Review On: Importance of Probiotic and Their Mechanism Of Action

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Abstract: Probiotics are live microorganisms that provide health benefits to the host when ingested in adequate amounts. The strains most frequently used as probiotics include lactic acid bacteria and bifid bacteria. Probiotics have demonstrated significant potential as therapeutic options for a variety of diseases, but the mechanisms responsible for these effects have not been fully elucidated yet. Several important mechanisms underlying the antagonistic effects of probiotics on various microorganisms include the following: modification of the gut micro biota, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier and modulation of the immune system to convey an advantage to the host. Accumulating evidence demonstrates that probiotics communicate with the host by pattern recognition receptors, such as toll-like receptors and nucleotide binding oligomerization domain-containing protein-like receptors, which modulate key signaling pathways, such as nuclear factor- _ B and mitogen-activated protein kinase, to enhance or suppress activation and influence downstream pathways. This recognition is crucial for eliciting measured antimicrobial responses with minimal inflammatory tissue damage. A clear understanding of these mechanisms will allow for appropriate probiotic strain selection for specific applications and may uncover novel probiotic functions. The goal of this systematic review was to explore probiotic modes of action focusing on how gut microbes influence the host.

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1. INTRODUCTION

According to the Food and Agriculture Organization of the United Nations and the World Health Organization, probiotics are live microorganisms that confer a health benefit to the host when administered in adequate amounts (FAO, 2001).

In particular, strains belonging to *Bifidobacterium* and *Lactobacillus*, which are the predominant and subdominant groups of the gastrointestinal microbiota, respectively are the most widely used probiotic bacteria and are included in many functional foods and dietary supplements (Denery et al., 2011).

After a long history of safe use of probiotics in fermented dairy products and an increased recognition of their beneficial effects on human health, the food industry has become increasingly interested in these types of microorganisms (Liong2011). Often the criteria for the selection of probiotics include the tolerance to gastrointestinal conditions (gastric acid and bile), ability to adhere to the gastrointestinal mucosa and competitive exclusion of pathogens (Collins, 2002).

The mechanisms underlying the beneficial effects of probiotics are largely unknown but are likely to be multifactorial. Several mechanisms related to the antagonistic effects of probiotics on various microorganisms include the following mechanisms: secretion of antimicrobial substances, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier and modulation of the immune system (Gueimonde et al., 2010).

The results of evidence-based analyses from human studies and animal models have shown the clinical potential of probiotics against many diseases (Yan and Polk, 2011). Probiotics have been reported to suppress diarrhea, alleviate lactose intolerance and postoperative complications, exhibit antimicrobial and anti-colorectal cancer activities, reduce irritable bowel symptoms and prevent inflammatory bowel disease (Oelschlaeger, 2010).

However, generalizations concerning the potential health benefits of probiotics should not be made because probiotic effects tend to be strain specific. Thus, the health benefit attributed to one strain is not necessarily applicable to another strain even within one species (Williams, 2010).

1.1 Probiotic

Probiotic concept was first described by Russian scientist Elie Metchnikoff, who in the beginning of the 20th century suggested that it would be possible to modify the gut flora and to replace harmful microbes with useful microbes Metchnikoff proposed that consumption of fermented milk would "seed" the intestine with harmless LAB and decrease the intestinal pH and that this would suppress the growth of proteolytic bacteria. His work inspired Japanese scientist

Minoru Shirota to begin investigating the causal relationship between bacteria and good intestinal health, which eventually led to the launching of "Yakult" (yoghurt based drink) in 1935. The term "Probiotics" was first coined by Parker (1974) who described this as "microorganism or substance which contributes to the intestinal microbial balance". A probiotic is a live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance. Literal meaning of probiotic is "for life" while that of antibiotic is "against life". According to FAO probiotic is "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". Probiotics are preparations of non-pathogenic microorganisms, prepared for animal and human use, that have beneficial effects on the digestive ecosystem and confer resistance to infection (Fuller, 1992).

1.2 Importance of Probiotic Action

According to the Food and Agriculture Organization of the United Nations and the World Health Organization, probiotics are live microorganisms that confer a health benefit to the host when administered in adequate amounts (FAO, 2001).

