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A Contextual Analysis through Cellular Signaling Pathway, Immunogenicity and Mechanism of Action in T- Cell Activation on Gut Microbiome

Review Article

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Abstract

The gut, or digestive tract, is the main functional system of the human body that controls the intestine for accumulating gut microbes in the epithelial tissue. Intestinal immune cells are helping the gut microbiome environment to differentiate between intestinal epithelial barrier and immune function. The gut microbiota, or microbial community of the intestine, is the active companion of human health and includes the necessary functions of the intestine along with the distal and proximal organs. The gut ecosystem depends upon bidirectional microbiota-host communication without any direct cellular contact. According to the microbiota and host-derived extracellular vesicles (EVs), the main emphasis is given on performing inter-kingdom crosslinking. It is proven from previous accumulation of body that gut microbiota derived from bacterial secretion of certain vesicles helps to transport and deliver inside host cell effector molecules, which causes the modulation of host cell signaling pathways and cellular programming. But the gut microbiota, which secretes vesicles, has efficient effects on healthy or diseased conditions of the body. The recent background on microbiota EVs for controlling host metabolism, intestinal barrier, host pathogenic integrity, and immune training is highlighted in this study. [1]

The metabolic receptors of enigmatic inflammasomes in auto-immune diseases and crosstalk with innate immune regulators are dependent upon nucleotide binding domain and leucine rich repeat receptor (NLR). This NLR mediation of inflammatory activation is essential in host pathogenic response and danger-associated molecular patterns (DAMPs)-related metabolic disease. Several cellular metabolic pathways can cause interaction with NLRs, and in contrast to negative regulation, tumorigenesis and autoimmune disorders interact with multiple innate immune receptors and disease modulation. In the host pathogenic response, NLR activation is necessary in controlling metabolic pathways, which further target various levels of immune-metabolic diseases or syndrmes. The lesser known NLR studies of inflammasomes, which are activated by particular modes, further help to interact with metabolites and immune receptors, but however, the function of the procession of metabolic diseases is not described thoroughly. So, this study is evidence of targeted NLR activity in metabolic pathways and crosslinking with immune receptor connections in GPCR signaling, gut microbiome, and also the complement pathways of the immune system to understand the disease procedures. [2].

Keywords: Gut Microbiome; Bacterial Extracellular Vesicles (Bevs); Immunomodulation; GPCR Signaling; Homeostasis; Gastro-Intestinal Epithelium; Helicobacter Pylori

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Introduction

The gut environment in the human body is largely colonized by microbes that is all together called microbiome. In the intestinal tract microbial colonies are excess in number i.e., 10 times organisms per gram of wet mass of fecal composition in the colon. The gut microbiota or symbiotic microbial community is generally composed of symbiotic bacteria. In a combination gut microbiota contains huge genes which conveys human genome encoded genetic information. As a hidden organ gut microbiota contributes essential host cell functions. Gut microbiota provides immunogenic capacity of homeostasis and inflammation towards pathogenic interaction along with nutritional, metabolic and energy mediated activities. The gastrointestinal immune response has been associated with pivotal functional activities of the gut microbiota. [3]

Mammalian host pathogenic interaction is involved with the gut microbiota. This gut microbiome provides immunogenic protection of synergistic recognition. Pathogen associated molecular patterns are identified by pattern recognition receptors (PRRs) actively specify innate immune cellular functions. But downstream signaling process directly proceeds to phagocytic activities pathogens thus further it regulates effector immune cells. The structural and functional immune activity are in turn associated with the gut microbiome. Antigen processing cells APCs and peptide epitopes help to engulf foreign molecules and MHC class proteins are highly associated with TCR affinity by high specificity. The peptide antigen involves with the T cells activity for development of specificity and cellular or humoral receptor activities. [4]

