

## Microbiota in Immune Pathogenesis and the Prospects for Pre and Probiotic Dietetics in Psoriasis

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Psoriasis is a common autoimmune inflammatory disease wherein pathogenesis is advanced by fundamental genetic predisposition/s in concert with environmental triggers. Inflammation in psoriasis may represent efforts of innate immune system to target pathogens for restoring immune homeostasis. Aberrant microbiota may resist elimination efforts by sheer advantage of several fold gene pool as compared to the host. The microbes deregulate gene expression by the molecular insults targeting host immune system. Role of microbiota in autoimmunity dictates establishment of microbiome homeostasis and suppress host immune response; as a treatment approach. Dietary prebiotics and probiotics are of particular interest for prevention and amelioration of autoimmune inflammatory diseases, due to their potential to foster healthy host-microbiome relationship. The rational dietetics aims towards balancing friendly versus enemical microbes via manipulation of gut environment and modulation of immune system to improve regulation of inflammatory and autoimmune mechanisms.

### INTRODUCTION

Increasing prevalence of autoimmune disorders and global epidemic of 'modern age' chronic inflammatory diseases due to changing lifestyle and environment is currently witnessed (Pandey *et al.*, 2014). A genetic predisposition underlies autoimmune diseases, with immune, hormonal and environmental factors contributing to the clinical manifestations. Clinical manifestations are restricted to susceptible individuals, although the autoimmunity processes have wider occurrence. Genetic predisposition influences the disease precipitation by exposure to environmental triggers as sunlight, diet, allergens, infectious agents and several other environmental insults. Infectious agents commonly trigger autoimmune diseases. Microbial products can aggravate T cell responses to self as well as non self antigens. Environmental factors may shift the balance of T cells

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between inflammatory interferon gamma producing Th1 cells and IL-4 and IL-5 producing Th2 cells in an individual. Lifestyle factors apparently affect immune function. Interaction between dietary factors and other exposure/s are current significant research areas of pathogenesis and therapeutics of autoimmune disorders (Pandey and Pandey, 2013).

The microbial flora in the gut interacts with diet and influences the host immune cells with mutual benefit to both the microbes and the host (Lee and Mazamania, 2010; Lee *et al.*, 2010). This aspect has major implication for prevention and mitigation of psoriasis, the most common immune mediated inflammatory disease.

### **The Gut Microbiome**

The gut mucosal immune system is the largest lymphoid organ in our body, intricately involved in regulation of immunity and inflammation characterizing autoimmune disorders. Gut immune system is strongly subject to changes by dysbiosis or imbalance among microbial species (Maynard *et al.*, 2012). Change in population of singular species of segmented filamentous bacteria in the gut may markedly influence emergence and stability of specific T lymphocyte subsets (Prakash *et al.*, 2011). Biochemical interactions of colonic microbes and immune cells have

implications for immune homeostasis. Examples include, action of serum amyloid A on dendritic cells (Ivanov *et al.*, 2009), ATP mediated activation of dendritic cells (Atarashi *et al.*, 2008), induction of TGF-beta expression by gut epithelial cells (Atarashi *et al.*, 2011), bacillus fragile derived polysaccharide A action on dendritic cells (Mazamania *et al.*, 2005) and TR-2 regulatory T cell function (Round *et al.*, 2011). Changes in gut microbiota in response to diet, sanitation, antibiotic use, environmental chemicals, etc. can influence and impact maturation and balance of immune responses.

### **Dysbiosis and Immune Disorder**

Innate immune system provocation in autoimmunity involves a crucial role of the Toll like receptors. These recognize specific forms of microbial nucleic acids and bind them to induce proinflammatory signals. The TLRs also recognize certain self antigens and mediate autoimmunity against cells with parallel expression of proinflammatory cytokines (Trivedi and Greidenger, 2009). The common proinflammatory autoimmune phenotypes are due to CD4+ T helper lymphocytes. Organ specific autoimmunity is driven by cell mediated immune responses aimed to attack intracellular foreign element. The Th1 cytokines IL-2 and interferon-gamma predominance foster development of such