1.3 Increased Adhesion to Intestinal Mucosa

Adhesion to intestinal mucosa is regarded as a prerequisite for colonization and is important for the interaction between probiotic strains and the host (Juntunen et al., 2001). Adhesion of probiotics to the intestinal mucosa is also important for modulation of the immune system and antagonism against pathogens (Hirano et al., 2003). Thus, adhesion has been one of the main selection criteria for new probiotic strains and has been related to certain beneficial effects of probiotics (Castagliuolo et al., 2005).

Lactic acid bacteria (LABs) display various surface determinants that are involved in their interaction with intestinal epithelial cells (IECs) and mucus. IECs secrete mucin, which is a complex glycoprotein mixture that is the principal component of mucous, thereby preventing the adhesion of pathogenic bacteria (González et al., 2012).

Probiotics also cause qualitative alterations in intestinal mucins that prevent pathogen binding (Kim, 2010). The bacterial component involved in the adhesion of the LB and BG2FO4 *L. acidophilus* strains is protease resistant and is associated with the bacterial surface (Bernet,1992).

Interestingly, the bacterial component is also degraded into an antimicrobial peptide, which lends anti-pathogenic properties to the host and provides an example of how large surface proteins may exhibit evolutionarily beneficial pleiotropic effects (Gopal, 2001).

Probiotic strains can also induce the release of defensing from epithelial cells. These small peptides/proteins are active against bacteria, fungi and viruses. Moreover, these small peptides/proteins stabilize the gut barrier function (Furrie et al., 2005). Observations have indicated that in response to attack by pathogenic bacteria, the host engages its first line of chemical defense by increasing the production of antimicrobial proteins (AMPs), such as defensins, cathelicidins, C type lectins and ribonucleases (Gallo and Hooper 2012) .

Finally, probiotic bacteria are able to produce so-called de-conjugated bile acids, which are derivatives of bile salts. De-conjugated bile acids show a stronger antimicrobial activity compared to that of the bile salts synthesized by the host organism. It remains to be elucidated how probiotics protect themselves from their own bactericidal metabolites or if they are resistant to de-conjugatedbile acids at all (Diep et al., 2012).

1.4 Probiotics and the Immune System

It is well known that probiotic bacteria can exert an immunomodulatory effect. These bacteria have the ability to interact with epithelial and dendritic cells (DCs) and with monocytes/macrophages and lymphocytes. The immune system can be divided between the innate and adaptive systems. The adaptive immune response depends on B and T lymphocytes, which are specific for particular antigens. In contrast, the innate immune system responds to common structures called pathogen-associated molecular patterns (PAMPs) shared by the vast majority of pathogens (Gil et al., 2010).

The primary response to pathogens is triggered by pattern recognition receptors (PPRs), which bind PAMPs. The best-studied PPRs are toll-like receptors (TLRs). In addition, extracellular Ctype lectin receptors (CLRs) and intracellular nucleotidebinding oligomerization domain-containing protein (NOD)-like receptors (NLRs) are known to transmit signals upon interaction with bacteria (Lebeer et al., 2010).

1.5 TLRs and Probiotics

TLRs are transmembrane proteins expressed on various immune and non-immune cells, such as B cells, natural killer cells, DCs, macrophages, fibroblasts, epithelial cells and endothelial cells. In mammals, the TLR family includes eleven proteins (TLR1–TLR11). However, there is a stop codon in the human TLR11 gene that results in a lack of production of human TLR11. Activation of TLRs occurs after binding of the ligand to extracellular leucinerich repeats. In humans, TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10 are outer membrane associated and primarily respond to bacterial surface-associated PAMPs. TLR3, TLR7, TLR8 and TLR9 are found on the surface of endosomes where they respond primarily to nucleic acidbased PAMPs from viruses and bacteria (Gil et al., 2010).

