Chapter

Prebiotics, Probiotics, and Bacterial Infections

Christina C. Tam, Kirkwood M. Land and Luisa W. Cheng

Abstract

Bacterial pathogens have developed exquisite virulence mechanisms to survive in the host cells. These virulence mechanisms help them bind and internalize into host cells, replicate, and evade the host immune response. The mammalian host itself has developed its own repertoire of weapons to prevent this from happening. One important component of host response in preventing infections in the gut lumen is the diverse commensal microbiota present. Dysbiosis of the gut microbiota has been implicated in the development of many gastrointestinal diseases. A potential therapeutic pathway to solve these diseases would be by providing probiotics and/or prebiotics to help stimulate growth of the beneficial commensal bacteria. Here, we will present evidence of commensal microbiota imbalance in the development of disease as well as potential therapies to restore gut harmony.

Keywords: probiotics, bacterial infections, prebiotics, microbiota, therapeutics

1. Introduction

Probiotic microorganisms have been extensively studied for their beneficial effects in not only maintaining the normal gut mucosa but also protection from allergens, pathogens, and toxins [1, 2]. The gastrointestinal tract (GI) and its associated microbiota is a complex system that allows for the digestion and absorption of critical nutrients. Additionally, the presence of the commensal bacteria leads to the development and regulation of the mucosal immune system [3]. It is believed that 60% of all fecal matter mass in humans consists of bacteria and that there are between 10^{10} and 10^{12} colony-forming units per gram of intestinal content in the colon [4]. The intestinal epithelium is a physical and biochemical barrier that seeks to protect mammalian cells from infection and injury from contaminants such as toxins, pathogenic bacteria, commensal bacteria, and even other luminal contents. Specialized intestinal epithelial cells (IECs) are able to sense and respond to these stimuli with appropriate responses such as increasing their barrier function to activation of anti-pathogenic immune mechanisms [3].

The International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2014 agreed on a consensus definition of probiotics based on the previous Food and Agriculture Organization of the United Nations and World Health Organization (WHO) definition. ISAPP defines probiotics as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [5]. Probiotics have been used for the treatment of *Helicobacter pylori* infection, irritable bowl syndrome, and inflammatory bowel disease (ulcerative colitis and Crohn's disease) in addition to enhancing the immune system of healthy individuals [6–12].

Though *in vivo* and *in vitro* studies suggest that probiotics can be beneficial [1, 2, 13], the exact mechanism(s) remains to be fully explained. Four mechanism are believed to be involved: (a) maintenance of the gut epithelial barrier, (b) competitive exclusion of pathogenic organisms, (c) secretion of antimicrobial products, and (d) regulation of the mucosal immune system in favor of the hosts.

The major defensive mechanism of the gut is the intestinal barrier which maintains epithelial integrity and to protect the host from the environment. In defense of this barrier, there exists the mucous layer, antimicrobial peptides, secretory IgA and the epithelial junction adhesion complex [14]. Disruption of these defense mechanisms allows for the bacteria and food antigens to reach the submucosa, which can induce an inflammatory response potentially leading to the intestinal disorders such as inflammatory bowel disease [15, 16].

1.1 Probiotics

The most common probiotic strains used are *Lactobacillus*, *Bifidobacteria*, and the yeast strain *Saccharomyces cerevisiae* var. *boulardii*. Lactic acid bacteria and bifidobacteria have been shown to remove heavy metals [17], cyanotoxins [18], and mycotoxin from *in vitro* aqueous solutions [19, 20].

In regards to maintenance of the gut epithelial barrier, one can upregulate the genes important for this process [21]. Lactobacilli treatment has been shown to affect several genes including E-cadherin and β-catenin that affect adherence cell junctions in a cell culture model. The phosphorylation and abundance of adherence junction proteins including PKCδ [22] has been seen with Lactobacilli treatment. The probiotic *Escherichia coli* Nissle 1917 strain (EcN1917) can initiate repair of the intestinal barrier after damage by enteropathogenic *E. coli* by enhancing the expression and redistribution of tight junction proteins of the zonula occludens (ZO-2) and PKC [23, 24]. Treatment with *Lactobacillus casei* DN-114001 [25] and VSL#3 (an eight combination probiotic strain mixture) [26] also affect the gut barrier.

