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Mitigating colon cancer with a novel strain of *Lactobacillus acidophilus*: a (re-)balancing act

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Gut-specific malignancies represent a global concern, with over 1 million new colorectal cancer (CRC) diagnoses and over 600,000 deaths annually [1]. Although a genetic basis for CRC exists, inherited predisposition accounts for only a fraction of CRC patients [2], with the majority of the sporadic cases being attributed to environmental factors, such as a sedentary lifestyle, smoking, diet and the composition of the gastrointestinal microbiome [3,4]. Normal gut immune responses allow resident innate and adaptive immune cells to coexist with the astronomical number of microbes inhabiting the GI tract while still being able to mount an immune response against invading pathogens. This maintenance of immune homeostasis toward commensal bacteria and their microbial gene products is essential in the prevention of chronic inflammation in the gut. Overt intestinal inflammation can be detrimental to the host and lead to inflammatory disorders, such as inflammatory bowel diseases (IBDs). In addition, chronic inflammation is a significant risk factor for cancer development due to the local production of proinflammatory cytokines and chemokines that promote tumor growth and survival [5]. Not surprisingly, colitis-associated cancer, a high-mortality subtype of CRC, is linked with IBD [6]. Within 30 years of disease

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onset, the prevalence of colitis-associated cancer among IBD patients is approximately 20%, and colitis-associated cancer is responsible for 10–15% of all deaths in these patients [7]. Therefore, inappropriate reactions to gut microbiota and the ensuing pathogenic inflammatory responses may impact susceptibility to intestinal tumor progression. Indeed, even in the absence of clinical IBD, colorectal tumors are associated with significant proinflammatory cytokine production and immune infiltration [8]. Correspondingly, a major goal in the prevention of CRC should be the attenuation of pathogenic intestinal inflammation.

Colon cancer progresses in stages that include the formation of polyps, adenomas and carcinomas. Among the proinflammatory cytokines shown to promote tumor development, IL-6 and TNF- α have been well characterized as playing important roles in tumor initiation, promotion and progression [9]. Increased serum levels of IL-6 and TNF- α have been associated with a higher risk for colorectal adenomas in man [10], and suppression of TNF- α signaling has been shown to lead to a reduction in the number and size of polyps in an animal model genetically predisposed to polyposis [11]. Similarly, blocking IL-6 signal transduction results in decreased colon carcinogenesis [12]. By contrast, compensatory pathways may be also triggered as a consequence of pro-inflammatory insults in an effort to counteract tissue damage and cytotoxicity. A member of the IL-10 family, IL-22, is thought to be involved in epithelial immune responses, gut homeostasis and mucosal tissue healing [13]. As evidence, targeted expression of IL-22 in the inflamed intestine of an experimental model of IBD curtailed inflammation and ameliorated disease via the induction of mucus-producing cells [14]. The main moderators of cancer-promoting inflammation, however, are well-functioning gut Tregs. Unfortunately, in polyposis and colon cancer, these cells have been shown to gain a proinflammatory phenotype [15]. Proinflammatory colonic Tregs suppress helper T-cell responses (anti-tumor immunity) but produce deleterious cytokines, thereby contributing to the inflammatory milieu. One would expect then, that in the fight to maintain intestinal homeostasis, proneness to cancer development would be enhanced when the balance is tilted such that mediators aiming to tune down inflammation and promote tissue repair cannot keep up with the proinflammatory actions of cytokines like IL-6 and TNF- α .

As further support for a tumor-promoting role of detrimental inflammation in the context of CRC, our recently published work demonstrates that precancerous colonic polyps were diminished after pacifying pathogenic intestinal inflammation through oral treatment with a novel probiotic *Lactobacillus acidophilus* NCFM strain [16]. In the long history of probiotic consumption by humans, multiple health benefits have been noted with only few adverse effects observed in a small cohort of susceptible individuals [17]. Given that beneficial gut bacteria can survive in GI tract without colonizing it, these microbes are attractive vehicles to deliver immunomodulating molecules or biological agents to the intestine for the treatment of mucosal-associated diseases and for antigen-specific vaccination. Nonetheless, for these purposes, extensive preclinical testing is required to validate the safety and efficacy of ‘designer’ probiotics as the expression of foreign genes may alter the intestinal immune response induced by the bacterium of interest as well as the ability to permanently colonize the gut. In this respect, genetic manipulation of the cell surface proteins of intestinal microorganisms represents a promising and less intrusive alternative to control the local immune response in the gut by modifying the bacteria–host cell interactions. After successfully ameliorating chemical- and pathogenic T cell transfer-induced colitis with a *L.acidophilus* NCFM strain lacking the gene responsible for the biosynthesis of the surface layer protein lipoteichoic acid (LTA) [18], our group sought to test this bacterium as a therapeutic for the treatment of colon cancer with satisfactory results [16]. Notably, as anticipated, positive outcomes after oral treatment with LTA-deficient *L. acidophilus* NCFM correlated with significant reductions in intrapolyp immune infiltration, reduced serum

levels of IL-6 and TNF- α , and increased expression of IL-22 [16]. Additionally, the quality of the colonic Tregs found in the polyps of mice treated with LTA-deficient *L. acidophilus* NCFM reverted from proinflammatory to protective, thus demonstrating that this novel *L. acidophilus* NCFM strain is able to reconstitute gut homeostasis. As not all of these effects were observed after treatment with the wild-type bacterium, the absence of LTA expression seems to be key to protection.

Although our model clearly correlates uncontrolled intestinal inflammation to colon cancer, the link between carcinogenesis in the gut and inflammation may vary during the different stages of colon cancer development (tumor initiation, promotion and progression). Expectantly, future studies will provide data on the benefit of LTA-deficient *L. acidophilus* NCFM oral treatment for the prevention or regression of CRC with the use of experimental models of invasive colon cancer. Moreover, the molecular events preceding colonic polyposis mitigation must be revisited and explored in detail. In conclusion, the documented ability of LTA-deficient *L. acidophilus* NCFM to dampen chronic intestinal inflammation and restore gut homeostasis supports its use as a treatment for intestinal maladies, including IBD and colon cancer. By the same token, the absence of heterologous genetic material in LTA-deficient *L. acidophilus* NCFM, should allow for a swift transition from bench to bedside.

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