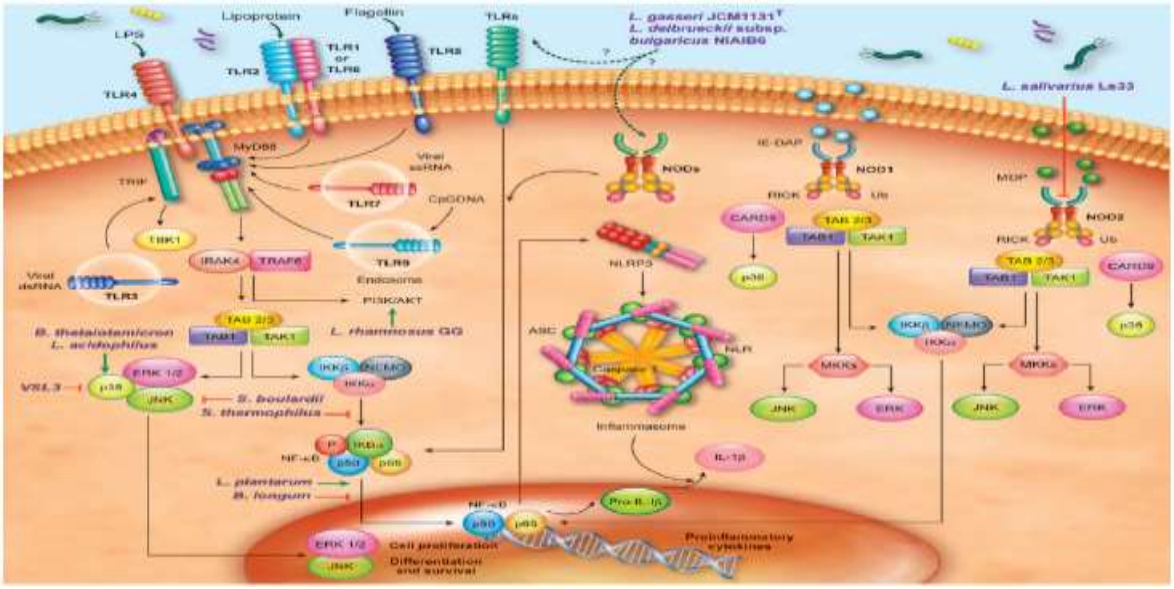

Fig. 2. *Interaction of probiotics with the gut-associated immune system. ASC=Apoptosis-associated speck-like protein containing a CARD; B.thetaiotamicron=Bacteroides thetaiotamicron ; CARD9 = caspase recruitment domain-containing protein 9; ERK = extracellular regulated kinase; IE-DAP = D-gamma-glutamyl- meso-DAP; IKK = I _ B kinase; IRAK4 = IL-1 receptor-associated kinase 4; JNK = Jun N-terminal kinase; MDP = muramyl dipeptide; MKK = mitogen-activated kinase kinase; NEMO = NF- _ B essential modulator; TAB1/2/3 = TAK binding proteins; TAK1 = ubiquitin-dependent kinase of MKK and IKK; TBK1 = serine/threonine-protein kinase 1; TRAF6 = TNF receptor-associated factor 6; Ub = ubiquitin (Gil et al., 2010).*

The TLR signaling pathway, except for TLR3, involves the recruitment of MyD88, which activates the MAPK and nuclear factor (NF)-B signaling pathways (Gil et al., 2010). TLR3 utilizes the adaptor protein TRIF, leading to the expression of type 1 IFNs (Gil et al., 2010). Furthermore, TLR-mediated signaling has been shown to control DC maturation inducing the up regulation of various maturation markers, such as CD80, CD83 and CD86, as well as the CCR7 chemokine receptor. Moreover, commensal and probiotic microorganisms can create an overall tolerant state mediated by the action of TLRs on DCs. It is clear that TLR9 signaling is essential to mediate the anti-inflammatory effect of probiotics. However, different studies have implicated other TLRs, such as TLR3 and TLR7, in the tolerance induced by commensal and probiotic bacteria. After activation by commensal and probiotic microorganisms, DCs initiate an appropriate response, such as the differentiation of Th 0 to T reg , which has an inhibitory effect on Th 1 , Th 2 and Th 17 inflammatory responses (Gil et al., 2010).

