mice (SAMP8) and H3K27m3, H3K79me, and H3K79me2 increase in these aged mouse brains.[159] The silent information regulator 2 (Sir2) in yeast and its mammalian orthologs, sirtuin 1–7 (SIRT1–7), are histone-modifying enzymes that tend to be downregulated in aging, especially SIRT1. Activation of sirtuins may extend lifespan, modulating calorie restriction mechanisms[160] and promoting healthy aging, which delays the onset of neurodegenerative processes.[161] In the epidermis, aging is associated with a limited destabilization of the epigenome at gene regulatory elements.[162] Wound treatment with sirtuin activators and class I HDAC inhibitors induces keratinocyte proliferation and enhances healing *via* a nitric oxide (NO)-dependent mechanism. Acetylation of α-tubulin and histone H3 Lysine 9 may activate cell function and gene expression to foster tissue repair. The direct activation of *P300*/*CBP*-associated factor (PCAF) by the histone acetylase activator pentadecylidenemalonate 1b (SPV-106) induces lysine acetylation in the wound area. An impairment of PCAF and/or other GCN5 family acetylases may delay skin repair in physiopathological conditions.[163]

5.4.1.3 Non-Coding RNAs

There is a correlation between changes in miRNA expression and aging. miRNA lin-4 regulates lifespan in *C. elegans*; several miRNAs (miRNAs-34, -669c, -709, -93, -214) were found to be upregulated with age, while others (miRNAs-103, -107,-128, -130a, -155, -24, -221, -496, -1538, -17, -19b, -20a, -106a) appeared downregulated in peripheral tissues.[164,165] 70 miRNAs were found to be upregulated in the aging brain; 27 of these miRNAs may target genes of mitochondrial complexes III, IV, and F_0F_1-ATPase involved in oxidative phosphorylation and reduced expression in aging.[166]

5.4.2 Neurodegenerative Disorders

Epigenetic dysregulation is an attractive mechanism to explain in part enigmatic areas of confusion associated with the pathogenesis of age-related neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (Table 5.3), where it may mediate interactions between genetic and environmental risk factors, or directly interact with disease-specific pathological factors.[13–16,153,167]

Several pathogenic genes (Table 5.3) and many other AD-related susceptibility genes with direct or indirect influence on the AD or PD phenotype (*i.e.* genes associated with vascular risk factors and lipid metabolism) (Figures 5.4 and 5.5) contain methylated CpG sites that exhibit alterations in DNA methylation.[13,153,168] Different modalities of histone aberrations are present in AD.[13–16,153,168–170] Alterations in epigenetically-regulated miRNAs may contribute to the abnormal expression of pathogenic genes in AD.[171,172] Several lncRNAs are dysregulated in AD (*Sox2OT*, *1810014B01Rik*, *BC200*,