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Research Article

FACTORS INFLUENCE INTESTINAL MICROBIOTA IN PATHOGENESIS OF INFLAMMATION BOWEL DISEASE

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ABSTRACT

Pattern diversity has been reinforced in various body inhabitant include gut. Gut as a microbial inhabitants interact with host immune system and influence both innate and adaptive immune function. Emerging studies referred gut among the major sites of microbial inhabitant in human body.

Commensal enteric bacterial and fungi gives antigenic stimulation that rides pathogenic adaptive immune response both in genetically defects and innate bacterial killing cause recruitment of microbial antigens that can lead to activation of immunological tolerance by the mucosal immune system.

Alteration of microbial composition and function in IBD causes increase immune stimulation and mucosal permeability enhanced and epithelial dysfunction, as a result of continuous stimulation of pathogenic immune response that may cause host genetic defects in mucosal barrier function, innate bacterial killing and immunoregulation.

Studies had it that antitumor necrosis factor-α (TNF-α) therapy reduced mucosal inflammation and reduced intestinal permeability in IBD. Other agents such as butyrate, zinc and probiotics also ameliorate mucosal barrier dysfunction but availability are limited. More research is needed to identify the potential therapeutic target in IBD.

INTRODUCTION

Inflammatory bowel disease is the group of intestinal disorders that affect digestive tract system (mouth, esophagus, stomach, small and large intestine)which are responsible for breaking down food, extracting nutrients, removal of unwanted material and waste products. IBD can be very discomforting and impede the normal process of digestive tract system. The two major diseases under umbrella of IBD are Crohn's diseases and ulcerative colitis.

Crohn's diseases is a one form of IBD, a disorder that characterized by inflammation in the gastrointestinal tract GIT. It can affect any area in the GIT, from the mouth to the anus, inflammation usually in the ileus or end of small intestine.
Ulcerative colitis is a persistent or long-lasting condition which results in ulcers and inflammation of the colon. The initials symptoms are abdominal pain and diarrhea mixed with blood. Others like fever, anemia, loss of appetite and weight loss. These symptoms can range from mild to severe or intermittently as the case may be.

Colitis is an inflammation of colon (large intestine). It may be acute and long-term but most of the time, the cause is unknown, although they are other possible causes but not yet ascertain. Colitis can be referred to crohn disease at a time when diagnosis is unknown while ulcerative colitis applied when known cause of disease is determined. These associated with dysregulation of mucosal immune system response and level of stress experience [1,2], in line with report on different life exposure of stress [3]. However, exacerbation also reported in acute colitis [4].

Inflammatory bowel diseases is the main agitator of colon and intestinal dysfunction that engineering these deadly diseases, although it can influence by different factors [5,6]. Study emphasized caused by genetic [7] and environmental factors [8-11]. The causes remain misery but from recent findings from different researchers show great hope. These causes includegenetic factor, environmental factor, immune system disorders and normal gut bacterial changes. There is increase rate of this disease in developed countries and as a result of

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lifestyle, diets or exposure to floral infection. Removals of inflamed appendix at an early age have decreased significant protection of ulcerative colitis than in Crohn's diseases[5], these promising therapies of ulcerative colitis.

Acute versus chronic Crohn's disease and ulcerative colitis Crohn's diseases and ulcerative colitis UC are two main inflammatory bowel diseases. Both are chronic diseases that cause inflammation in the digestive tracts, showing symptoms like stomach pain, diarrhea, weight loss, loss of appetite, anemia, bleeding ulcers (hemattochezia). UC is most common form but sometimes can be mistaken as Crohn's diseases. Causes are unknown but emphasis is pointing at genetic, environmental factors, microbiological factor and immune system. There are differences in both conditions which their treatment may vary[5,6].

Study has been reported to promote chronic stress [12]. Of note the composition of gut microbiota changed after stress induction. Also has been reported to affect the pathogenesis of disease immunological animal models[13]. Chronic stress disturbs gut microbiota, triggered immune system response and facilitate DSS-induce colitis in animal model[12]. In other hand exacerbation was also reported in acute colitis[4].Continuous exposure to psychological stress with DSS-induced colitis was reported to aggravate the colitis in murine model[14], which also reported in another study[15]. However, chronic stress has been known to induce variation in GI microbiota which accelerate the inflammation of the gut, revealed significant reduction in intestinal microbial species and an increase in pathogenic intestinal murine[16,17]. Correspondingly, study on psychological stress impact on gut microbiota[18].