1.6 NLRs and Probiotics

As mentioned before, there is another family of membrane-bound receptors: NLRs. They are located in the cytoplasm and are important in tissues where TLRs are expressed at low levels. The most thoroughly characterized members are NOD1 and NOD2, but currently more than 20 different NLRs have been identified (Hakansson et al., 2011).

Unlike NOD1, which is ubiquitously expressed, the expression of NOD2 is restricted to DCs, macrophages, Paneth cells, intestinal cells, lung cells and oral epithelial cells, and it is expressed at low levels in T cells. NOD1 can sense peptidoglycan moieties containing meso diaminopimelic acid, which are associated with Gram-negative bacteria, but NOD2 senses muramyl dipeptide motifs, which can be found in a wide range of bacteria (Biswas et al., 2012). Upon recognittion of their agonist, both NOD1 and NOD2 self oligomerize to recruit and activate the adaptor protein RICK, a protein kinase that regulates CD95-mediated apoptosis, which is essential for the activation of NF- _ B and MAPKs, resulting in the up regulation of transcription and production of inflammatory mediators (e.g. cytokines, chemo attractants, COX-2 and inducible nitric oxide synthase (Biswas et al., 2012).

Another important pathway activated by NLRs involves apoptosis-associated speck-like protein with caspase recruitment to activated caspase 1, an adaptor protein which is necessary for the cleavage of pro-IL-1 and pro-IL-18 into their mature and biologically active forms. NLRs participate in the formation of inflammasomes, which leads to the activation of caspase-1. There are three principal inflammasomes named after the NLR involved as follows: NOD-

like receptor family, prying domain containing protein (NLRP) 1, NLRP3 and NLRC4. NLRP3 detects LPS, muramyl dipeptide, bacterial RNA and viral RNA (Chen et al., 2009).

2. Characteristic of good probiotics

1. The culture should exert a positive effect on the host. it should be gram positive, and acid resistant, bile resistant and contain a minimum 30×109 CFU per gram.
2. The culture should posses high survival rate and multiply faster in the digestive tract. It should be strain specific.
3. The cultured organism neither be pathogenic or nor toxic to the host.
4. The adhesive capacity of a microorganism must be firm and faster.

3. Mechanism of action of probiotic

3.1 Mechanism of action of probiotic

Major Probiotic mechanisms of action include enhancement of the epithelial barrier, increased adhesion to the intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive exclusion of pathogenic microorganisms, production of anti-microorganism substances and modulation of the immune system. The intestinal barrier is a major defense mechanism used to maintain epithelial integrity and to protect the organism from the environment. Defenses of the intestinal barrier consist of the mucous layer, antimicrobial peptides, secretory IgA and the epithelial junction adhesion complex (Ohland *et al*.,2010).

This barrier function is disrupted, bacterial and food antigens can reach the sub mucosa and can induce inflammatory responses, which may result in intestinal disorders. Consumption of non-pathogenic bacteria can contribute to intestinal barrier function, and probiotic bacteria have been extensively studied for their involvement in the maintenance of this barrier. However, the mechanisms by which probiotics enhance the intestinal barrier function are not fully understood. Several studies have indicated that enhancing the expression of genes involved in tight junction signaling is a possible mechanism to reinforce the intestinal barrier integrity (Anderson *et al*., 2010).

Probiotic bacteria may be able to adhere to epithelial cells, thus blocking pathogens. That mechanism exerts an important effect on the host's health condition. Moreover, the adhesion of probiotic microorganisms to epithelial cells may trigger a signaling cascade, leading to immunological modulation. Alternatively, the release of some soluble components may cause a direct or indirect (through epithelial cells) activation of immunological cells. This effect plays an important role in the prevention and treatment of contagious diseases, as well as in chronic inflammation of the alimentary tract or of a part thereof (Oelschlaeger, 2010)

3.2 Enhancement of the Epithelial Barrier

The intestinal epithelium is in permanent contact with luminal contents and the variable, dynamic enteric flora. The intestinal barrier is a major defense mechanism used to maintain epithelial integrity and to protect the organism from the environment. Defenses of the intestinal barrier consist of the mucous layer, antimicrobial peptides, secretory IgA and the epithelial junction adhesion complex (Ohland and Macnaughton, 2010).

