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Commentary

Vitamin D as a Potential Therapeutic Target and Prognostic Marker for Colorectal Cancer

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Despite significant improvements in chemotherapy regimens and surgical technique, colorectal cancer is nowadays one of the leading causes of death worldwide in the developed countries while its incidence in other regions of the world is rapidly rising. Therefore, the quest to find new and more effecting tools for its prevention and treatment is ongoing at a fast pace.

Aside from its role in the homeostasis of calcium, vitamin D has been recently reported to be involved in the complex processes of cell differentiation and apoptosis. It seems to have an inhibitory effect on proliferation and angiogenesis of gastrointestinal derived cancers which might give it new perspectives in the future as an anti-tumoral agent [1]. Could vitamin D gain its place as an additional therapeutic tool in the management of colorectal cancer? That is a hot topic nowadays and the authors of the present article have tried to provide a comprehensive answer.

The relation between the metabolism of vitamin D and tumorigenesis is more intimate than previously thought. Synthesized in the skin, vitamin D becomes biologically active after two steps of hydroxylation, one taking place in the liver and the second one in the kidney and in the human colon tissue under the action of cytochromes P450 and CYP27B1. Inactivation of Vitamin D may also be influenced by tumor cells, one of the inactivating enzymes, CYP24A1, being also overexpressed in colon cancer cells [2]. Moreover, the biologic effects of vitamin D are mediated by its receptor (VDR) which is expressed in a multitude of tissues, including human colon cells [2].

In the last decade an increased number of clinical studies aimed to address the role of vitamin D in the management of colorectal cancer. Observational studies have shown that higher levels of vitamin D are associated with a reduced risk of colorectal cancer and improved survival of patients [3] while several prospective studies have reported increased mortality in colorectal cancer patients with low level of vitamin D [4]. Recently, a meta-analysis of five studies including 2330 patients with colorectal cancer reported better overall survival (HR 0,71; 95% CI, 0.55–0.91) and lower disease-specific mortality (HR 0,65; 95% CI, 0.49–0.86) in patients with higher vitamin D levels [5]. But, although the anti-tumoral effects of vitamin D seem to be a reality, the exact mechanisms of action are still under investigation. According to several reports, it may be linked to the regulation of inflammatory processes that are involved in cancer progression, such as expression of the cyclooxygenase 2 enzyme, the NF-kB pathway and synthesis of the various proinflamatory cytokines such as TNFα, IL1β, IL6, IL8, IL17, and TGFβ1 [6].

In *EBioMedicine*, Zhu et al. offer additional insight about the intrinsic mechanisms by which vitamin D could influence tumorigenesis in colorectal cancer [7]. According to their studies, vitamin D may express its antitumoral effect by mediating the *MEG3*/clusterin signaling pathway. A long non-coding RNAs (lncRNAs), the maternally expressed gene 3 (*MEG3*) is involved in diverse cellular processes including cell proliferation, migration and invasion and is present in multiple cancer cell types including prostate, breast, colorectal, gastrointestinal and pancreatic [8]. The role of lncRNAs in tumor progression is another hot topic nowadays, several reports from the literature demonstrating that these genes have either a protective effect, such as the case of *MEG3* whose low levels were associated with increased incidence of liver metastasis [9] or a stimulative effect, such as the case of *BC200,* another lncRNAs, which is up-regulated in colon cancer tissue, its knockdown inhibiting proliferation and invasion of certain cancer cells lines [10]. The authors of the present paper have found that *MEG3* over-expression suppressed colorectal cancer cell (CRC) proliferation and metastasis in-vivo and in-vitro, that it reduced transcription of clusterin, a protumoral protein, in CRC cells and that vitamin D achieved its anti-tumoral role by activating *MEG3* expression in CRC cells via its nuclear receptor (VDR). These results confirm the actual trend within the scientific community that looks at vitamin D as a potential therapeutic target and prognostic marker for various tumors, including colorectal cancer.

So where do we stand now? Is vitamin D an effective adjuvant tool in the prevention and management of colorectal cancer? Latest reports from the literature add high-quality data on the role of vitamin D in colorectal cancer progressions, the present paper included, suggest that its beneficial potential is real. However current therapeutic protocols do not include it yet nor recommend any screening of serum values or therapeutic supplementation [11]. The future will surely provide the answer as the topic is widely investigated. As new data is gathered from additional studies looking in-depth into the delicate and interconnected mechanisms of action of vitamin D doubled by well design randomized control trials on large cohorts of patients we will be able to recommend or not vitamin D to our colorectal cancer patients.

Disclosure

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