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Epigenetic changes in Alzheimer's disease: Decrements in DNA methylation

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Abstract

DNA methylation is a vital component of the epigenetic machinery that orchestrates changes in multiple genes and helps regulate gene expression in all known vertebrates. We evaluated immunoreactivity for two markers of DNA methylation and eight methylation maintenance factors in entorhinal cortex layer II, a region exhibiting substantial Alzheimer's disease (AD) pathology in which expression changes have been reported for a wide variety of genes. We show, for the first time, neuronal immunoreactivity for all 10 of the epigenetic markers and factors, with highly significant decrements in AD cases. These decrements were particularly marked in PHF1/PS396 immunoreactive, neurofibrillary tangle-bearing neurons. In addition, two of the DNA methylation maintenance factors, DNMT1 and MBD2, have been reported also to interact with ribosomal RNAs and ribosome synthesis. Consistent with these findings, DNMT1 and MBD2, as well as p66α, exhibited punctate cytoplasmic immunoreactivity that co-localized with the ribosome markers RPL26 and 5.8 s rRNA in ND neurons. By contrast, AD neurons generally lacked such staining, and there was a qualitative decrease in RPL26 and 5.8 s rRNA immunoreactivity. Collectively, these findings suggest epigenetic dysfunction in AD-vulnerable neurons.

Introduction

Gene expression in the Alzheimer's disease (AD) brain has been shown to be altered in a wide variety of reports (Robinson et al., 1994, Loring et al., 2001, Dunckley et al., 2006, Weeraratna et al., 2007, Liang et al., 2008a, Liang et al., 2008b, Liang et al., 2008c), including a recent large-scale expression array study of single cell laser-captured entorhinal cortex layer II neurons (Dunckley et al., 2006). Multiple physiologic and molecular pathways are affected, including energy metabolism (Liang et al., 2008c) inflammation (Loring et al., 2001, Weeraratna et al., 2007) and aberrant cell cycle events (Arendt, 2000, Bowser and Smith, 2002), among others. Although individual pathogenic factors such as amyloid β peptide (Aβ) and tau phosphorylation are clearly critical links, no over-arching principle to explain the consistency, extent, and breadth of the gene expression, physiologic, and molecular changes reported in AD has received consensus acceptance. Epigenetic mechanisms such as histone modification (Mclachlan et al., 1984), binding of non-histone proteins, and DNA methylation (Adcock et al., 2007, Suzuki and Bird, 2008) are capable of modulating coordinate expression of large numbers of genes across many different pathways, and may therefore warrant investigation for their potential role in AD pathogenesis.

DNA methylation is a highly conserved process that has been implicated in many different modalities of gene expression. The factors responsible for the methylation process are a family of DNA methyltransferases that have been shown to catalyze the transfer of a methyl group to single-stranded DNA using *S*-adenosyl methionine as the methyl donor. The recognition sequence for the mammalian DNA methyltransferase is relatively invariant, with nearly all cytosine methylations occurring on 5′-C-p-G-3′ (CpG) (Bird, 1986, Bird, 1992). There are four known active DNA methyltransferases in mammals, DNMT1, DNMT2, DNMT3A and DNMT3B. Of these, DNMT1 is the most abundant in mammalian cells. DNMT1 has been reported to be a key player in maintaining methylation in somatic cells, and loss of this enzyme has been shown to lead to nuclear disorganization, increased histone acetylation, and apoptosis (Chan et al., 2001, Fan et al., 2001, Jackson et al., 2004, Milutinovic et al., 2004, Espada et al., 2007).

Once methylation has occurred, methylation stability is maintained by the binding of specific complexes, MeCP1, to methylated regions of DNA. MeCP1 is not bound directly to methylated DNA, but rather to a single methyl-CpG-binding domain protein, MBD2. The resulting MeCP1/MBD2 complex is composed of 10 known proteins that include the complete nucleosome remodeling and histone deacetylase (NuRD) core, as well as MBD2. This group of proteins, in conjunction with CDK2AP1 (Doc1), make up a complex capable of nucleosome remodeling and histone deacetylation (Feng and Zhang, 2001, Feng and Zhang, 2003).

Because methylation and methylation maintenance factors can orchestrate changes in expression of a wide range of genes (Ashraf and Ip, 1998, Nan et al., 1998, Fujita et al., 1999, Ng et al., 1999, Feng and Zhang, 2001, Adcock et al., 2007, Suzuki and Bird, 2008), we hypothesized that alterations in methylation and methylation stability might provide an over-arching mechanism that could help explain expression differences in the thousands of genes that are reportedly altered in AD (Robinson et al., 1994, Loring et al., 2001, Dunckley et al., 2006, Liang et al., 2007, Liang et al., 2008a, Liang et al., 2008b, Liang et al., 2008c, Weeraratna et al., 2007). Here, we report highly significant decrements in immunoreactivity for two markers of DNA methylation and eight DNA methylation maintenance factors in AD neurons of entorhinal cortex layer II, one of the most consistently vulnerable brain regions to AD pathology (Braak et al., 1993, Kordower et al., 2001).

Section snippets

Subjects and brain samples

Brain tissue was obtained through the Sun Health Research Institute Brain and Body Donation Program (Sun City, AZ). Specimens were collected under IRB-approved protocols and informed consents that permitted use of the samples for research by the investigators. Cases included in the study had received antemortem evaluation by board-certified neurologists and neuropsychologists, as well as postmortem evaluation by a board-certified neuropathologist. Evaluations and diagnostic criteria followed…

Immunoreactivity for markers of DNA methylation

Nuclear labeling with 5-methylcytosine and 5-methylcytidine has been used to assess methylation status in many reports (e.g., Halle et al., 1995, Havlis and Trbusek, 2002). In

addition, both of these markers have also been reported to be associated with ribosomal RNA (rRNA) (Dunn, 1960, Tantravahi et al., 1981, Obara et al., 1982, Negre et al., 1989)….

Discussion

Perhaps because epigenetics is itself a relatively new field and has been primarily investigated in the context of oncology, epigenetic changes in AD are just beginning to be explored (Scarpa et al., 2003, Siegmund et al., 2007, Silva et al., 2008, Spremo-Potparevic et al., 2008, Wang et al., 2008, Wu et al., 2008). However, the changes in manifold individual genes in multiple cellular pathways that are emerging from large-scale gene expression array studies of AD (Robinson et al., 1994, Loring …

Conflict of interest

To the best of their knowledge, the authors do not have an actual or potential conflict of interest with regard to the present research.…

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