responses, as in psoriasis (Smith and Germolec, 1999; Street and Mossman, 1991). The Th17 lymphocyte phenotype contributes to autoimmunity through procuring neutrophil chemo-attractant and activator cytokine IL-23 (Wild *et al.*, 1994). Several intracellular signal transduction pathways in the Treg (Suppressor) lymphocytes may be deregulated leading to inappropriate activation of naïve T cells and persistence of autoreactive cells in organ (Jain *et al.*, 2010). Altered quantities of STAT-3 (signal transducers and activators of transcription) influence autoimmunity in varied ways. There is direct selection, favouring Th-17 pro-inflammatory phenotype over the immune-inhibitory Treg phenotype of lymphocyte subsets. STAT-3 also influences vital T-cell biology of growth and survival as well as transcription of pro-inflammatory genes (Egwuagh, 2009).

The microbes may initiate autoreactivity by several mechanisms (Ercolini and Miller, 2009). Infection induced general proinflammatory environment serves as a bystander to promote deregulation of immune response and modification of endogenous proteins to autoantigens. Alternatively some microbial antigens may mimic structurally homologous self peptide of the host which initiates immune response. The increasingly emphasized mechanism

however, is production of super-antigens by certain microbes. These nonspecifically crosslink MHC-II to T cells primed to other antigens including self-antigens, leading to unintended stimulation and massive release of cytokines (Freidman *et al.*, 1991; Schiffenbouer *et al.*, 1998).

Intestinal dysbiosis generates endotoxin-peptidoglycan super antigens inducing autoimmune/inflammatory pathology in psoriasis. Immune response is directed at toxins produced by microorganisms in the gut, and psoriatic patients exhibit positive skin test to gut bacterial antigens (Baker *et al.*, 2006a; 2006b; Gyurcsovics and Bertok, 2003; Karotkii and Peslyak, 2005; Qayoom and Ahmed 2003; Stenina *et al.*, 2003). Gut and skin colonization by *Staphylococcus aureus*, malassezia, and candida, etc. cause exacerbation in psoriasis (Fry and Baker 2007). Autoimmune reactions can be advanced or blocked by commensal bacteria affecting the innate and adaptive arms of immune responses and interlinking mechanisms. Whether immunity and autoimmunity is affected by specific or multiple lineages of microbes that may shift the homeostatic balance toward reduced or exaggerated reactivity in host-microbiota interaction, is yet unsettled (Chervonsky, 2013).

New genomic understanding indicates collective metagenome (Interactive

microbe-host genomes) as determinant of outcome of host-microbiome interactions. Diverse microbial metabolites may affect expression of genes associated with immune responses and autoimmunity. Microbiota accumulates incurring adaptations to persist, with the genes impacting the disease process. Success in reversing autoimmunity by reduction of microbes that have evolved capability to block vitamin-D receptors and thus evade immune-elimination supports the view (Proal *et al.*, 2009). Huge load of metabolites resulting from over million microbial genes, are juxtaposed to interact with small number of proteins made by human genes. Immune function thus is manipulated (Honda and Littman, 2012). Genetic predisposition leads to adverse consequences following interaction with other entities. Altered cytokine profile can change cellular milieu and xenobiotic exposures may vitiate the micro-world of immune cells. Altered gene expression as a result of an epigenetic change and surge of proinflammatory mediators weakens immune regulation and tolerance. The risk of autoantigen availability and consequent autoimmune disease therefore increases (Pillai, 2013).

### **Involvement of Gut-brain Neuro-immune axis**

Dendritic cells in the gastrointestinal (GI) tract send processes throughout the gut

epithelium in the lumen to interact with microbes. The signals to humoral immune system to produce immunoglobulin A secretion prevails (Corthesy and Spertini, 1999). The secreted IgA checks microbes from penetrating gut epithelium. The dendritic cells are in close proximity to the nerves in GI tract and their function is modulated by sensory neuropeptide CGRP (Calcitonin gene related peptide) (Hosoi *et al.*, 1993). The brain is informed about microbiota via the vagus nerve (Gochler *et al.*, 1999). Bacterial endotoxins or inflammatory cytokines like IL-1 $\beta$  and TNF- $\alpha$  may stimulate the vagus nerve. The vagal reflex in response, suppresses proinflammatory cytokine release by intestinal macrophages (Borovikova *et al.*, 2000).