Many commensal bacteria are the source of enzymes neither encoded by host nor intrinsic genome thus helping to the dietary components in digestive system and accumulating supplementary food items such as vitamins. Gut microbiota also protected from pathogenic infection by intestinal pathogenic bacteria or gastro-enteric pathogens through nutrient competitive environment. Mucus epithelium of intestine get immunity from gut microbiota. Microbial colonies in lumen and epithelial tissues are subjected to diversification by cellular vicinity. Mucosa in intestine is covered with finger like bulging called villi and glandular septum called crypts which accumulates nutrients and produce covered stem cell background. The sub-epithelium of intestine is composed of stem cells, goblet cells, neuroendocrine cells etc. [5]

Goblet cells secrets glycosylated mucins which further generates mucus matrix in the surface of epithelium to form large or small bowel. The luminal antigens are subjected to sub-epithelial APCs. The spongy mucus layer generated by goblet cells is locally releasing antimicrobial peptides in Paneth cells crypts. Apically situated microvilli exposed vesicles by IECs that have been affecting antimicrobial function. Catalytic activities of endometric vesicles secrets alkaline phosphatase to detoxify harmful bacterial endotoxins and prevents clumping of cells and also cease the cell division of entero pathogenic bacteria. Absorptive cells of gastro-enteric epithelium are diversified from gene expression and phenotypical characterization according with proximal-distal axis of intestine along with their anatomical integrity with different cell types or sub epithelial lymphoid structures, Peyer's patches, lymphoid follicles, FAE cells, M cells and phagocytes. [6]

The large and small intestine are structurally and functionally different and separated between duodenum, jejunum, ileum, caecum and colon. The composition is also varied from different pH level, oxygen tension, retention time of luminal composition, microbiota and bacterial capacity, density of immune stimulatory microbial ligands, cellular density of mucus layer, regulating gastro-enteric antimicrobial peptides, anatomy and surface structure. Villi structures, epithelial cell subtypes, enzyme secretion and metabolism of trans epithelial cells and transport capacities with immune cell subtypes. Intraepithelial lymphocytes (IELs) penetrate the epithelium between phagocytosis and dendritic cells to the antigenic luminal epithelial cells. [7]

Not only the microorganisms are present inside the human body but also gastro enteric tract is contained with diversified number of commensal, mutualistic or symbiotic bacteria mainly named as bacteroidetes, actinobacteria, proteobacteria etc. the microbial capacity inside the gastro-enteric tract is about 10_{12} CFU/ml to 10^7 CFU/ml in the intestine and 10_{14} CFU/ml in the colon. Due to the lesser oxygen consumption in the upper intestine itself present gram (+) ve coccus such as *Streptococcus sp.* but the anaerobic bacteria in the intestine and colon are like *Clostridium sp.* Luminal epithelium and mucus epithelium consist of microorganisms based on their mucus degradation. *Bacteroidesfragilis, Bifidobacteriumbifidium*are the most specific bacteria within mucus layer and it utilizes glycans body as a source of glycosidase, sulphatase and sialidase enzymes. Beyond the colony formation of commensal bacteria in the gastro-intestinal tract by glycan formation further targeted on the less polysaccharide content and the necessary host pathogenic mucin as an energy resource in the gut microbiome. [8]

Review of Literature

Gut Microbiota in relation to Unconventional T Cell Ligands and Immune Modulation

Multiple types of PRRs and TLRs, Nodded receptor, C- type lectin receptors helped to suppress diverse foreign molecules in diversified spatial or dynamic spectrum along with polar virus containing nucleic acids to adhering bacterial lipoproteins as in extracellular or intracellular environment. With similar structural and functional properties host pathogenic interaction proceeds to rapid activity of innate leukocytes. PRR ligands are specifically non self, ubiquitous structurally similar as microbial contents such as LPSs, TLR4 ligand or peptidoglycan agonist and virus or bacteria stimulatory nucleic acid ligands. Individual PRR ligands can possess as stringent structural properties to suppress wide variety of foreign molecules. However, a large variety of cells can treat against the common microbial pathogens that is an immediate response against host pathogenic interaction. Biochemical pathways developed pathogenic interaction to emphasize structural PRR ligands to recognize their necessary functions. Efficient immune response can process host pathogenic interactions with genetic diversity. [9]

