

# Epigenetic regulation of BDNF-TrkB signaling in the pathophysiology and treatment of mood disorders

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## Summary

Mood disorders are among the major health problems worldwide due to the high prevalence and recurrence in the general population, and the significant burden for individual life quality and the repercussion on healthcare systems and society. Up to date, the etiology and biological mechanisms underlying mood disorders are still poorly understood. Mounting evidences suggest that a complex interaction between genes and environment might account in the development and course of major depression i.e. one of the most prevalent affective disorders. Accordingly, complex epigenetic regulations - consisting of key mechanisms by which environmental factors induce enduring changes in gene expression without altering the DNA code - have been suspected to plays a pivotal role in the pathophysiology of depression. More specifically, epigenetic repression of the gene encoding for brain-derived neurotrophic factor (BDNF) - a small-secreted growth factor implicated in brain development and neuronal plasticity - may have a preponderant role in the onset of depression and other mood disorders.

In this context, the research presented in this thesis aimed at exploring the role of BDNF signaling and its downstream epigenetic regulations in the pathophysiology and treatment of mood disorders.

Our findings indicate that epigenetic regulation at BDNF/TrkB signaling is critically important in the establishment and maintenance of neuronal plasticity. Moreover, environmental variations, especially when occurring in development, are able to induce stable and enduring epigenetic reprogramming involving aberrant BDNF/TrkB signaling and impaired neuroplasticity, thereby increasing vulnerability to stress and mood disorders. Interestingly, antidepressants require TrkB to exert some of their neurochemical and behavioral effects. Hence, targeting the BDNF receptor TrkB to restore a normal epigenetic regulation and neuronal functioning appears to be a promising strategy for the treatment of mood disorders.