Another method to promote epithelial barrier function may be to increase mucin production thereby leading to increased barrier function as well as exclusion of pathogens and toxins. There have been contradictory data for both *in vitro* and *in vivo* experiments as to whether mucin production occurs in response to probiotic treatment. Some studies have suggested *Lactobacillus* adhesion is required to increase mucin production, which may not occur *in vivo* [27, 28]. However, a *Lactobacillus acidophilus* A4 cell extract has been shown to increase *MUC2* expression in HT29 cells independent of attachment [29]. VSL#3 has also been shown to increase expression of *MUC2*, *MUC3*, and *MUC5AC* in HT-29 cells [26]. *In vivo* studies of mucin production have also been inconsistent. VSL#3 given to mice for 14 days did not show any increase in mucin production or thickness [30] whereas rats given VSL#3 for 7 days have a 60-fold increase in *MUC2* expression and secretion [31].

1.2 Prebiotics

Prebiotics and their beneficial effects on human health have been of interest in recent years because of their perceived safety since they are derived from dietary products. The definition of prebiotics has changed somewhat from their initial description in 1995 by Glenn Gibson and Marcel Roberfroid [32]. Today, the general consensus is that “dietary prebiotics” are “selectively fermented ingredients that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health” [33]. There are many types of prebiotics but they can be segregated into the following groups [33]: (1) fructans,

(2) galacto-oligosaccharides (GOS), (3) starch and glucose-derived oligosaccharides, (4) other oligosaccharides, and (5) non-carbohydrate oligosaccharides.

Fructans, such as inulin and fructose-oligosaccharides (FOS)/oligofructose, generally have a linear chain of fructose with a β(2 + 1) linkage usually with terminal glucose units with a β(2 + 1) linkage with variable degrees of polymerization (DP) [33–36]. GOS is the product of lactose extension that can be classified into two subgroups: (i) excess galactose at C_3, C_4 or C_6 and (ii) derived from enzymatic trans-glycosylation [33]. The product of the enzymatic trans-glycosylation is a mixture of tri-to pentasaccharides with galactose known as trans-galacto-oligosaccharides (TOS) [37, 38]. In addition, there are GOSs derived from lactulose, an isomer of lactose, as well as raffinose family of oligosaccharides (RFO) [33, 37]. Starch that is resistant to the upper gut digestion is known as resistant starch (RS) and is considered a prebiotic along with polydextrose (glucose-derived oligosaccharide) [39, 40]. Pectin derived oligosaccharides (POS) are derived from an extension of galacturonic acid or rhamnose [33]. The carboxyl groups of POS can be modified with methyl esterification as well as acetylated at C_2 or C_3. Additionally, many different types of sugars (i.e. arabinose, galactose, and xylose) or ferulic acid can be linked to the side chains of POS [41, 42]. Though most of the accepted compounds defined as prebiotics are carbohydrates, there are some non-carbohydrate compounds that are recommended to be classified as prebiotics, i.e. cocoa-derived flavanols [33, 43].

How do prebiotics affect human health? What mechanism(s) are involved? Since prebiotics are derived from dietary products, they provide the metabolic energy for the gut microbiota. This means that they can affect the composition and function of these microorganisms. For example, GOSs can stimulate the growth of *Bifidobacteria* and *Lactobacilli* to a high degree while *Enterobacteria*, *Bacteroidetes*, and *Firmicutes* growth levels occurred at a lower level [35]. Cross-feeding, the production of a by-product that can sustain another microorganism, can occur and an example is the degradation of resistant starch by *Ruminococcus bromii* to provide energy for several other species [44].

In addition to feeding the gut microbiota, the fermentation of prebiotics can generate metabolites such as short chain fatty acids (SCFA) (i.e. lactic acid, butyric acid, and propionic acid) that have dramatic effects not only on the intestinal environment but can affect distant organ sites as well as the immune system. SCFAs decrease the pH of the gut that can alter the composition of the microbiota [45, 46]. A pH unit decrease affects acid sensitive species such as *Bacteroides* and increases butyrate production by *Firmicutes* [45]. Butyrate itself has been shown to be important for intestinal cell development [47]. As reviewed in [33], propionate affects the TH_2 helper cells, macrophages, and dendritic cells while peptidoglycan stimulates the innate system.

2. Bacterial infections and the disruption of gut homeostasis

Bacterial pathogens are microorganisms that have the ability to cause disease due to their specialized virulence factors or that can arise from a dysbiosis such as from antibiotic treatment that can eliminate the normal healthy flora of the gut leading to opportunistic infections from commensals or normally non-pathogenic organisms.