As an effective complement activation of PRR type recognition and mammalian host derived foreign ligand recognition are contrary to each other. MHC class I and II components proceed to peptidoglycan and structural invariability. Structurally variable foreign molecules

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are active in mutation as T cell receptor recognizes mutated peptides. The unrequired and detrimental immune response activated by self-antigen capacity by eliminating peptide responding naive T cells is a negative selection. This Ag recognition by maintaining activated lymphocytes has been recognized with limited protection with known resource. Adaptive immunity and innate immunity are the first line defense mechanism which critically specifies host pathogenic interaction. [10]

Microbial regulation in the Gut responsive T cells through Interleukin- 6 produced by Enteric neurons

Enteric neurons to prevent inducing iTreg: Crosstalk between ENS neurons and Treg cells it is using "iTreg" system to induce FoxP3+. Muscle layers surrounding myenteric plexus were detached and inoculated into progenitor cell culture medium to activate ENS *in vitro*. Inhibition of iTreg by enteric neurons caused sensitivity by approximately 1/100 neurons per cultured CD4+ T cells. [1]

Inhibition of iTreg by Enteric neurons through cytokine factors: Expression of T cell mediated receptors inhibit iTreg to distinguish neurons and T cells. Cytokine receptors added to iTreg inducing cultures to induce T cell death through diethylenetriamine. But in classical pathway neurotransmitters or neuropeptides were not inducing the inhibition. Through gene expression the neurons distinguish between iTreg cells from Foxp3 reporter mice with or except neuron assimilated co cultures. [12]

Microbial assimilation on the neuron- Treg axis: Commensal gut microbes such as *Clostridium ramosum* induces RORγ+ Treg cells thus triggers neurons *in vitro*. The effect of mono colonization of GF mice on ENS structure and composition while high Treg inducer *C. ramosum* or non-inducer *Peptostreptococcusmagnus* affecting immunofluorescent imaging by colon segments like as antibodies recognized neuron cell bodies. [13]

Commensal bacteria by accumulating peripheral regulatory T cells produces metabolites

ExtrathymicTreg cells were generated through microbial metabolites in the specific pathogen free (SPF) mice but not antibiotics treated microbiota deficient mice or germ free (GF) treatment of mice. Few contaminated Treg cells expanded in CD4+ T cell population it is more effective in less Foxp3 containing mice. ExtrathymicTreg cell was involved *in vivo* by promotion of butyrate in antibiotic treated mice or in untreated SPF mice. Treg cell was increased in colonic lamina propia in CNS1 sufficient mice but not in CNS1 deficient mice thus it suggests that bacterial metabolite also suppress prominent Treg cell populations through Foxp3 protein stabilization. Treg cell population in butyrate treated mice is greater in Foxp3 protein concentration than butyrate free cultures. The ability of T cells and DC cells in preparing Treg cells *in vitro* the butyrate expression levels were non-mutually exclusive. Direct Treg cell promotes on CD4+ T cells to prosecute DCs by butyrate facilitation and differentiation. Treatment with DCs was able to facilitate Foxp3 expression in naïve T cells precursored by CD3 antibody and TGF- β except butyrate expression. Upon testing HDAC inhibitory activity two different types of HDAC inhibitors with distinct chemical nature a butyrate derivative known as phenylbutyrate used as a standard for controlling the experiment. However, through HDAC inhibition TSA and butyrate assimilated Treg cell was proceed for further DCs treated binding with butyrate and optimum TSA. [14]

