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Auditorium IGBMC
Séminaire Dr. LAMBERT Jean-Charles

Search for molecular determinants of Alzheimer's disease

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Alzheimer's disease (AD) is a complex multifactorial neurodegenerative disease and a leading cause of dementia among elderly people. The main pathological features of AD are neurofibrillary tangle and senile plaque formation. The later is caused by the progressive deposition of amyloid â peptides (Aâ) in the brain, generated through proteolytic cleavage of the A precursor protein (APP).
The systematic association of pathogenic mutations in AD monogenic forms with modifications in the APP metabolism has led to the "amyloid cascade" hypothesis. However, the exact place of APP in the physiopathological process is still under debate and the characterization of molecular determinants involved in this process are still needed to confirm or infirm the "amyloid cascade" hypothesis.
In this context, we have developed systematic genomic approaches to pick-up new key players of the AD process and to establish their potential involvement in the "amyloid cascade" hypothesis. For instance, we recently conducted a genome-wide association study in 2,032 French AD cases and 5,328 controls. Following replication in collections from Belgium, Finland, Italy and Spain, we characterized two new genetic determinants of AD, suggesting that genetic variants in these new loci may influence susceptibility to AD. Variants in these genes may lead to dysfunction in A peptides clearance. We have also performed transcriptomic analyses in the brain of AD cases and controls and we characterized a new metalloproteinase, strongly modifying the APP metabolism in vitro. This protease may limit the APP trafficking to the membrane in directing this protein to lysosome, a process not previously described.
In conclusion our different approaches have allowed to propose new determinants involved in the APP metabolism/catabolism. If the amyloid cascade hypothesis is confirmed, these determinants could be as consequence potential therapeutic targets.

Host : Yann Hérault and Tania Sorg

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