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Review

Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy

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ABSTRACT

The vast majority of Alzheimer's disease (AD) are late-onset forms (LOAD) likely due to the interplay of environmental influences and individual genetic susceptibility. Epigenetic mechanisms, including DNA methylation, histone modifications and non-coding RNAs, constitute dynamic intracellular processes for translating environmental stimuli into modifications in gene expression. Over the past decade it has become increasingly clear that epigenetic mechanisms play a pivotal role in aging the pathogenesis of AD. Here, we provide a review of the major mechanisms for epigenetic modification and how they are reportedly altered in aging and AD. Moreover, we also consider how aberrant epigenetic modifications may lead to AD pathogenesis, and we review the therapeutic potential of epigenetic treatments for AD.

Contents

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder and the most common form of dementia in the elderly. The disease is clinically characterized by progressive memory loss and cognitive impairment. The pathological features are senile plaques (SP) and neurofibrillary tangles (NFTs), combined with massive neuronal loss, mainly in the hippocampus and association regions of the neocortex (Hardy, 2006). To date, the pathogenesis of AD is not yet fully understood. In light of recent studies, epigenetic modification has emerged as one of the pathogenic mechanisms of AD. Epigenetics refers to the study of heritable changes in phenotype that do not involve alterations in the DNA sequence (Berger et al., 2009). The three pillars of epigenetic mechanisms include DNA methylation, histone modifications and non-coding RNAs. Alterations of these epigenetic mechanisms affect most nuclear processes, such as gene transcription and silencing, DNA replication and repair, cell cycle progression. Previous epigenetic researches have focused primarily on dividing cells, particularly in cancer. However, recent studies have shown rapid, dynamic, and persistent epigenetic modifications in neurons and in neurodegenerative diseases. In this review, we aim to describe the three major epigenetic mechanisms, show recent evidence for their alterations in aging and in AD, and discuss their role in AD pathogenesis. Here, we also present the recent advances and challenges in epigenetic mechanisms for AD therapy.

2. Epigenetic modifications

2.1. DNA methylation

DNA methylation refers to the addition of methyl groups to cytosines by the DNA methyltransferases (DNMTs), resulting in the formation of 5-methylcytosyine (Fig. 1). In most cases, it is responsible for transcription suppression. Recent observations suggested that methylation of CpGs at a gene promotor repressed transcription, while methylation of CpGs in gene-bodies promoted transcription (Laurent et al., 2010). DNA methylation inhibits transcription directly, by interfering the binding of specific transcription factors to their recognition sites in their respective promoters, and indirectly, by recruiting and binding specific transcriptional repressors, methyl-CpG-binding proteins (MBDs), and altering chromatin structure into an inactive state (Singal and Ginder, 1999). In addition, recent studies have also proposed another possible mechanism that 5-methylcytosines are hydroxylated (oxidized) to form 5-hydroxymethylcytosine (Kriaucionis and Heintz, 2009; Tahiliani et al., 2009), which reduce the interaction of DNA with DNA-binding proteins to an even greater extent than 5-methylcytosines do (Valinluck et al., 2004). Currently, accumulating evidences of DNA demethylation have been found in mammalian cells (Hajkova et al., 2002; Oswald et al., 2000). And three enzymatic families have been connected to DNA demathylation: the ten-eleven translocation (TET) family that are mediators of 5mC to 5hmC conversion (Ito et al., 2011); the AID/APOBEC family that are mediators of 5mC or 5hmC deamination (Popp et al., 2010); and the BER glycosylase family that are mediators of DNA repair (Cortellino et al., 2011).

In light of the essential roles of DNA methylation in various biological processes, aberrant DNA methylation is widely implicated in human diseases, including cancer, imprinting disease, neurodegenerative diseases such as Alzheimer's disease (Mastroeni et al., 2011), Parkinson's disease (Jowaed et al., 2010), and disorders such as ischemic stroke and epilepsy (Hwang et al., 2013).

2.2. Histone modifications

Within a cell nucleus, nucleosomes are the fundamental units of chromatin. Each nucleosome is formed by 147 DNA base pairs wrapped tightly around an octamer of histone proteins, which is assembled by two copies of each of the four core histones, H2A, H2B, H3 and H4. The linker histone H1 binds to the DNA between the nucleosomal core particles, and is essential to stabilize higher order chromatin structures. Each histone protein consists of a central globular domain and an N-terminal tail that contains multiple sites for potential modifications (Fig. 1). Here, we clarify the modifications of nucleosomal organization into two types: rapid sliding movements that occur locally using ATP hydrolysis to expose specific DNA regions, such as ATP-dependent chromatin remodeling complexes, and post-translational modifications of aminoacids on histone tails, such as histone acetylation, methylation, phosphorylation, sumoylation, and ubiquitylation.

2.2.1. ATP-dependent chromatin remodeling complexes

ATP-dependent chromatin remodeling complexes (remodelers) bind nucleosomes in an energy-independent manner, and then use the energy of ATP hydrolysis to move, destabilize, eject, or restructure nucleosomes, which allows the access of transcription factors and large transcriptional complexes to DNA. The transcriptional effect of these remodelers, activation or suppression, depends on the recruitment of coactivator or corepressor complexes. These remodelers can be separated into four distinct families: the SWI/SNF (switching defective/sucrose nonfermenting) family, the ISWI (imitation SWI) family, the CHD (chromodomain, helicase, DNA binding) family, the INO (inosital requiring 80) family (Clapier and Cairns, 2009). They have critical roles in development, cancer, and stem cell biology (Hargreaves and Crabtree, 2011).

2.2.2. Post-translational histone modifications

Post-translational modifications of aminoacids on histone tails include but not limited to acetylation, ubiquitylation, or sumoylation at lysine (K) residues, methylation at K, arginine (R) or histidine (H) residues, and phosphorylation at serine (S), threonine (T) or