GPCR signaling mediated Cross Talk between metabolism and inflammatory response

ExtrathymicTreg cells were generated through microbial metabolites in the specific pathogen free (SPF) mice but not antibiotics treated microbiota deficient mice or germ free (GF) treatment of mice. Few contaminated Treg cells expanded in CD4+ T cell population it is more effective in less Foxp3 containing mice. ExtrathymicTreg cell was involved *in vivo* by promotion of butyrate in antibiotic treated mice or in untreated SPF mice. Treg cell was increased in colonic lamina propia in CNS1 sufficient mice but not in CNS1 deficient mice thus it suggests that bacterial metabolite also suppress prominent Treg cell populations through Foxp3 protein stabilization. Treg cell population in butyrate treated mice is greater in Foxp3 protein concentration than butyrate free cultures. The ability of T cells and DC cells in preparing Treg cells *in vitro* the butyrate expression levels were non-mutually exclusive. Direct Treg cell promotes on CD4+ T cells to prosecute DCs by butyrate facilitation and differentiation. Treatment with DCs was able to facilitate Foxp3 expression in naïve T cells precursored by CD3 antibody and TGF- β except butyrate expression. Upon testing HDAC inhibitory activity two different types of HDAC inhibitors with distinct chemical nature a butyrate derivative known as phenylbutyrate used as a standard for controlling the experiment. However, through HDAC inhibition TSA and butyrate assimilated Treg cell was proceed for further DCs treated binding with butyrate and optimum TSA. [14]

GPCR signaling: G protein coupled receptor (GPCRs) are an extensive family of membrane receptor factors a part seven transmembrane α- helix domains with intracellular C terminal and extracellular N terminal. Canonical forms of GPCRs are containing intracellular region ligands, G proteins that targeted downstream signaling and β- arrestins that controls excessive activation. Occasionally NLRP3 can be interacted via GPCRs through different metabolites, ions, neurotransmitters, hormones such interaction triggers cross talk between metabolism, GPCR and NLRP3 signaling and inflammatory activities. Though acetate leads to GPR43 dependence on inflammatory activities through K+ efflux, Ca2+ influx and downstream hyperpolarization. In contrary acetate correlates with GPR43 in bone marrow derived macrophages (BMDMs) which suppress NLRP3 inflammasome via Ca2+ machinery through seizing of Ca2+ mobilization. [15]

Host-Microbiota Communication: Gut microbiota has commensal interaction with the microbes and enteric environment and metabolic activities in the gut are sensibly changing in the microbiota and gave signal transduction for regulating cellular mechanism including host PRRs such as inflammatory activation. In microbiota regulated metabolism inflammasomes were subjected upon regulation by metabolites NLRP6, NLRP3 and pyrin. In the higher expression of NLRP6 in the intestine ligand activities with bacterial components have been shown in the gut. Metabolomics and metagenomics studies in the caecum subjected to microbiota related metabolism and NLRP6 inflammatory activationwith downstream

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epithelial IL-18 metabolism and development of microbiota composition NLRP6 inflammatory protection. [16]

The complement system: The complement anaphylatoxin receptor in myeloid cells processed into NLRP3 inflammatory activation. ATP inflammasome complement axis is corresponded with DAMPs by inflammatory activation to promote sterile inflammation. High concentration of metabolite controls cholesterol metabolism and homeostasis by precipitating cholesterol crystals for inflammasome and pathogenicity in atherosclerosis. Autocrine complement activity initiates metabolic reprograming to activate T cell regulation and inflammation. Functional complement metabolism inflammasome axis specifically indicates T cells. [17]

Innate immune signaling in intestine for epithelial homeostasis and disease

Cell polarization and receptor signaling : Intestinal epithelial cells have the polarity to express cell to cell contact to distinguish plasma membrane into the apex and the basal region to facilitate exo and endocytic metabolic trafficking. Enteric microbiota and environmental nutrient stimuli protect the gut against microbial attack. The stimulus expression is highly suppressed in basal bodies of polarized human epithelial cell and murine mucosa cells in colon by exposing into luminal flagellin on disrupted epithelial barrier. [18]

