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Expression and function of blood receptors RORα, REVERBA and BMAL1 in human colorectal cancer

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Background: Colorectal cancer (CRC) is the most common gastrointestinal cancer in the world. Angiogenesis plays an important role in the growth and development of tumors, including CRC. But therapy failure in patients with advanced CRC is a major obstacle to curative treatment and survival. Nuclear blood receptors (RORα, REVERBA and BMAL1) might be as potential future biomarkers and/or druggable targets which may improve the response to anti-angiogenic therapy in human CRC. The overall aim of the thesis was analysis of the expression and function of RORα, REVERBA, and BMAL1 in human CRC cells and tissues.
Methods: Expression of the transcriptional activator RORα and its antagonist REVERBA and their downstream target BMAL1 were explored in mice (response or non-response/resistance to anti-angiogenesis treatment) and CRC patients by immunohistochemistry. RORα, REVERBA, and BMAL1 functions were studied in human CRC cell lines using colorimetric growth, DNA-binding and reporter assays.
Results: We found that RORα is downregulated in CRC, BMAL1 is downregulated in CRC as well, however REVERBA is upregulated in CRC. We demonstrated that the expression of RORα, REVERBA and BMAL1 is associated with the preclinical response to anti-angiogenesis treatment in mice, and evinced the expression level of RORα, REVERBA and BMAL1 in various normal mouse tissues and in different colorectal cancer cell lines. Furthermore, we demonstrated that REVERBA increases the proliferation of colorectal cancer cells, and that overexpression of REVERBA in colorectal cancer cells increases human VEGFa transcriptional expression and VEGFa secretion in vitro. We also demonstrated that REVERBA enhances the VEGFa promoter activity by binding directly to the promoter region of the human VEGFa gene, and that REVERBA induced resistance of colorectal cancer to anti-angiogenesis treatment by activation of oncogenic signaling pathways (Ras, Wnt).