Genome-wide epigenetic analysis in knock-in mice with the human polymorphism (Val66Met) of BDNF gene

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Epigenetic mechanisms, changes in chromatin condensation state that alter gene expression, have been shown to regulate CNS physiology and have a role in both neuropsychiatric pathophysiology and drug action.
Several lines of evidence suggest an important role for BDNF in the pathogenesis of anxiety and mood disorder. Moreover, a human polymorphism in the BDNF gene (Val66Met) that causes a Met/Val substitution in codon 66 of proBDNF was associated with major susceptibility to neuropsychiatric diseases. The BDNF Val66Met knock-in mouse is the only existing animal model that recapitulates the phenotypic effect of the human polymorphism. Indeed, both human and mice $BDNF_{Met}$ allele carriers show reduced hippocampal volume and deficit in fear extinction learning.
We performed a whole genome sequencing of immunoprecipitation-enriched chromatin (ChIP-Seq). We used anti-trimethyl histone H3 lysine 27 (H3K27me3) and anti-acetyl histone H3 (H3Ac), in order to analyze epigenetic changes induced by the presence of the BDNF Val66Met polymorphism in hippocampus from wild-type ($BDNF^{Val/Val}$) and transgenic ($BDNF^{Met/Met}$) mice. Immunoprecipitated DNA fragments were sequenced on SOLiD sequencer and SICER peak-finding algorithm was used to identify the H3K27me3 and H3KAc-enriched sites throughout the genome. GREAT tool was used to extract the peaks mapped to promoter regions of annotated genes in which the center of the peak was within the -2000 bp and +500 bp interval from gene transcription starting site. H3K27me3 tags were detected in the promoter region of 1928 genes in the $BDNF^{Val/Val}$ mice and 2552 genes in $BDNF^{Met/Met}$. H3Ac was detected in the promoter region of 5648 genes in the $BDNF^{Val/Val}$ mice and 7859 genes in $BDNF^{Met/Met}$. Among the H3K27me3-enriched gene promoters, 182 were exclusively found in $BDNF^{Val/Val}$ while 655 were found only in $BDNF^{Met/Met}$. In the H3KAc-enriched gene promoters, 108 were found only in $BDNF^{Val/Val}$ while 1760 were found only in $BDNF^{Met/Met}$. Bioinformatic analysis of genes with epigenetic changes in their promoters, found only in $BDNF^{Val/Val}$ or $BDNF^{Met/Met}$, revealed the involvement of the KEGG 'Wnt signaling', 'Neuroactive ligand-receptor', 'MAPK signaling', and 'Regulation of actin cytoskeleton' pathways. In addition, networks related to 'lipid metabolism, small molecule biochemistry', 'cell death, cellular development' functions, among others, were found associated to H3K27me3- or H3Ac-enriched gene promoters.
Our results reveal genome-wide alteration of histone H3K27 trimethylation or histone H3 acetylation resulting from the presence of the Val66Met polymorphism. Changes in several functional pathways and their respective genes may be associated with the $BDNF^{Met/Met}$ phenotype.