Homeostasis and barrier integrity: Less innate immune signal transduction with lack of epithelial specificity in signal molecules and an expressed (-) ve form of MyD88 generates a barrier dysfunction along with mucosal damage and inflammasome. Spontaneous inflammation and Tnfdependant epithelial apoptosis were identified in epithelial specific Tak 1 lesser mice. In contrary to the MyD88 initiated proinflammatory signaling the sub-epithelial immunity on non haematopoetic cell signaling protects from homeostasis and inflammation. [19]

Epithelial barrier integrity on mucus epithelium: Most frequent model of mucus epithelium stabilizes and facilitates in penetration of commensal bacteria into the gut. Epithelial specific deletion and NLRs correspondingly support mucus level host defense. DSS induction on inflammatory aggravation and epithelial deletion of NF- Ƙβ subunits thus downstream dominant signaling pathways have been activated. [20]

Innate immunity in the Human Epithelium: Intestinal epithelial gene expression helps in innate immunity in humans. Individuals with lack of genetic compatibility suffers from diarrhea, colitis that was not triggered by bone marrow transplantation. Homozygote human allele have abnormal Paneth cells. Human polymorphism expression is correlated with inflammatory bowel disease and also dislocation of epithelial barrier is directed to detailed cell specific analysis. [21]

Bacterial membrane vesicle which is extracellular in nature

Extracellular vesicles in *Vibrio cholerae*have been shown under electron microscopy which was growing in log phase of bacterial cells and from outer membrane it secrets spherical membrane structure bound with the membranous periphery. Toxin secretion system and vesicle type particles are considered as a structural articulation. Bacterial cell physiology is related with the structural membranous vesicle and their biogenesis, compositions and functional efficacy. Bacterial membrane vesicles are consisting of lipid bilayer which is a nano particle in nature. Mainly gram (+) ve and gram (-) vebacteria are composed of lipopolysachharides (LPS), peptidoglycans, protein, lipid, nucleic acid etc. Direct contact of intracellular compound in delivery of bacterial composites for the activation of bacterial metabolites are necessary for membranous vesicle extra and intracellular activities. [22]

Bacterial extracellular vesicles are associated with the Biogenesis of membranous components: Extracellular cell wall turnover rate are the leading cause of conditional production of bacterial extracellular vesicle. Peptidoglycan fragments or misfolded proteins causes the periplasmic outer membrane to protrusion. Antibiotic ciprofloxacin assisted with the high potency in heterogenous population of bacterial extracellular vesicles. Cationic concentration and electronegative LPS resulted into local negative charges which is further proceeds to coupling and repulsion between LPS molecule and thus distortion of bacterial membrane and vesicular detachment happened. Previous research articles suggested that membrane phospholipid has been transferred between the outer and inner vesicles that in turn causes membrane shrinkage and lipopolysachharides have been triggered into outer vesicle membrane through an acetylated disachharide named as lipid A. the gram (+) ve bacterial extracellular vesicles transferred through porous cell wall through cell membrane generated turgor pressure. *P. aeruginosa* cells swelled up and burst and *Bacillus subtilis* released CMVs through porous cell wall. *Staphylococcus aureus* bacterial cell wall releases phenol soluble modulins and autolysins proteins which increases membranous fluidity thus proceeds to production of CMVs. [23]

Formulation of gut immunity and activation of immune response: The commensal bacteria and probiotic regulate host immune response on bacterial extracellular vesicle to activate immune cells through intestinal epithelium for interacting microbiota derived immune cells on bacterial extracellular vesicles. [24]

Microbiota derived immune response on bacterial extracellular vesicle through intestinal epithelium: Commensal bacteria has been imposed for the in vivo controlling of immune system in the intestine. The cross talk between the microbiota, intestinal epithelium and the immune system is considered as a human monolayer IECs stimulation in the epithelial barrier and leads to the growth of immature dendritic cells in the baso-lateral chamber to directly involve with the immune system of lamina propia. [25]

Activating of immune cells through microbiota derived Extra Cellular Vesicles: To balancing the immune system in gut endothelium it must stimulates extracellular antigens and target antibodies to provide barrier against host pathogens and infections.

