, in 1890 described for the first time a particular class of lipids very abundant in the brain, the sphingolipids. Since then, thanks to advancement in new technologies, many studies have been carried out in order to understand the role and the metabolic changes of these structural lipids in healthy and diseased brains. In fact, the production and maintenance of the concentration of lipids are highly regulated processes fundamental to keep a healthy brain. When this balance is disrupted, a brain disorder, such as AD, might arise. Furthermore, as a cause- consequence of that, the network of proteins (e.g. sphingolipid transporters) and small molecules that governs this lipid balance, is also often disrupted in the brain of neurological patients.

Therefore, detecting lipid disbalance and the disrupted network of proteins and enzymes involved in the synthesis, degradation and regulation of lipids in the brain of patients suffering from AD, can be used as a powerful tool to prevent or intervene in this disease in order to reduce its un-estimated burden.

Exchange of novel findings on lipid metabolism within the scientific community, pharmaceutical companies and commercial parties would be of great help to understand basic mechanisms driving pathological events during neurodegeneration. Dissemination of knowledge trough seminars,

conferences, publications, or newspapers would be beneficial in order to reach a wider audience and impact.

Particularly crucial is that all relevant findings will be communicated with appropriate stakeholders that may benefit. In particular:

- Patients suffering from diseases associated directly or indirectly with neurodegeneration/dementia
- The general public by dissemination of the knowledge about SL, evidence-based and personalized medicine
- Medical experts by gaining insight into and access to state-of-the-art of therapeutic and diagnostic options, reducing health care costs
- Early-stage researchers
- Industries as novel biomarkers and diagnostics tools will allow more focused clinical trials to identify early signs of dementia and patients' subpopulations that might potentially profit from a sphingolipid metabolism drug
- The knowledge generated can help to understand other neurodegenerative diseases with similar underlying pathogenic mechanisms

My research opens new opportunities for possible clinical trials of therapeutic opportunities, commercialization of assays and new drugs. In line with this, the implementation of these results in further research, by public organizations or private companies, can be beneficial to provide major societal and economic advantages.

Targeting lipids and the associated proteins pharmacologically, would, therefore, possibly mean to resolve AD and decrease the huge impact that neurogenerative disorders are bringing to societies and global economy.

Moreover, since it has been shown that sphingolipid disbalance characterizes other CNS disorders, lipid studies will in the future also benefit not only other forms of dementia, neurodegenerative (Huntington's, Parkinson's, ALS) and neuroinflammatory (multiple sclerosis) diseases but also other neurological diseases depression and schizophrenia.

Therefore, the studies reported in this thesis, were conceived and designed in order to tackle and to fill the knowledge gap on the roles of sphingolipids and sphingolipids transporters intent to develop possible biochemical and pharmacological targets for fighting neuroinflammation and AD.

The results reported in **chapter 2** and **3** assessed the biological role of lipid transporters as part of the EV machinery. Since many years, EV are studied to be used as pharmacological cargo to target specific physiological cascades or pathological triggers. Having unravel that sphingolipid transporters are able to modulate EV content, opened up new strategies to control EV composition, that could be used to treat several neurological diseases.

The data generated in **chapter 4**, strengthen the hypothesis of the role of CERTs in inflammatory processes and neurodegeneration. In fact, we have demonstrated that CERTs bind to several proteins involved in immune response, oxidative stress and neurodegenerative processes. We have also showed that, the co-expression of CERTs and STAT6 modulates the sphingolipid balance. However, at this stage, these results are too preliminary, and further research needs to be done in order to validate, reproduce and concretize these findings. Nevertheless, this knowledge is of great help to earmark triggers during neurodegeneration or unravel pathological pathways involved in neuroinflammation that can be used as possible target to resolve AD.

Previous studies showed that there is a correlation between disbalance in sphingolipid concentration and exacerbation of AD, however, it is still unclear in which extent the genes and proteins in the lipid network are dysregulated. Therefore, in **chapter 7** we studied how and which the genes involved in sphingolipid pathways are altered in AD patients. We have showed that several genes, mainly linked to cholesterol and membrane lipids genes, are dysfunctional in patients with AD. These findings could open up new research opportunities to investigate the role for these genes in the progression of AD. This study contributed to take a comprehensive picture on the genetic regulation of sphingolipid metabolism during the exacerbation of the AD.

Overall, in this thesis we have generated fundamental knowledge about the lipids and lipid transporters and how they affect membrane dynamics, immune alterations, and neurodegeneration. These findings on lipid metabolism and transporters could be seen as a small piece of a bigger puzzle where neurological disorders belong to.

1. *Marešová, P., et al., Socio-economic Aspects of Alzheimer's Disease. Curr Alzheimer Res, 2015.* ***12****(9): p. 903-11.*

2. *Bourre, J.M., 12 - Brain lipids and ageing, in Food for the Ageing Population, M. Raats, L. de Groot, and W. van Staveren, Editors. 2009, Woodhead Publishing. p. 219-251.*