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Reprogramming intestinal immunity is the answer to induced pathogenic inflammation

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Intestinal inflammation is a complex immunologic process involving both cellular and soluble molecules that are produced in response to transient or permanent imbalances in the gut microbiota and/or their gene products. This inflammatory process is tightly controlled via specific checkpoints that regulate the progression or suppression of the immune response. Thus, a number of pathways utilizing a myriad of gene products are involved in the homeostasis between the intestinal epithelium, the gut microbiota and the host immune system [1]. This homeostasis is a delicate balance, and dysregulation of any aspect of host–microbe interactions in the intestinal environment can have devastating immune consequences that may lead to diseases such as inflammatory bowel disease (IBD). In this respect, IBD is characterized by exaggerated inflammation induced by various factors, including microbial products [2–5] that influence the differentiation of infiltrating pathogenic $CD4^+$ T cells that are the driving force behind intestinal tissue destruction [6–8]. These $CD4^+$ T cells are induced by proinflammatory cytokines produced by cells of the intestinal innate immune system, including highly activated intestinal dendritic cells (DCs), macrophages or mast cells. All of these innate cells can be involved in serious acute or systemic inflammatory processes wherein intestinal disease will be imprinted.

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Emerging data from well-designed studies are beginning to shed light on the causes of gastrointestinal disease, including IBD, in an attempt to determine the etiologies and epidemiologies of these pathologic processes. To this end, studies are underway to address the following questions:

- What are the immunologic mechanisms that modify intestinal homeostasis and the interactions between microbes and host immune cells [9]?
- How can overt inflammation be downregulated to mitigate autoimmune disease?
- What molecules regulate intestinal cytokine production, which in turn, determines the differentiation and expansion of discrete T lymphocyte populations that have very different effects on the severity of induced colitis, contributions to epithelial wound healing and defense against microbial infection?

Undoubtedly, genetic predisposition plays a pivotal role in the susceptibility to disease. However, we now also appreciate that the gastrointestinal microbiota are critical mediators of various signaling events within host cells via gene products that have been estimated to exceed that of the human genome by more than 100-fold [10–12]. Such gene products initiate digestion and the production of nutrients, detoxification and the development of tolerance or host defense against microbes [12,13]. Thus, our laboratory and others have clearly demonstrated that the microbiota and the immune system are intricately linked and constantly influence each other [14–18]. The incomplete state of the intestinal immune system in germ-free conditions and in neonatal individuals confirms that its normal maturation is strongly influenced by commensal microbes [12,19], with the absence of these microbes resulting in devastating developmental consequences. Permutation of only a single species of the resident intestinal microflora can significantly impact the commitment and/or maintenance of various $CD4^+$ T-cell subsets [20], including systemic IFN-γ^+ $CD4^+$ T cells, Th17 cells or Tregs [19]. Data clearly show that in both scenarios, innate cells (i.e., DC subsets) are the critical initial target involved in the recognition of microbes and their bacterial products [20]. Given these tight associations and immune synapses, it is not surprising that gut microbiota and their bacterial products have been linked to pathology of the immune system (i.e., autoimmunity) [12]. While a relationship between bacteria and IBD is easy to understand, the specific cellular and molecular mechanisms by which intestinal commensals and their bacterial products result in IBD and proinflammatory responses at distal sites remain enigmatic. Moreover, the potential of probiotics for the treatment or prevention of various diseases, including IBD, continues to be unsettled and controversial, as the question remains about how probiotics can be employed in order to rebalance uncontrolled inflammation and avoid side effects in the intestine.

> "…using genetic tools to generate novel beneficial strains of L. acidophilus, we may be able to open up new avenues in disease treatment by reprogramming mucosal immunity…"

Targeted preventive or therapeutic strategies are most effective when cellular interactions are fully understood and critical molecules involved in bacterial-induced inflammation are identified. To this end, we have set out to further elucidate the molecular mechanisms

involved in inflammation, autoimmunity and suppression of the immune response by applying new and emerging knowledge about the composition and properties of bacterial gene products involved in exaggerated intestinal inflammation. Manipulation of the bacterial gene products have and will allow us to better understand the dynamic activities of colonic T-cell subsets (i.e., Tregs) and DC subsets (regulatory vs proinflammatory) in disease progression and to dissect immunological mechanisms in IBD. Our focus is currently centered on the role of *Lactobacillus acidophilus* NCFM surface layer proteins and lipoteichoic acid. Following the genome sequencing of *L. acidophilus* and the development of genetic tools such as a targeting the plasmid integration system for gene deletion or modification, it is now possible to study the impact of *L. acidophilus* surface layer proteins on innate immune cells (i.e., DCs and macrophages) and their role in IBD, polyposis and colon cancer, all of which are elicited by dysregulated inflammation. This beneficial bacterium has been consumed by humans in various probiotic supplements, foods and yogurts since the mid-1970s. Because of this history, it is generally recognized as safe for human consumption and can be consumed at levels reaching 10^8 bacteria/g. Because this bacterium is acid and bile tolerant, it successfully passes through the stomach and reaches the small and large intestines where it interacts with the intestinal epithelium and mucosa. Our group and others are investigating the use of beneficial probiotic bacteria as oral delivery vehicles for vaccines and therapeutics or as immune modulators. Using a targeting plasmid integration system, a gene responsible for the synthesis of lipoteichoic acid on *L. acidophilus* NCFM was completely deleted to generate a new strain of *L. acidophilus*. As a result, the generated bacterium contains no heterologous DNA or genetic markers, but simply has an empty space where the gene was originally located. We have demonstrated that such a derivative of *L. acidophilus* is highly anti-inflammatory and can prevent induced colitis or polyposis *in vivo*. We hope to evaluate the anti-inflammatory effects of this *L. acidophilus* in a variety of animal and human studies to determine its efficacy for the treatment and prevention of intestinal inflammation, local (Crohn's disease) and systemic (diabetes) autoimmune diseases and colon cancer.

In conclusion, using genetic tools to generate novel beneficial strains of *L. acidophilus*, we may be able to open up new avenues in disease treatment by reprogramming mucosal immunity, resulting in directed systemic immune responses. This new and novel vehicle will have several benefits, mainly:

- It does not have side effects upon consumption;
- It is cost effective;
- It can be used as needed because *L. acidophilus* does not permanently colonize the gut.

This last property of the bacterium is significant, as one does not want to constantly suppress naturally occurring inflammation, which is essential in host defense and the clearance of intestinal pathogens.

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