i) ***Bacteroides sp.:*** The commensal bacteria *B. fragilis* benefitted on the bacterial extracellular vesicle in food metabolism and the gut ecosystem. Capsular polysachharide containing *B. fragilis* is administrated against colitis and suppress immunity of pro inflammatory and anti-inflammatory cytokines.

ii) ***Escherichia coli :***Probiotic *E. coli* provides balance between

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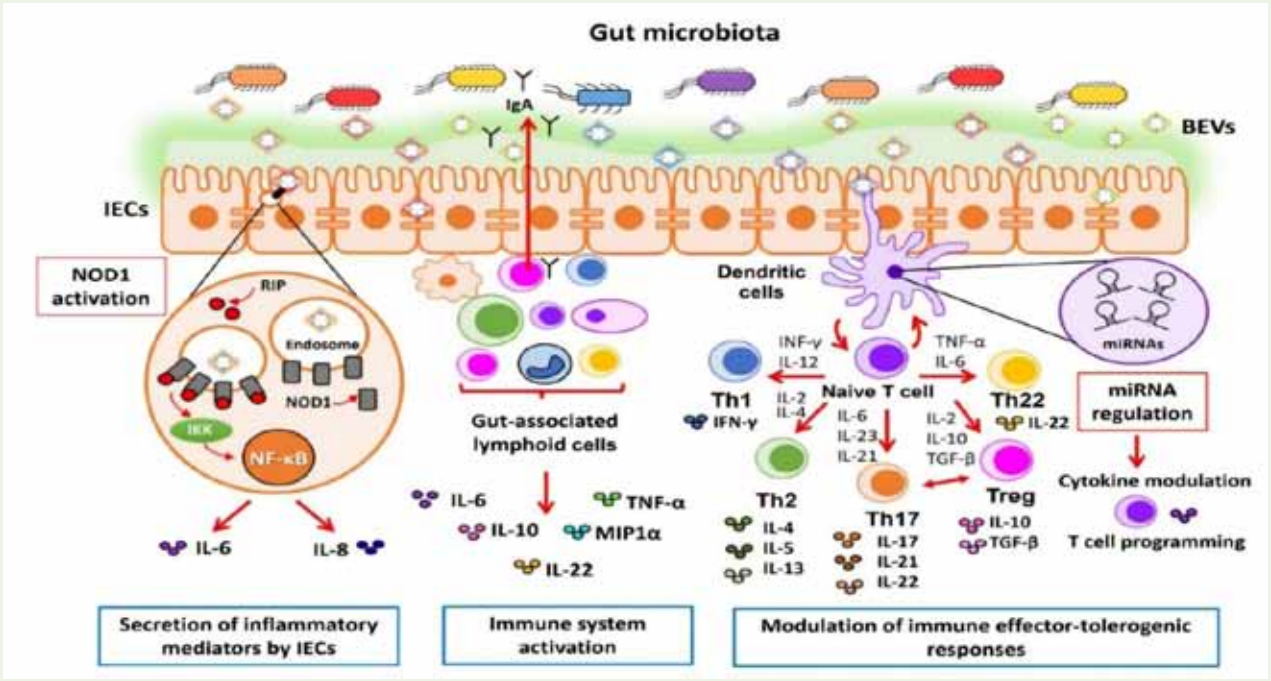

Figure 1: Immunomodulatory effects through Bacterial Extracellular Vesicles in the Gut Microbiome

