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Depressive-Like Behavior in a Murine Model of Colorectal Cancer Associated with Altered Cytokine Levels in Stress-Related Brain Regions

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Abstract : Background: The Colorectal cancer (CRC) is one of the most common cancers and the fourth leading cause of cancer death in the world. The prevalence of psychiatric-disorders among CRC patients, mainly depression, is high, resulting in impaired quality of life and side effects of primary treatment. High levels of proinflammatory cytokines at tumor microenvironment is a feature of CRC and the literature suggests that those mediators could contribute to the development of psychiatric disorders. Nevertheless, the ability of tumor-associated biological processes to affect the central nervous system (CNS) has only recently been explored in the context of symptoms of depression and is still not well understood. Therefore, the aim of the present study was to test the hypothesis that depressive-like behavior in an experimental model of CCR induced by N-methyl-N-nitro-N-nitrosoguanidine (MNNG) was correlated to proinflammatory profile in the periphery and in the brain. Methods: Colorectal carcinogenesis was induced in adult C57BL/6 mice (n=12) by administration of MNNG (5mg/kg, 0.1ml/intrarectal instillation) 2 times a week, for 2 week. Control group (n=12) received saline (0.1ml/intrarectal instillation). Eight weeks after beginning of MNNG administration animals were submitted to the forced swim test (FST) and the sucrose preference test for evaluation, respectively, of depressive- and anhedonia-like behaviors. After behavioral evaluation, the colon was collected and brain regions dissected (cortex-C, striatum-ST and hippocampus-HIP) for posterior evaluation of cytokine levels (IL-1β, IL-10, IL-17, and CX3CL1) by ELISA. Results: MNNG induced depressive-like behavior, represented by increased immobility time in the FST (Student t test, $p < 0.05$) and lower sucrose preference (Student t test, $p < 0.05$). Moreover, there were increased levels of IL-1β, IL-17 and CX3CL1 in the colonic tissue (Student t test, $p < 0.05$) and in the brain (IL-1 β in the ST and HIP, Student t test, $p < 0.05$; IL-17 and CX3CL1 in the C and HIP, $p < 0.05$). IL-10 levels, in contrast, were decreased in both the colon ($p < 0.05$) and the brain (C and HIP, $p < 0.05$). Conclusions: The results obtained in the present work support the notion that tumor growth induces neuroinflammation in stress-related brain regions and depressive-like behavior, which could be related to the high incidence of depression in colorectal carcinogenesis. This work have important clinical and research implications, taken into account that cytokine levels may be a marker promissory for the developing depression in CRC patients. New therapeutic strategies to assist in alleviating mental suffering in cancer patients might result from a better understanding of the role of cytokines in the pathophysiology of depression in these subjects.

Keywords : cytokines, brain, depression, colorectal cancer
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