Francesc Guix

Center for human genetics
Laboratory for the Research of Neurodegenerative Diseases
Department of Molecular and Developmental Genetics, VIB
University of Leuven

BSc of Human Biology, Faculty of Health and Life Sciences, Universitat Pompeu Fabra, Barcelona (Spain), 2004.
PhD in Science, University Pompeu Fabra, Barcelona (Spain), 2009

Postdoctoral researcher at the University of Leuven, since 2009

E-mail: Francesc.Guix@cme.vib-kuleuven.be

Phone: +32 (16) 34 58 78

Keywords

Alzheimer's disease; aging; gamma-secretase; lipid metabolism; oxidative stress

Science

Despite the striking fact that Alzheimer's Disease (AD) is an age-dependent pathology, we lack still a satisfactory explanation at the molecular level linking the age-associated changes that occur in neurons and the triggering of the disease. Aging, the first risk factor for developing AD, is characterized by dramatic alterations of the cell function due to the increase of oxidants and changes in gene expression patterns. Although superoxide anion can be produced from a variety of ROS sources, the mitochondrial electron transport chain is probably the major source of this reactive species.
Neurons are especially susceptible to oxidative stress for several reasons. Firstly, the brain is the main consumer of glucose of the body (20%). This high metabolism rate produces not only a large amount of oxidants, but also neurotoxic by-side products coming from the glycolytic pathway such as methylglyoxal (MG). Secondly, neurons are a highly differentiated type of cells which cannot divide. Thus, any important damage will theoretically remain until the death of the cell. The lipid metabolism is also known to be altered during aging. An increase of sphingomyelin, long chain ceramides (which are toxic) and changes in cholesterol levels are described in the brain of old people and in AD. Since AD is an age-related disease, it is logical to suppose that all the above changes are somehow involved in the onset of the disorder.
The two pathological hallmarks of the disease are the presence of extraneuronal senile plaques and intraneuronal neurofibrillary tangles (NFT), composed of Amyloid beta-peptide (Aβ) and deposits of *tau* protein, respectively. Mostly based on studies of families with inherited AD, it is assumed that abnormal Aβ generation is the initial trigger of the disease process (the amyloid hypothesis). Aβ is produced when a single type I transmembrane glycoprotein called Amyloid Precursor Protein (APP) is consecutively cleaved by two different activities belonging to the amyloidogenic pathway: the γ-

secretase and the β-secretase. The steady state levels of Aβ in the brain are also determined by its clearance, for instance via uptake in smooth muscle and endothelial cells of the blood vessel walls. An important fraction of Aβ is directly degraded in the brain by proteases. Thus both changes in the production or in the clearance can cause theoretically accumulation of Aβ peptide in the brain. Amyloid peptides display heterogeneity at their amino and carboxyterminus which is explained by proteolysis and additional enzymatic modifications of Aβ. In the current project we focus on the carboxy-terminal heterogeneity of Aβ which is readily demonstrated in cell culture and in γ-secretase cell free assays, suggesting that this heterogeneity is largely generated by the intrinsic properties of the γ-secretase itself. Interestingly the longer Aβ peptides (especially Aβ42) have very different biophysical properties compared to Aβ40 and it is quite generally believed that the relative balance of Aβ42 versus Aβ40 is pathogenic relevant.

The γ–secretase is in that regard particularly important. γ-Secretase is a high molecular complex composed of PS1 or PS2, nicastrin (Nct), anterior pharynx-defective phenotype 1 (Aph1) and PS enhancer 2 (Pen2). The catalytic activity of the complex resides on PS, a protein with 9 transmembrane domains. Moreover, more than 150 mutations in PS1 and 10 mutations in PS2 have been associated with AD. Interestingly these mutations affect directly the proteolytic processing of APP, resulting in a relative increase of the Aβ42 species γ-secretase aging versus the Aβ40 species. Recent insights suggest that this change in ration is the consequence of loss of function of the γ-secretase complex, which raises a series of important questions with regard to the role of γ-secretase in the pathogenesis of sporadic AD as well. It is enormously important to clarify whether γ-secretase indeed displays also a loss of function in aging, since the efforts for the design of a treatment must be driven towards the correct direction. The inhibitors of γ-secretase are an example to this dilemma. If the disease is mainly caused by an impaired γ-secretase activity, then the design of complex inhibitors to treat the disease is a bad strategy. However, if the total activity of the complex is increased or not affected and the levels of both Aβ40 and Aβ42 are incremented e.g. by decreased clearance as the leading hypothesis propose, then the use of inhibitors of the complex is a right strategy. Because AD is a heterogeneous disease, it might even be conceived that a mix of causes exist, with a group of sporadic patients characterized by decreased turnover of Aβ generated by a normal γ-secretase complex and another group with affected γ-secretase causing changes in the overall production of the peptide ratio’s and affecting in that way the formation of toxic oligomers, mimicking the situation in patients with presenilin mutations. Thus it is extremely equally important to find out if a percentage of AD cases are due to an impaired or altered γ-secretase activity in order to direct the research for a better treatment.

Aβ42 levels become indeed increased not only in sporadic AD, but also with aging in humans. This could account for the strong relationship that exists between aging and AD. Unfortunately, it remains unclear why Aβ42 levels increment in old age and sporadic AD. Recently, It has been found that the activity of the γ-secretase of old wild type mice is shifted towards an increased production of Aβ42 at expense of Aβ40. However, there is no clue about the ultimate mechanism behind this molecular event. On the other hand, it is known that mutations in the PS1 gene, which are responsible for a large number of familiar AD, increase the production of Aβ42 while decreasing or maintaining the production of Aβ40.

It is likely that some of the changes occurring during the aging process can account for the modified γ-secretase activity. In fact neuronal oxidative stress precedes fibrillar Aβ deposition in Down syndrome and in a transgenic model *C. elegans* for AD. The levels of

oxidants and lipid peroxidation are incremented in a triple transgenic mouse model of AD before Aβ diposition appears. In addition changes in the composition of biological membranes could have a role in this switch, since it has been recently reported that the lipid environment seems to affect the γ–secretase activity. However, though this is an interesting finding, the authors do not explain these outcomes from a pathophysiological point of view, into the context of AD. Moreover there are no evidences showing that the lipid composition of aged neurons can trigger an increase of the Aβ42/Aβ40 ratio.
To date there are no *in vivo* evidences neither a satisfactory molecular explanation linking the aging-related hallmarks with the γ-secretase-dependent switch towards a higher Aβ42/Aβ40 ratio. In a society with an expanding lifespan, it is highly important to understand which age-associated molecular events are responsible for the onset of AD in order to prevent them before the first symptoms strike. From all above, an increased Aβ42/Aβ40 ratio seems to be a plausible explanation for the onset of the disease in a group of sporadic AD cases Since γ-secretase is responsible for directing the production of Aβ towards Aβ42 or Aβ40, it is logical and necessary γ-secretase aging to investigate how aging and by which molecular mechanisms affect the γ-secretase complex activity.

Selected publications

Guix FX, Ill-Raga G, Bravo R, Nakaya T, de Fabritiis G, Coma M, Miscione GP, Villà-Freixa J, Suzuki T, Fernàndez-Busquets X, Valverde MA, de Strooper B, Muñoz FJ. (2009) Amyloid-dependent triosephosphate isomerase nitrotyrosination induces glycation and tau fibrillation. Brain 132(Pt 5): 1335-1345.