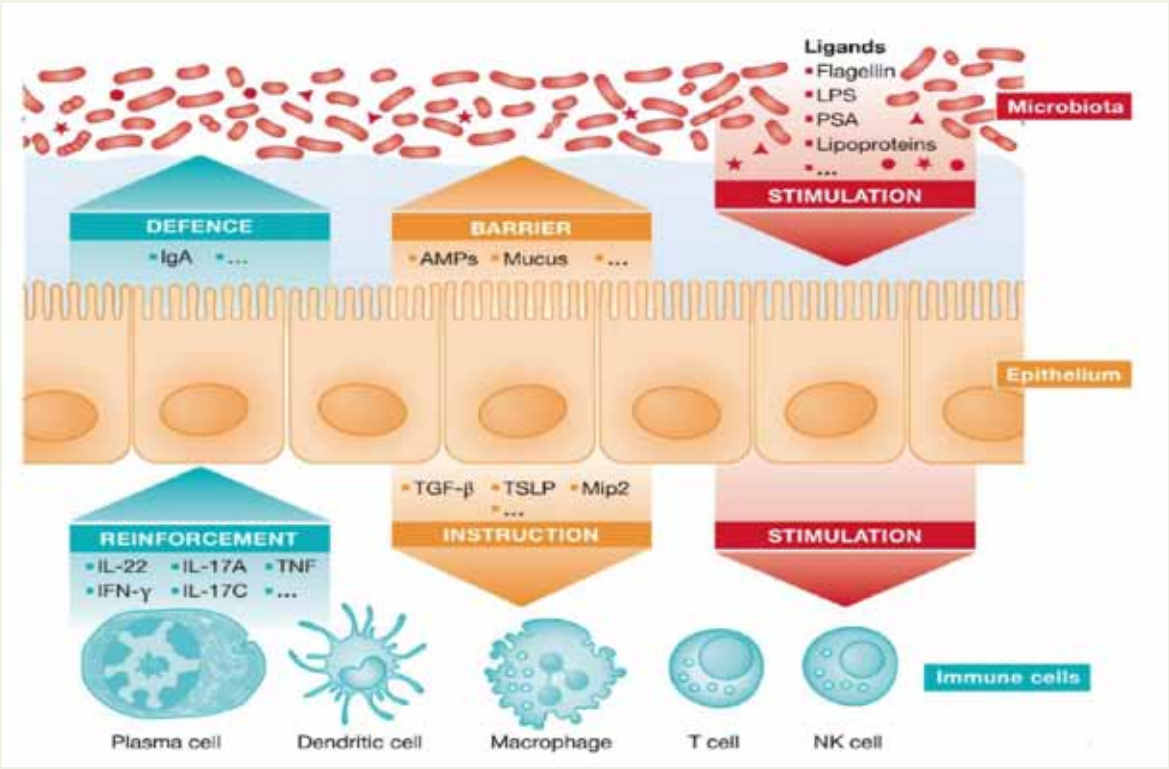

Figure 2: Microbial homeostasis in Epithelial cells of Intestine

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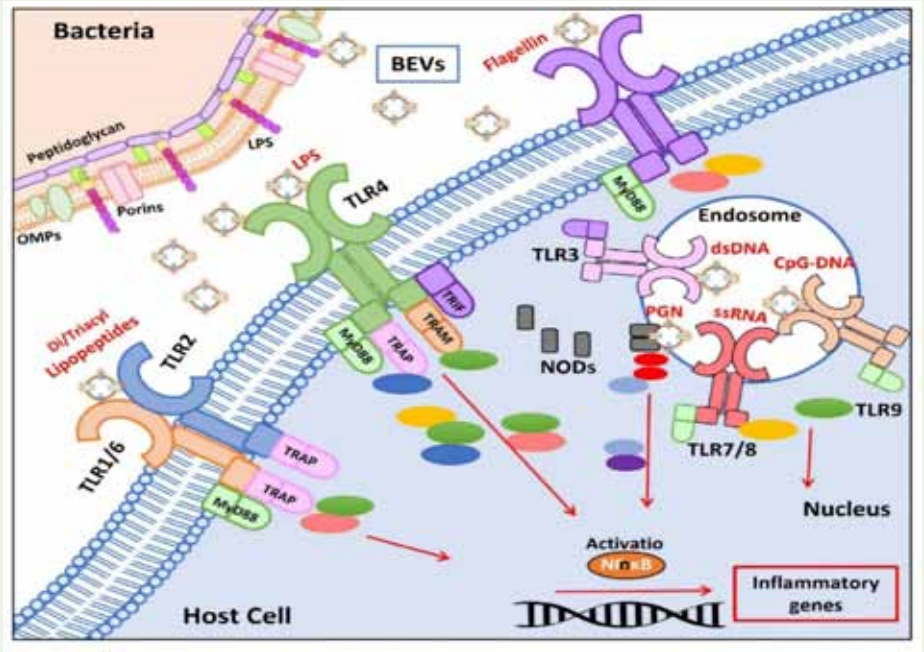

