Alzheimer's disease genes in zebrafish (Danio rerio)

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BIBLIOGRAPHY

REFERENCES
ABSTRACT

Accumulation of amyloid β peptide (Aβ) is an early event in the cascade of neurogenerative processes leading to Alzheimer's disease (AD). Aβ is generated by enzymatic cleavages by two sequentially acting proteases, β-secretase and γ-secretase, which liberate the Aβ from its precursor, the amyloid precursor protein (APP). Aberrant processing of the APP by γ-secretase has been suggested to lead to increased formation of a neurotoxic Aβ variant and deposition of amyloid plaques, consequently leading to Alzheimer's disease. Presenilin is essential for cleavage of APP and may be the catalytic subunit of γ-secretase, an intramembrane-cleaving protease. γ-secretase is a multiprotein complex, which in addition to Presenilin consists of three other core components, Nicastrin, APH-1 and PEN-2, that constitute its biological activity. AD pathology is likely to involve the perturbation of numerous molecular mechanisms and signalling pathways, including FGF signalling.

Whereas considerable effort has been undertaken to understand the molecular pathogenesis of Alzheimer's disease, and some genes likely to play pivotal roles in the progression of the disease have been identified, fundamental aspects of its aetiology remain unresolved. Importantly, the normal functions of the major AD-related genes identified so far, and the identity of the genetic networks they interact with, are unknown. Recently it has been realised that genes associated with Alzheimer's disease, and other degenerative diseases, also play important functions during embryogenesis.
The interactions between many important signalling pathways are highly conserved during embryo development and may control cellular responses in widely different embryonic structures, such as the brain, heart and somites (Pires-daSilva and Sommer, 2003). Consequently, it is likely that some of the highly conserved AD-related genes, for example the presenilins, may be components in evolutionarily preserved signalling networks operating to control the development of many different embryonic tissues.

This suggests that investigations of the genetic mechanisms controlling developmental processes in different embryonic tissues may be a relevant approach in order to gain insight into the normal biological functions of AD-related genes and, ultimately, the cause of neurodegeneration, as well as other pathological conditions, in the adult. Thus, I decided to dissect the functions of Alzheimer’s disease genes during embryo development using the zebrafish (Danio rerio) as a model organism.

In chapter 1 our current understanding of the key mechanisms and pathways involved in AD pathology is reviewed. In chapter 2 and 4 the embryonic expression patterns of the zebrafish, presenilin and APP genes are investigated. In chapter 3 the role of γ-secretase activity during embryogenesis is analysed using a potent γ-secretase inhibitor. In chapter 5 the expression pattern of zebrafish fibroblast growth factor receptor 1, a central component in FGF signalling, is described in order to establish the foundation for further investigations of possible interactions between established Alzheimer’s disease genes and other pathways in embryonic zebrafish.