

# Chapter 11

## Amyloid Beta: The Foremost Protagonist in Alzheimer's Disease

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### ABSTRACT

*Alzheimer's disease (AD), exhibiting accumulation of amyloid beta ( $A\beta$ ) peptide as a foremost protagonist, is one of the top five causes of deaths. It is a neurodegenerative disorder (ND) that causes a progressive decline in memory and cognitive abilities. It is characterized by deposition of  $A\beta$  plaques and neurofibrillary tangles (NFTs) in the neurons, which in turn causes a decline in the brain acetylcholine levels.  $A\beta$  hypothesis is the most accepted hypothesis pertaining to the pathogenesis of AD. Amyloid Precursor Protein (APP) is constitutively present in brain and it is cleaved by three proteolytic enzymes (i.e., alpha, beta, and gamma secretases). Beta and gamma secretases cleave APP to form  $A\beta$ . Ubiquitin Proteasome System (UPS) is involved in the clearing of  $A\beta$  plaques. AD also involves impairment in UPS. The novel disease-modifying approaches involve inhibition of beta and gamma secretases. A number of clinical trials are going on worldwide with moieties targeting beta and gamma secretases. This chapter deals with an overview of APP and its enzymatic cleavage leading to AD.*

## INTRODUCTION

Dementia is considered to be an aggregation of symptoms affecting memory, cognition, social abilities on a severe magnitude. These adverse effects affecting the daily activities result from physical changes in brain. Dementia can further be of several types depending upon the underlying pathological condition and symptoms (Anand, Khurana, Chawla, Sharma, & Khurana, 2017). Dementias are progressive in nature. The sufferers may have troubles with short-term memory in the beginning which evolves into a loss of memory altogether. While there are varied symptoms of dementia, impairment in at least two of the following mentioned core mental functions should be there for the condition to be considered as dementia. These include deficit in memory, language and communication, ability to focus, capability to reason and judge and visual perception (Alzheimer's Association, 2017c). AD is the most common form of dementia. Over 47.5 million people globally were estimated to be suffering from dementia in 2016. By 2030, the figure is expected to reach as high as 75.6 million (World Health Organization, 2016). AD generally appears in mid to late adulthood. It is associated with a progressive and rather irreversible decline in memory and various other cognitive capabilities. In AD, there is neuronal destruction and deterioration of neural connections in the cerebral cortex region of the brain along with a substantial loss of brain mass (Perl, 2010). AD is lethal within 5–10 years of its onset (Dwyer et al., 2009). Mortality usually ensues due to complications of the chronic illness.

AD is characterized by the presence of two neuropathological hallmarks i.e. extracellular A $\beta$  plaques and intracellular NFTs. The plaques constitute chiefly of the neurotoxic peptide A $\beta$ , which forms after the sequential cleavage of a large precursor protein i.e. APP by two enzymes, namely,  $\beta$ -secretase (commonly known as BACE1) and  $\gamma$ -secretase (involving four proteins, including presenilin). However, A $\beta$  is not formed if APP is first acted upon and cleaved by the enzyme  $\alpha$ -secretase instead of  $\beta$ -secretase. NFTs comprise mainly of the protein tau which is a microtubule associated protein (MAP) i.e. it binds microtubules in cells to facilitate the neuronal transport system. In the development of AD, Tau uncouples from microtubules and aggregates into tangles thereby inhibiting transport and resulting in microtubule disassembly. It also depends on the phosphorylation of Tau (Anand, Patience, Sharma, & Khurana, 2017; Nisbet, Polanco, Ittner, & Götz, 2015).

The actual causes at play behind the development of AD are still not well defined. However, certain factors like anomaly in the phosphorylation of tau protein, alterations in calcium metabolism, oxidative stress, neuro-inflammation, abnormal energy metabolism and protein processing i.e. undesired A $\beta$  formation and aggregation, are considered to be important factors in the pathogenesis of AD (Butterfield et al., 2002; Habibyar, Sharma, & Khurana, 2016; J Hardy & Selkoe, 2002). In the present chapter, role of A $\beta$  formation and aggregation as the foremost protagonist in AD is discussed with special emphasis on APP and enzymes involved in its cleavage along with involvement of UPS in amyloid hypothesis of AD.

## BACKGROUND

AD was first described by a German neuropathologist Alois Alzheimer in 1906 (Editors of Encyclopædia Britannica, 2016). AD was recognized as the most prevalent form of dementia among geriatric persons by the commencement of 21<sup>st</sup> century. It is one of the top five most common causes of mortality in population of the United States (Centers for Disease Control and Prevention, 2017). In rare cases, it may appear in people in their 40s and 50s, but otherwise it is a disease of old age. Based on clinical, population-

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