The gut-brain axis modulates the feeding behavior as well (Bercik *et al.*, 2009). Peripheral afferent nerves transmit “danger” signals and elicit neural reflexes, regulating immune responses. Prototype inflammatory reflex operates through afferent sensory and efferent motor vagus nerve fibers (Tracey, 2009). The central projections regulate hypothalamic-pituitary-adrenal (HPA) neuro-humoral axis and causes glucocorticosteroid release. The afferent vagal activity triggered by endotoxins and cytokines, also sends efferent signals to thymes and the splenic nerve (Rossa-Ballima *et al.*, 2008). Spleen is the primary target for

signals in the efferent pathway of vagal antiinflammatory reflex. Over 90% of systemically released TNF- $\alpha$  during early endotoxaemia, is of splenic origin. Vagal stimulation attenuates TNF- $\alpha$  release. Vagus effect is mediated through adrenergic splenic nerve activation and  $\beta$ -2 adrenoceptors mediate inhibition of TNF- $\alpha$  release (Vida *et al.*, 2011). The mechanism of precipitation and aggravation of psoriasis lesions by  $\beta$ -adrenergic blocking drugs is thus explained. The innervating vagus nerve fibers coordinate with the gut microbiome via bidirectional communications (Lee and Mazmanian, 2010).

### **Dietetic Management of Gut Microbiota**

Diverse commensal bacteria reside in the gut. Individual species appear to have distinct and opposite roles in gut immune response. Certain commensal microbes preferentially drive regulatory Treg lymphocyte development, while others promote pro-inflammatory Th1 $\gamma$  cell development in gut lymphoid tissue (Kamada and Nunez 2013). Altered microbiota associates with several inflammatory diseases (Kamada *et al.*, 2013).

Microbiota in gut serves a number of nutritional health effects. The composition and performance is influenced by diet, as a key factor. Dietetic strategy attempts to

suppress harmful bacterial species while stimulating beneficial bacteria. Such a strategy implies selective consumption of probiotics and/or prebiotics and diet rich in fiber content.

### **Prebiotics**

Most plant origin foods contain dietary fiber. The fibers undergoing bacterial degradation include polysaccharides e.g., resistant starch, pectin, inulin, guar gum and oligosaccharides. Structural polysaccharide like cellulose and lignin are insoluble and are not degraded by bacteria e.g., wheat bran. Such components have ability to hold water and thus increase mass of stool. This facilitates motility and cleansing of gut microbial mass. Soluble fibers also increase fecal output and promote bacterial biomass via fermentation. Prebiotics are non digestible food components that selectively enhance growth and/or activity of one or limited bacterial species with beneficial health consequences. Prebiotic has to remain undigested and unabsorbed in upper segment of GI tract. The majority of prebiotics are oligosaccharides, however some polysaccharides also serve as substrates to colonic bacteria and stimulate their activity. Prominent prebiotic activity is seen with non-digestible oligosaccharides including xylo-oligosaccharides, galacto-oligosaccharides and isomalt-

oligosaccharides (Van Loo *et al.*, 1999). Anaerobes constitute over 99% of fecal flora. These break down the available carbohydrate substrate to short chain fatty acids, acetate, propionate, butyrate and gas hydrogen and carbon dioxide. Propionates and acetates are absorbed and contribute to the fuel resource of the body. Butyrate is a preferred energy resource for colonic epithelium and plays a role in proliferation and differentiation (Litvak *et al.*, 1998). The hydrogen generated through fermentation reactions is primarily used by methanogenic, acetogenic or sulfate reducing microorganisms (Gibson *et al.*, 1990).

