Microbial Links to Inflammatory Bowel Disease Development: Potential Intervenional Strategies in Treatment

Udai P. Singh¹, Narendra P. Singh¹, Brandon Busbee¹, Guan H², Robert L. Price³, Dennis D. Taub⁴, Manoj K. Mishra⁴, Mitzi Nagarkatti¹ and Prakash S. Nagarkatti¹

1Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia, SC 29208, USA
2Department of Cell and Developmental Biology, University of South Carolina, Columbia, SC 29208 USA
3Laboratory of Molecular Biology and Immunology, NIA-IRP, NIH, Baltimore, MD 21224, USA
4Department of Math and Sciences, Alabama State University, 1627 Hall, St. Montgomery, AL 36104, USA

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Commentary

The two major forms of Inflammatory Bowel Disease (IBD), Crohn’s disease (CD) and ulcerative colitis (UC), affect an estimated 3.6 million people globally [1]. The main mechanisms responsible for the induction and pathogenesis of IBD remain unknown, but there is a general agreement, those intestinal microbiota that mediate dysregulation of the immune system resulting in progression and development of IBD, are involved [2]. More recent studies have demonstrated that luminal antigens play an active role, to mediate mucosal immune responses that induce IBD progression. In humans, inflammation is most severe in the part of the gut that contains the highest bacterial concentration [3,4]. It is well known that mice fail to develop colitis or have a reduced severity under germ-free conditions, suggesting a pathologic connection between immune cells and commensal enteric bacteria to develop IBD [5-8]. Due to prolonged mucosal contact in parts of the ileum, rectum and caecum regions, the pathogenic germ(s) may decrease the protective bacteria that induce mucosal permeability and lead to enhanced exposure of bacterial products to Toll-like receptors (TLR), and antigens that directly activate the pathogenic T cell immune responses to induce IBD. This induction also mediates regulatory T cell dysfunction or antigen-presenting cells (APC) that might lead to further decreased tolerance to microbial antigens [9].

The essential features for normal gut function are that the host immune system should be tolerant towards the antigens of commensal gut microbiota. The intestinal bacterial flora contributes in IBD pathogenesis, is supported by several experimental models of colitis as well as clinical studies. In the nineteenth century, Koch’s postulation was confirmed later on, that Mycobacterium avium subsp. paratuberculosis (MAP) is the causative agent of Johnne’s disease (JD) in cattle [10,11]. After this, a series of studies by many investigators in the field indicate that MAP is a contributing pathogen for CD [12-17]. The granulomas of CD patients also show the presence of E. coli, suggesting a secondary role for non-specific pathogen involvement in this disease [18]. Furthermore, rectal mucosa-associated bacterial floras in IBD have demonstrated a reduction in Bifidobacteria and an increase in E. coli and Clostridia [19]. Several reports indicate that childhood environmental factors are involved in pediatric IBD development. The high prevalence of adherent-invasive E. coli is associated with CD [20]. Further support at molecular level, suggests a mutation of caspase recruitment domain-15 (CARD-15)/ nucleotide-binding oligomerization domain-2 (NOD-2), in CD patients leads to a loss of antibacterial function in intestinal epithelial cells [21,22]. In summary, Bacteroides spp, Enterococcus faucalis, Enterobacter cloacae, intestinal Helicobacter spp, Fusobacterium Spp., adherent/invasive E. coli strains, Eubacterium and Peptostreptococcus were reported to be harmful bacteria [23] that mediate or contribute to IBD development and pathology. Based on this information, it is safe to speculate that colonic bacteria manipulation with antibiotic drugs or by probiotic agents will be proven to be more effective than the currently available and utilized immunosuppressive agents in IBD treatment, in the future.