Genetics of gut Microbiome in IBD

The gut is among the major sites of microbial inhabitants in human body, it harbor diverse microbes that plays important roles in the well-being of their host. The diversity and composition of human microbiome and microbes in healthy and disease is complex[19]. The human microbiome composition can be affected by different factors like genetics, environment such as dietary[20,21], drugs and intestinal motility[22], physiology[23]. The microbial composition between mucosal immune response and intestinal microbiota of IBD and CD are being disturbed[24], thus genetic susceptible to disease influence on the gut microbiome varies among human distinct in genus and species[22]. The individual connection and human associated inhabitants between microbes[25], immune function[26], and metabolites[27]which influence the development of microbes starting from birth (infant) to disease state[28-31], in the early interaction of immune system to commensal believed to occur through the passage of birth canal and colostrum of which certain factors in the breast milk like immunoglobulin –A, immune cells-cytokines metabolites, living microbes in breast milk[29,32] involved. However, association of specific disease to the taxa should be intense[22].

The human genetic variant studiesassociated with different human diseases[33], have been established such as in obesity[34,35] alcoholic liver disease[36], IBD[37]. But microbiota diversity of uncharacterized gene and species based on large scale microbiome profiling project[23,38-41] are rare variants of small effect which are very hard to identify by genetic means[42] but systematic identification[43].Alteration of microbial composition and function in IBD may cause an increase in immune stimulation, mucosal permeability enhanced and epithelial dysfunction. These as a result of continuous microbial antigenic stimulation of pathogenic immune response which cause by host genetic defects in mucosal barrier function, innate bacterial killing and immunoregulation such as in Escherichia coli[24].Another study showed mdr1 exonic single nucleotide polymorphism (SNP) association in UC, T-allelic frequency significantly increased[44].

Microbial Influences in Intestinal Inflammation

The highest intestinal bacterial concentration is mainly in the intestine of which Crohn's disease and ulcerative colitis are occurring at the colon and distal ileum. The microbial agents in the pathogenesis of IBD are suggested by experimental and clinical studies[24], of which the composition and function of microbiota in IBD showed abnormal pathogenesis[37,45]. Study was shown of bacteria increase associated in mucosal of CD[46]. More study in patients with functional alterations in CD was identified showing adherent-invasive E.coli (AIEC) that colonized the GIT[47], consistent with another report of E.coli strain at high frequency isolated from ileal mucosal of patient with CD[48,49].AIEC strain can invade epithelial cells which has been confirmed in mucosal ulcers of CD[24] and patients reported of high level of elevated of AIEC[47,50], these suggested that mucosal-associated flora correlate with CD phenotype in dysbiosis of the ileal and could be the therapeutic value in CD.
The factors underlying IBD which was established with a dominant negative N-cadherin mutant in mice, showing functions of epithelial barrier on intestinal inflammation[51]. The development of ileal inflammation as a defect in the epithelium shown by SAMP mice in the absence of commensal bacteria decreased barrier function[52]. The defect originated by nonhematopoietic cells. Also in murine multiple drug resistance (mdr) genes showed a severe intestinal inflammation seen in mydra$^{-/-}$ knockout mice[53].

Pathogenesis of IBD

The gut commensal microbes shape the mucosal immune system[54,55], and induce colonic regulatory T-cells[56]. The human microbiota and microbiome inhabitant are really diverse. And pattern of diversity has been reinforced in various body inhabitant[23,57], and gut[25,58]. Changes in microbiota composition are sufficient to motivate disease. Abnormal composition of intestinal bacteria dysbiosis is characterized by CD[59]. Studies showed that alterations in the composition of the intestinal microbiota are characterized by reduced diversityin IBD caused intestinal inflammation. The interaction between host and environmental factors (microbiota) are said to be implicated in IBD[60].

The functional changes of epithelial cells and macrophages of GIT patient with IBD showed AIEC colonization[47]. These were also confirmed of the ileal mucosal-associated microflora in CD showing correlation with an ileal CD phenotype ICD[50]. E.coli strains association with granulomatous colitis of boxer dogs GCD of which study reported to have AI phenotype and E.coli in phylogeny[61].