Stimulation of Bifidobacteria and Lactobacilli is advantageous due to their immuno-modulatory abilities and inhibitory potential against pathogens. These reduce ammonia formation and lower blood cholesterol, and serve to restore gut microbiota damaged by antibiotics (Goldin, 1998). Selective stimulation of indigenous beneficent microbe strains, impart antimicrobial potential of prebiotics. The beneficent microbes selectively possess exoglycosidase enzymes that enable utilization of oligosaccharides (Perrin *et al.*, 2001). The uptake and intracellular metabolism by the microbes as an alternate strategy (even by non-beneficent microbe) is a possibility. Prebiotic selection needs refinement for avoiding the later alternate

pathways. Antimicrobial potential is particularly vested in smaller prebiotic molecules e.g., chito-oligosaccharides (Vishnukumar *et al.*, 2005). Bacterial species have different preferences for energy substrates. Diet is a strong direct means of influencing gut microbial colonization. Dietary fiber effectively causes major shifts in composition of gut microbiota and directly affects mucosal immune system. Fiber therefore improves chronic inflammatory disorders and systemic immune responses. Anti-inflammatory potential is contributed through short chain fatty acids generated upon microbial fermentation of prebiotic components (Huda-Faujan *et al.*, 2010). Butyrate is richly produced from resistance starch, soluble fiber, and inulin foods and increases the regulatory Treg lymphocyte percentage with reduced production of interferon- $\gamma$ . As a consequence, there is down regulation of inflammation (Vieira *et al.*, 2013). Higher levels of butyrate causes activation of nuclear transcription factor and peroxisome proliferator activator receptor gamma PPAR- $\gamma$  (Luhrs *et al.*, 2002; Schwab *et al.*, 2006). PPAR- $\gamma$  activity inhibits proinflammatory pathways like STAT, AP-1 and NF $\kappa$ B pathways, specifically desired in psoriasis management (Sertzing *et al.*, 2008).

Acetate is produced in greater abundance than butyrate following

fermentation. Acetate levels are raised more in circulation than in the gut due to absorption. Immune cells bear specific G-protein coupled receptors for binding the small chain fatty acid ligands. Specific GPR43 receptor mediated protection against colitis through induction of Fox P3+ IL-10 producing regulatory Treg cells has been demonstrated (Smith *et al.*, 2013). Prebiotics inhibit pathogen adherence to gut epithelium, with positive effects on lipid metabolism and stimulation of mineral (especially calcium) absorption in colon, through influencing the gut microbiota (Gibson and Roberfroid, 1995).

### **Polyphenolic Bioactive Food Constituents**

Colonic microbiota serves as primary agents for metabolism of polyphenolic dietary constituents. These are esters, glycosides and polymers contained in fruits and vegetables and bear protective antioxidant potential. Citrus fruits, apples, grapes, berries, wine, tea, soy and many vegetables including onion are rich sources of dietary polyphenols comprising complex mixtures. The nature of the gut microbiome therefore, determines extraction of their bioactive antioxidant and anti-inflammatory principles. Polyphenolics like isoflavones and flavonones are absorbed to a small extent. Proanthocyanidines and anthocyanidines

are obligatorily metabolized by gut microbiota (Manach *et al.*, 2005). Strategic modulation of composition of gut microbiota may enhance utilization and bioavailability of polyphenols and their potential health benefits. Synergistic benefit of simultaneous oligosaccharide consumption is observed with isoflavones (Mathey *et al.*, 2004; Piazza *et al.*, 2007).

### **Probiotics**

Two bacterial phyla, Bacterioides (bifidobacteria) and firmicutes (lactobacilli) comprise over 90% of the gut microbiota (Mariat *et al.*, 2009). These produce large number of vitamins including the B group vitamins; synthesize amino acids; and carry out bio-transformation of bile; and ferment undigested fiber and mucus. Beneficent microbes produce antimicrobial substances and promote mucin secretion and directly interfere with pathogen adherence to the epithelium (Rogier *et al.*, 2014). The bifidobacteria and lactobacilli can be introduced in the gut and encouraged to multiply as probiotics by supplementing prebiotic rich diet. Administration of these probiotic strains in healthy individual enhances mucin and nonspecific IgA secretion and the phagocytotic potential of surveillance cells.