Figure 3: Bacterial Extracellular Vesicles associated molecular pattern recognition by host cell immune receptors

intestinal homeostasis and microbiota environment. The immunomodulatory effects are associated with gut microbes *E. coli* on immune activity of DCs and other innate immune response. The differential expression of the miRNAs is assimilated by triggering bacterial extra cellular vesicles on DCs.

iii) Gram (+) ve commensal bacteria Lactobacillus sp. and Bifidobacterium sp: Due to health benefits and immunomodulatory effects bacterial extracellular vesicles of *Lactobacillus rhamnosus*has been well studied for probiotic functionality and neuron stimulating activities by activating host pathogenic nervous system in enteric epithelial system. Similarly,*Bifidobacteriumbifidum* targeted a tolerogenic response by subcellular functions of probiotic on the dendritic cells to prove immunomodulation mediated bacterial extracellular vesicles. [27]

Role of probiotic immune system on gut microbiota Helicobacter pylori: Intestinal immune system varies between distinct mutualistic and symbiotic microorganisms from host pathogenic activities to the tolerance level of commensal bacteria. Gastrointestinal microbiota may cause to persistent and metabolic disorders. In contrary to *Helicobacter pylori*intestinal epithelium can produce a physiochemical barrier to the prevention of pathogenic colonization on the surface of mucus epithelium to recreate immune tolerogenic factors against commensal bacteria. [28]

Microbial Dysbiosis: Commensal bacteria are the key providers of energy resources for the host cellular enterocytes, inhibiting pathogen colony formation, protecting against lymphoid tissue and directing the immune response. Modulating the host pathogenic response, formulating cell signaling, diminishing epithelial cell polarity, altering gastric ulcer are the key primary resources on alternation of gut microbiota in *H. pylori* infection. [29]

H. pylori and gut epithelium: Though *H. pylori* insisted gastric microbiota has been preferred for strain specificity and host pathogenic colony formation. The influence of *H. pylori* on gastric microbiota has been suggested as Bacteroidetes regulated elimination of *H. pylori* infection. This pathogen initiates activity of nuclear factor kappa B (NF- κβ) proceeds to transcription factor stimulated activities of MCP-1 from epithelium to monocytic extraction and monocytic activation by LPS correlation with TL4. *H. pylori* infection initiates excessive secretion of pro inflammatory cytokines such as iNOS, TNF- α, IFN- γ , IL-8, IL-6, IL-4, IL-1β. [30]

Conclusion

Beyond relevant research publications on gut microbiota intrinsic and extrinsic functionality of microbiome system and stimulation of receptors, regulation of effectors to the target cells yet has to be explored. These research findings are very much important for developing translational mechanisms of microbiota derived diseases in human health. The potency of applications of microbiota and bacterial extracellular vesicles is very essential as a treatment purpose or to overcome therapeutic challenges upon intestinal infections, immune disorders and inflammation. The compositional diversity of gut microbiome in a great extent to disease including oncogenic, neurological, metabolic and immunogenic diseases has been essential for gut microbiome profiling as a diagnostic tool.

Current researchers have been suggested that the next generation

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sequencing in probiotics is intentionally targeted and genetically modified organisms has been promoted to the beneficial recombinant DNA technology for probiotic supplementation in gut microbiome for its pharmaceutical output. However,another strategy is the implementation of nanotechnology with micro-capsulation end point it may develop the probiotic integrity on human health system thus provide a thematic framework to eliminate the metabolic hazards in probiotic supplementation.

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