Commensal bacteria species can produce toxin and cause experimental and clinical intestinal inflammation[62], clostridium difficile has beenat high increase in IBD.Correspondingly,

another report associated enterotoxigenic Bacteroides fragilis (ETBF)with IBD which significantly enhances the colonic inflammation in DSS-treated mice[63,64], ETBF are strains of B.fragilis that secrete a 20 kDa heat-labile zinc dependent metalloprotease toxin (B.fragilis toxin) BFT[64]. Report on adherent-invasive Escherichia coli both in CD[47]and UC but different proportions[46,47].

Intestinal Microenvironment of Normal and Diseased

Intestinal mesenchymal cells IMCs can control immune reaction and inflammation and modify proliferation. The developments of intestinal environment associated with immune system in normal homeostasis are unique and in diseased state triggers by inflammation increase intestinal permeability. Normal mesenchymal cells protect intestinal structure and preserve homeostasis. The intestinal mesenchymal cells IMCs of the intestinal lamina propria was listed[65,66], others but does not in agreement with IMCs unique properties[67,68], although may have strong association with many human diseases character ices. Remarkably, GIT and intestinal cells of cajal physiological and pathological roles have been described[68]. However, fibroblasts are found in lamina propria of the colonic epithelium which regulates epithelial diversity and proliferation of extracellular matrix scaffold ECMs by cancer-associated fibroblast (CAF), also play roles in progression, growth and spread of cancer[69]. Another study confirms CAF to influence innate and adaptive immune responses in colorectal cancer CRC[70]. CAF regulate tumorigenesis, of which tumor microenvironment has emerged as a target in cancer therapy. Study had it that CAF promote tumor growth and invasion. Of note CAF and immune cells secreted by cytokines mediated by tumor immunity thereby exert promoting effect and tumor-suppressing[71,72]. Result to pathological situations in which failed to switch off from acute inflammationto adaptive immunity and tissue repair[73]. Therefore, CAFs have effect in stimulating tumor growth and progression[74].

In microenvironment of disease state, the inherent plasticity of fibroblasts such as CAFs modulates the tumor microenvironment and influence the behavior of neoplastic cells. Either bytumor inhibiting or promoting manner yet its origins and functional features is not established[75]. Although, many of the CAFs has been revealed to have poor prognosis. Study identify disease relapses associated with increased frequency of tumor initiating cells of note enhanced by transforming growth factors TGF-β signaling[76,77]. CAFs have been defined as heterogeneity in the field of tumor biology. Establishing the biomarkers of CAFs and drug targets to improve treatment of cancer, however described different subdivisions of diverse subsets of mesenchymal cells[78]. Studies have identified human origin of fibroblasts in various human tissues expression and roles, relating to multilineage potential which distinguish fibrocytes from fibroblasts and microphages[67]. Accordingly, confirm that fibrocytes transition is controlled by caspase activation and expresses various chemokine receptors which migrate in response to some factors[67,79]. Overexpressed stromal cell-derived factor-1(SDF-1) and CXCL12 induce gastric dysplasia and tumor formation resulting to epithelial hyper proliferation[80,81], also increases αSMA-positive myofibroblasts via recruitment of MSCs. In line with this report that elevated level of SDF-1 and CXCR4 associated in with gastric cancerin intestine-type[82]. However, in intestinal wound healing revealed mesothelium developmental restriction to smooth muscle but maintained fibroblasts[83], likewise in intestine of gut vasculature[84].

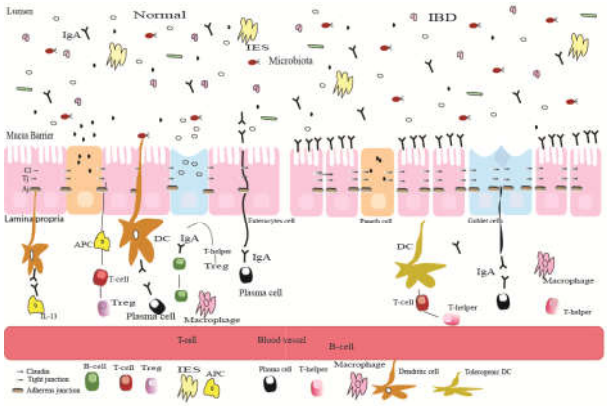

Figure 1.In normal sate, microbiota and host gut are supposed in mutual relationship. In diseased state, based on genetic factors, exposure to antibiotics, drugs result to an imbalance between mucosal barrier lead dysfunction of intestinal epithelial andalteration of gut microbiota composition trigger inflammation. Colonize intestinal mucosal became resistance and will activate pathogenic T-cell. In absence of commensal bacterial decreased barrier function and develop inflammation.