Thus, probiotic strengthens the gut barrier and opposes entry of foreign

antigens. Attenuation of proinflammatory responses adds to this. Probiotics compete for nutrients at the site of attachment to gut epithelium and inhibits colonization by pathogens with simultaneous release of antimicrobial products. Generation of lipopolysaccharides and peptidoglycans detrimental to the host is checked by probiotic mechanisms (Tlaskova-Hogenova *et al.*, 2004). A major role for peptidoglycans is emphasized in psoriasis pathogenesis (Baker *et al.*, 2006). The development of regulatory T cells, the Type1 and Type2 helper T cell and Th1 $\gamma$  helper cells are all subject to signals by intestinal microbiota. The pro-inflammatory responses attenuated by probiotics include IL-8, MCP-1, MIP-1 and RANTES, proinflammatory cytokines and lipid mediators evoked by pathogens. RANTES activation is of major pathogenic significance in psoriasis (Raychaudhuri *et al.*, 1999).

Stable health promoting relationships between host gut and microbiota is crucially determined by pattern recognition receptors viz. Toll like receptors (TLRs) and Nod like receptor (NLRs) (Abreu, 2010). Microbe associated molecular patterns signal to affect epithelial cytoprotection, survival/proliferation pathways and barrier function (Rakoff-Nohoum *et al.*, 2004). TLR activation upregulates proinflammatory mediators facilitating

immune defense. The NLRs are present in the cytoplasm of immune cells and their stimulation by commensal associated signals regulate inflammatory responses, contributing to gut homeostasis (Yeretssian 2012). Disturbed interaction of microbiota with pattern recognition receptors underlies diseases with exaggerated inflammation (Lavelle *et al.*, 2010; Maynard *et al.*, 2012). An investigation of mechanism by which specific probiotic strain triggers reaction can help to indicate appropriate choice of probiotic for prophylactic use in diverse inflammatory diseases. The probiotic benefit is external to gut through complex microbe-immune system interaction in immune mediated inflammatory diseases. The gut-brain axis and inflammation reflexes have a bearing in this context.

Dysbiosis of gut microbiome may be a secondary consequence of a primary adversary that must be diagnosed and managed. The metabolic phenotypes of individuals determine the composition of gut microflora independently of dietary pattern or even genotype (Serino *et al.*, 2012). Long term consumption of high fat diet impacts the microbiota directly, and indirectly through alteration of redox state. Antioxidant dietary supplements improve gut microbiota profile (Espley *et al.*, 2014). A protective potential of gut microbiota against pathogen invasion is promoted by prebiotic combination with



other bioactive plant principles and quality proteins in the diet. Lupine fermentation is noteworthy in this regard (Berthkiene *et al.*, 2013). Probiotic administration by rectal route is far superior to oral route for successful immuno-modulation (Matthes *et al.*, 2010).

### **The Pathogenic Gut-skin Linkage in Psoriasis**

Cytokinaemia and exaggerated inflammation in psoriasis is crucially linked to absorption of endotoxins from pathogenic gut bacteria (Gyurcsovics and Bertok, 2003). A strong evidence of defective barrier function of gut is observed (Scarpa *et al.*, 2000). Immunopathologic process in psoriasis extend from gut to skin (Michaelsson *et al.*, 1997). The evidence is compelling to address issues of gut barrier integrity and dysbiosis as a rational consideration in psoriasis therapy. Psoriasis therapies are conventionally focused on managing the consequences of immune mediated

inflammatory pathology and causes several adverse effects. Regular incorporation of prebiotic and probiotic dietetics is a rational consideration, neither too expensive nor unsafe. Its significance particularly appeals for prophylaxis in individuals with familial predisposition, and subjects bearing other heightened risk factors (Gupta *et al.*, 2013). Evidence based personalized pre- and pro-biotic dietetics in management of psoriasis has appeal. This is challenging however, microbiome management is subject to individual contexts and not amenable to ordinary laboratory means. Metagenomic investigations may be a solution to match the indications, with appropriate dietetic address. This may comprise a rational and lead to better quality management for psoriasis and autoimmune inflammatory diseases at large.

### **CONFLICT OF INTEREST**

The authors claim no conflict of interest.

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