We are excited by several recent reports describing an increase in Lactobacillus and Bifidobacterium after resveratrol treatment, 20 days prior to DSS induction of colitis [24]. In another report, red wine polyphenols (dimethylhydrazine) were also shown to increase Lactobacillus, after 15 weeks of treatment [25]. The increase in lactic acid bacteria after resveratrol treatment demonstrated protection against colitis, by affecting several inflammatory parameters including pro-inflammatory cytokines and oxidative markers of damage [26]. Moreover, there appears to be direct effects of Lactobacillus and Bifidobacterium administration in preventing proinflammatory responses, in intestinal epithelial cells exposed to pathogenic Enterobacteria [27]. Similarly, red wine polyphenols have also been shown to reduce the levels of Clostridium spp, and increase Bifidobacterium spp. to assist in the protection from IBD [28]. To date, the available treatments for IBD can only reduce the periods of active disease and help to maintain remission. Unfortunately, these treatments often bring marginal results and the disease becomes refractory with a number of side effects. Due to poor responses of this treatment by patients, their clinical use is quite limited [29]. This might be the reason that many IBD sufferers turn to unconventional natural treatments, in the hope of abating symptoms of active disease. It has been estimated that roughly 35-40% of IBD patients use some form of megavitamin therapy, herbal or natural dietary supplement [30]. Our laboratory is working on dietary and natural plant product effects on autoimmune diseases, and we noticed that a plant product, resveratrol, has strong anti-inflammatory and antioxidant properties. Based on the studies described above, there is little doubt that resveratrol influences the microbiota make-up in the gut to protect a host from active IBD. We have recently reported that resveratrol treatment reduces the severity of IBD, using multiple anti-inflammatory pathways as described below.

Resveratrol, a polyphenolic stilbene found in grape skins, berries,
and nuts was originally described as a plant anti-fungal resistance factor, that exerts several biological activities in humans and rodents [31,32]. Interestingly, resveratrol consumption in animals increases life span [33]. More recent studies have demonstrated that resveratrol treatment also reduces inflammation [34], prevents cancer [35], protects against neurodegeneration [36] and reduces severity in autoimmune diseases like EAE [37]. Resveratrol also modulates early inflammation in colitis [38]. While the anti-inflammatory mechanisms(s) of resveratrol administration is currently unknown, reductions in the expression of COX-1 and COX-2 after resveratrol treatment, have been reported [39]. Treatment with polyphenol has also been shown to prevent or delay the progression of IBD [40]. We have reported that orally administered resveratrol ameliorates both dextran sodium sulphate (DSS)-induced and IL-10-/- chronic colitis in mice [41,42]. Our studies suggest that resveratrol targets multiple signaling pathways, including silent mating type information regulation-1 (SIRT1) gene expression, which has not been previously investigated with regard to its association with colitis. To this end, colitis induction may down-regulate SIRT1 levels and promote both NF-κB activation and cytokine expression in the colon, and resveratrol reverses these effects by up-regulating SIRT1 [41]. Furthermore, resveratrol treatment suppresses all indicators of inflammation including cytokine production and Th1 cell development as well as COX-2 expression and activity, thereby diminishing colitis. We have also shown that resveratrol reduces tumor incidence and lesion numbers, in DSS-induced colon cancer models [43]. In additional studies, our data has also demonstrated that resveratrol induces the generation of immunosuppressive CD11b+Gr-1+ myeloid cells that express arginase-1 (ARG-1), which correlates with colitis amelioration [42]. The correlation between the induction of the immunosuppressive CD11b+Gr-1+ cells by resveratrol and the reversal of colitis, suggest that these cells may also contribute towards the reversal of chronic colitis in IL-10-/- mice. Resveratrol also reduced the number of CXCR3+ T cells in the spleen, mesenteric lymph nodes (MLN), and lamina propria (LP). It is well known that IL-10-/- mice display large amounts of CXCL10 in the colon, by the recruitment of CXCR3+ T cells.

In summary, these results demonstrate that resveratrol protects against colitis and colitis-associated colon cancer development through multiple pathways, primarily via the up-regulation of SIRT1, the down-regulation of NF-κB activation in immune cells, the induction of immunosuppressive myeloid-derivd suppressor cells (MDSCs), and the down-regulation of CXCR3+ expressing CD4+ T cells in the LP. Based on these studies, an overall concept emerges that resveratrol treatment reduces the systemic CXCL10 levels, as well as frequency of CXCR3+ T cells.

References


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