Epithelial cells dysfunction and proliferation

Intestinal epithelial cells IECs also play role in maintenance of relationship between gut microbiota and host by secreting various immunological mediators (cytokines and chemokine), delivering bacterial antigens and constructing mucosal barrier[85]. These IECs secretions modulate host immune response and maintained relationship between immune system and gut microbes by mediators, induced T-cells immune responses and deliver APC, also involves antigen specific responses immunoglobulin A (IgA)[86]. IEC expresses pattern recognition receptors PRR such as TLR and NOD.

Intestinal mesenchymal cells IMCs secretes transforming growth factor beta TGFβ, epidermal growth factor EGF, FGF2, PDGF, vascular endothelial growth factor VEGF, HGF to modulate IECs proliferation, differentiation, apoptosis, transformation, migration and invasion, of which TGFβ recruit and promote mesenchymal cells in order to activate initiation and progression of carcinogenesis[87,88]. They are various mucosal barrier covering epithelial cells such as goblets, paneth cells, of which they work hand in hand to maintain gut microbiota and host immune system. They also have different mucosal barriers (physical and chemical), that work by preventing intestinal inflammation between (gut microbiota and host immune cells) when existed[86].

Environmental factors and host immune dysfunction contributed to development of IBD[89], thus gut immune system involved in a symbiotic milieu. The relationship between mucosal barrier dysfunction and intestinal inflammation was confirmed in colitic mice showing (Muc2) mucus barrier separating bacteria from epithelia[90,91]. Consistent in goblet cells-induced mucus secretion, thus control intestinal host-microbial mutualism[92,93]. Furthermore, adaptive protein AP-

(1B) deficiency caused epithelia immune dysfunction by reduced expression of antimicrobial protein and impaired secretion of immunoglobulin A [94]. Of note that IECs that stimulated gut environmental factors, do interact with host immune cells to modulate gut immune responses, in the sense that host immunity require to adapt these alterations in the gut environment such as pathogenic bacterial infection and dysbiosis.

Mucosal Immune Response

The gut microbiome has intimate interaction with the host immune system and can influence by both innate and adaptive immune function[95], which include neutrophils, dendritic cells, natural killer cells. The development of T-cells subtypes associated to a particular microbiome[96], of which adaptive immune response involved in the B-cells and T-cells activation. Notably, gut microbiome function and bacterial composition change associated with dysbiosis in an increase of oxidative stress thereby motivate a chronic inflammation response[97], which indicated that inflammation response have connection between immune system and gut microbiome. Study identified organisms that have ability to exacerbate inflammation with a reduction among members of its microbial community known to produce short chain fatty acid SCFA[98], whereas in gut epithelium the deficiency of fatty acid: butyrate acids have ability to raise an inflammatory responses[99].

Cancer-associated fibroblasts CAF influence innate and adaptive immune response[70]. Disruption of homeostasis in intestinal epithelial cells or lamina propria innate or adaptive immune cells can results to pathogenic immune response to chronic intestinal inflammation and commensal bacterial[100]. Of note triggered environmental factors that which disrupt the mucosal barrier and altered balance. These changes were seen in patient with CD, UC[37,46,50,101].TGF-β1 and NF-$_K$B signaling induced in vivo bacterial colonization in colonic expression[102]. Signaling pathway maintained intestinal homeostasis to commensal bacterial. Demonstrated changes in intestinal microflora of DSS-induced colitis, and role commensal bacterial play in mucosal homeostasis[103]. In addition, study reveal that microbial composition alteration of balance between Treg and T helper cells resulted to an inflammation in IBD[10]. Intestinal myofibroblasts plays role in innate immune responses of CD-associated fibrosis which expresses TLR in activation[104,105]. Myofibroblasts are part of innate immune system and contribute to intestinal wound healing. Study showed an increased activation of intestinal immune system of pro-inflammatory cytokines secretion in stressed DSS mice[14]. A mutation in NOD2 caused significant decrease in alpha-defensin of paneth cell establishing link between Wnt-signaling pathway transcription factors Tcf-4 in IBD[106]. Likewise, TLR signaling pathway showed a protective role through Myd 88 in hematopoietic and nonhematopoietic cells mediate epithelial repair response, activation of an adaptive response and facilitate killing of bacteria[106-108]. Murine 2 deficient mice showed epithelial apoptosis that caused inflammation[91]. The effect of commensal bacterial is to maintain mucosal homeostasis by inhibiting pathogenic innate and adaptive immune responses.