Once this barrier function is disrupted, bacterial and food antigens can reach the submucosa and can induce inflammatory responses, which may result in intestinal disorders, such as inflammatory bowel disease (Gordon et al., 2003).

3.3 Competitive Exclusion of Pathogenic Microorganisms

The mechanisms used by one species of bacteria to exclude or reduce the growth of another species are varied, including the following mechanisms: creation of a hostile micro ecology, elimination of available bacterial receptor sites, production and secretion of antimicrobial substances and selective metabolites, and competitive depletion of essential nutrients (Rolfe, 1991).

Exclusion is the result of different mechanisms and properties of probiotics to inhibit pathogen adhesion, including the production of substances and the stimulation of IECs. Competitive exclusion by intestinal bacteria is based on a bacterium-to-bacterium interaction mediated by competition for available nutrients and for mucosal adhesion sites. To gain a competitive advantage, bacteria can also modify their environment to make it less suitable for their competitors. The production of antimicrobial substances, such as lactic and acetic acid, is one example of this type of environmental modification (Schiffrin and Blum 2002).

Some lactobacilli and bifid bacteria share carbohydrate-binding specificities with some enter pathogens, which makes it possible for the strains to compete with specific pathogens for the receptor sites on host cells (Asasaka et al., 2002) . In general, probiotic strains are able to inhibit the attachment of pathogenic bacteria by means of steric hindrance at enterocyte pathogen receptors (Bernet et al., 1993).

4. Conclusions

Probiotics have considerable potential for preventive or therapeutic applications in various gastrointestinal disorders. However, it is important to note that many probiotic health claims have not yet been substantiated by experimental evidence. In addition, the efficacy demonstrated for one given bacterial strain cannot necessarily be transferred to other probiotic organisms. Moreover, the mechanisms underlying probiotic action have not yet been fully elucidated. This study reviewed the mechanisms of action of probiotics. Several important mechanisms underlying the antagonistic effects of probiotics on various microorganisms include the following: modification of the gut micro biota, competitive adherence to the mucosa and epithelium, strengthening of the gut epithelial barrier and modulation of the immune system to convey an advantage to the host. The recent characterization of the host families of pattern-recognition molecules, such as TLR and NOD-like receptors, as well as modulating key signaling pathways, such as NF-B and MAPK, with respect to their ability to enhance or suppress activation and influence downstream pathways will shed light onto the complex interplay of host-microbe interactions. Stimulation of these receptors by commensal bacteria has a crucial role to elicit measured antimicrobial responses with minimal inflammatory tissue damage.

5. Recommendation

In the present review, we provided an overview of the mechanisms of action of probiotics. It must be noted that many reported mechanisms of probiotic action are the results of in vitro experiments. Considerable effort has been invested in the development of methods enabling
the in-depth analysis of the molecular mechanisms of probiotics.
The complex and dynamic interactions that exist between the intestinal epithelium and bacteria on the luminal side as well as between the epithelium and the underlying immune system on the basolateral side must be reconciled in co-culture experiments with probiotics, DCs and IECs as well as in 3D models. Other models include tissue explants, bioreactors and organoids.

In vitro models have improved our current knowledge regarding specific probiotic modes of action. However, a number of limitations have to be taken into account. For example, results obtained with different IECs have to be carefully interpreted because not all cell lines share the same characteristics.
It should also be noted that culture conditions may influence the expression of certain molecular characteristics. The molecular elucidation of probiotic action in vivo will help to identify true probiotics and to select the most suitable ones for the prevention and/or treatment of particular diseases. It is important to note that results obtained in animal models cannot be directly transferred to humans.
The physiology of animals differs considerably from that of humans, but this disadvantage is outweighed by the possibility of using animals with virtually identical genetic backgrounds, such as human microbiota-associated animals.
The quest for a better understanding of how probiotics operate has catalyzed an enormous interest in the molecular processes underlying host-microbe interactions. Gaining insight into the mechanisms of probiotic action may not only help to improve the credibility of the probiotic concept but also to foster the development of novel strategies for the treatment or prevention of gastrointestinal and autoimmune diseases.

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