2.1 Bacterial pathogens, virulence factors, and mechanisms of pathogenesis

Some of the best-known bacterial pathogens are *Salmonella enterica*, *Listeria monocytogenes*, *Vibrio cholera*, *Shigella flexneri*, Shiga toxin producing *E. coli*

(STEC) (i.e. *E. coli* 0157:H7), *Clostridium difficile*, *Clostridium perfringens*, and *Clostridium botulinum*. Both Gram-positive and Gram-negative pathogens must develop mechanisms to outcompete the normal gut microbiota, bind/invade cells, avoid detection and killing from the host immune system. Some important pathogen virulence mechanisms consist of specialized secretion systems that encode factors important for all the above steps in pathogenesis. The type III secretion systems (TTSS/T3SS) encoded by some Gram-negative pathogens such as *Salmonella*, *Vibrio*, *Shigella*, *Escherichia coli*, and *Yersinia* are well-known examples. Other specialized secretion systems are the T4SS and T6SS. T6SSs are prevalent in both pathogens and commensals suggesting their importance in the intestinal environment [48]. For non-intracellular pathogens, bacterial toxins [i.e., Listeriolysin O (LLO), botulinum neurotoxins (BoNTs), alpha toxin-*C. perfringens*, TcdA/TcdB-*C. difficile*] are important virulence factors that can bind to and enter the intestinal epithelium and/or their target cells to effect their functions (i.e. cytotoxicity).

One important growth restriction system on the part of hosts/intestinal flora is the sequestration of iron, which is absolutely required for growth. For example, *Salmonella enterica* can evade lipocalin-2-mediated growth restriction by producing modified siderophores that cannot be bound by lipocalin-2 [49]. The T4SS and T6SS systems can be utilized for intra-and-inter bacterial species warfare. *Bacteroides* strains encoding the T6SS have been shown to target sensitive *Bacteroides* spp. suggesting they limit their competition [50–52]. *Salmonella*, *Vibrio*, and *E. coli* have also been shown to use T6SS against their competition, the intestinal microbiota [53–55].

2.2 The mammalian host response to bacterial infections

Probiotic strains have been shown to induce the release of defensins, small peptides/proteins active against bacteria, fungi, and viruses but also are able to stabilize the gut barrier from epithelial cells. Host cells are able to mount as a first line of defense against pathogens increased production of antimicrobial proteins (AMPs) such as α- and β-defensins, cathelicidins, C-type lectins and ribonucleases. Many of these proteins disrupt the cell wall structures of the bacterial membrane either through enzymatic (i.e. lysozyme, phospholipase A2) or non-enzymatic mechanisms (i.e. pore formation by defensins and cathelicidins) [56–58].

The effect of commensal and probiotic bacteria on the host immune system is complex and not fully understood. It is believed that the effect of probiotic bacteria in modulating the immune system lies with its potential interactions with the host innate immune system by activating pattern recognition receptors (PRRs) that recognize common structures called pathogen-associated molecular patterns (PAMPs) shared by the vast majority of pathogens. Of note are the potential interactions with toll-like receptors (TLRs), extracellular C-type lectin receptors (CLRs), and intracellular nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors (NLRs) that recognize PAMPs such as lipopolysaccharide (LPS), peptidoglycan, lipoprotein, flagellin, and CpGDNA. Activation of these receptor complexes will activate multiple downstream signaling pathways that may induce a pro- or anti-inflammatory response. Dysregulation of the pro-inflammatory response has been implicated in Crohn's disease with human intestinal inflammation as well as human autoinflammatory disease [59]. However, expression levels of some of these PRRs are low in immune cells therefore the ability to rapidly induce the expression of the PRRs such as NLRP3 in response to PAMP stimuli are absolutely critical in the defense against potential pathogens [60–64].

3. Probiotic mechanisms of antagonism against bacterial growth and gene expression

In 1969, Greenberg [65] described the phenomena that *Salmonella typhimurium* was completely excluded from maggots of blowflies. The term "competitive exclusion" was used to define the scenario in which one species of bacteria more vigorously competes for the receptor sites in the intestinal tract than another species. There are a variety of mechanisms used by one bacterial species to exclude or reduce the growth of another species such as creation of a hostile environment, blocking available receptor sites, production and secretion of antimicrobial products and specific metabolites, and competitive depletion of essential nutrients [66].