Influence of drugs and chemical induced colitis in IBD

The human gut microbiome composition can be affected by different factors like genetic, environment such as diet, intestinal motility and drugs[22]. Exposure to antibiotics is the major stressor to the intestinal microbiota. Upon disruption of healthy gut microbiota, of which can caused by exposure to antibiotics and application of probiotic and drugs[109,110]. Defective microbial killing can result in an increase exposure to commensal bacterial and activation[24], consistent to pathogenic T-cells activation in CD[108]. These can disturb role innate immunity plays in early initiation of the inflammatory state. Contributeto the development of CD, study has reported that non-steroidal anti-inflammatory drugs influenced the innate immune system impairment[111], which suppressed oxidative function of neutrophil. Other study revealed intestinal microbiota changes upon antibiotic induced[112], suggested caused by mucosal immune defenses activation. Report counted antibiotic among intestinal domination as stated, when the diversity and stability of the intestinal flora are disrupt[113]. In addition, disruption caused by exposure to antibiotics, of which antibiotic kills native intestinal bacterial[114]. Inflammation of gut changes microbiota composition disrupt colonization resistance thereby enhance growth of enteric pathogens[110]. The relationship between microbiota and host supposed to be mutual in normal healthy gut, but the presence of microbiota disrupts the compositions which are introduced at birth[28,31]. Thus most pathogen colonized intestinal mucosa became resistance[110]. Furthermore, antibiotic disrupts the colonization resistance in normal gut by triggering mucosal inflammation[110], and this have been linked to pathogenesis of obesity[35,115].Alterations in intestinal permeability play role as a primary defects and may be an etiology factor in IBD[116], IL-13 identified as effector cytokines that influence epithelial barrier function, apoptosis and cell restitution[117], and familial permeability defect among relatives in CD[118].

DISCUSSIONS

The mutual relationship exists between microbiota and host disrupts the composition by the presence of microbiota in normal health gut which was introduced at birth[28,35], through canal and colostrum (IgA)[29,32].Changes in microbiota composition are sufficient to motivate disease. Alteration in the composition of intestinal microbiota are characterized by reduced diversity in IBD[60], which caused by intestinal inflammation are implicated in IBD[60], and intestinal bacterial dysbiosis characterized by CD[39]. Alteration of balance between T_{reg} and T_{helper} cells results to an inflammation, of which intestinal permeability play role as primary defect and etiology in IBD[116]. Various mucosal barrier covering epithelial cells are goblets cells and paneth cells of which they work together in order to maintain gut microbial and host immune system towards preventing intestinal inflammation when existed[86]. Exposure to antibiotics is a major stressor to intestinal microbiota, and application of probiotic and drugs[109,110]. Antibiotics destroy the colonization resistance in normal healthy gut by triggering mucosal inflammation which linked to pathogenesis of obesity[35,115]. Most pathogens colonized intestinal mucosal became resistance[110].The defective microbial killing increased exposure to commensal bacterial result in activation of pathogenic T-cell in CD, thus disturb role innate immunity plays in early initiation of inflammatory state[108]. In

the absence of commensal bacterial decreased barrier function, which developed ileal inflammation as a defect in the epithelium originated by nonhematopoietic cells[52]. As a result of continuous stimulation of pathogenic immune response that cause host genetic defects in mucosal barrier function, innate bacterial killing and immunoregulation[24].It has become a scourge in the treatment of IBD. Therapies usedin the treatment of IBD such as antitumor necrosis factor-α (TNF-α), zinc, butyrate and probiotics which ameliorated mucosal barrier dysfunction in IBD[119]. Still more researchis needed to identify potential therapeutic target in IBD of which availability are limited. Also necessary to monitor and regulate intestinal health.

Declaration of Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of this review.

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