Lactobacilli and bifidobacteria have been shown to inhibit a broad range of pathogens including *E. coli*, *Salmonella*, *Helicobacter pylori*, *Listeria monocytogenes* and *rotavirus* [6, 67–73]. Competition for host cell surface receptors by some probiotics has been successful against some enteropathogens [74–76]. *L. rhamnosus* can prevent enterohemorrhagic *E. coli* (EHEC) internalization [77]. Probiotic inhibition of pathogen binding to host cells relies heavily on steric hindrance [78].

Lactobacilli have been shown to produce bacteriocins that are active against some foodborne pathogens [79]. Additionally production of various metabolites and low molecular weight products by probiotics have been shown to have antimicrobial and antifungal properties such as low molecular weight species, deconjugated bile acids, and cyclic dipeptides among others [80–85]. *Enterococcus faecium* BGPAS1–3 has been shown to produce a cell wall product that has an anti-listerial effect, prevents tight junction disruption, as well as modulating the TLR2/TLR4 immune response to *Listeria monocytogenes* ATCC19111 [86]. *L. plantarum* ATCC 8014 has recently been shown to have *in vitro* antimicrobial activity against *C. butryicum* ATCC 860, *C. difficile* ATCC 9689, and *C. perfringens* ATCC 12924 suggesting that this probiotic strain may have therapeutic potential [87].

The production of antimicrobial substances such as lactic and acetic acid is one example of probiotics making the host environment hostile for pathogens. *Lactobacillus* co-cultivation with *E. coli* O157:H7 in broth culture produced organic acids which lead to a decrease in both pH and stx_{2A} expression [88]. Low pH also prevented the induction of Stx prophage [89]. Mice given *Lactobacillus reuteri* with *E. coli* O157:H7 had decreased intestinal pathogen count, weight gain, and less kidney damage than controls [90]. The presence of probiotics in cattle feed reduced the amount *E. coli* O157:H7 seen in cattle [91]. *Bifidobacterium* strains decrease STEC and *in vivo* expression of Shiga toxin due to low pH and production of acetate [92, 93]. Pre-treatment with live Lactobacilli before *Salmonella enterica Javiana* infection in a tissue culture model showed decrease expression of virulence genes, less cytotoxicity, and reduced host production of inflammatory cytokines [94].

4. Probiotics and inhibition of bacterial toxins

Clostridium botulinum is an ubiquitous, gram-positive, anaerobic spore-forming organism that is the causative agent of botulinum. The botulinum neurotoxins are one of the most lethal toxins known to mankind with a parenteral lethal dosage of 0.1–1 ng/kg and an oral dose of 1 μg/kg. Due to this high toxicity and potential for bioterrorism, botulinum neurotoxins (BoNTs) are considered Tier 1 category Select Agents by the Centers for Disease Control and Prevention (CDC). BoNTs are a public health and safety threat in the form of foodborne, wound, and infant botulism.

In order to cause disease for foodborne botulism, BoNTs must first be able to survive in the intestinal lumen, bind to and translocate through the intestinal epithelium to reach the bloodstream [95]. Once in the bloodstream, BoNTs bind to peripheral cholinergic neurons to cleave SNAREs and block exocytosis of neurotransmitters hence leading to flaccid muscle paralysis. Similar to other classic A-B chain toxins, the heavy chain (B chain) of BoNTs bind to carbohydrate and protein receptors on their target cell while the light chain (A chain) has the enzymatic function. Therefore, there are two potential therapeutic pathways to block BoNT intoxication: (1) blocking binding/translocation at the intestinal epithelium/target cells and (2) degradation or inactivation of the toxin It has been shown that pre-treatment with probiotics (*Saccharomyces cerevisiae* var. *boulardii*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* LGG, and *Lactobacillus reuteri*) was able to block toxin binding to cells in an *in vitro* Caco-2 cell culture model and that the mechanism most likely used by the probiotics was steric hindrance of binding to host receptors [96].

Another mechanism to inactivate bacterial toxins would to be to subject them to proteolysis thus rendering them inactive. *S. boulardii* has been shown to produce a 54-KDa protease that is able to cleave and inactivate the two main *C. difficile* toxins, TcdA and TcdB [97] in a HT-29 colonic cell model. Whether or not this occurs in any significant degree in human infection is still unclear.

5. Probiotics and/or prebiotics as therapeutics to combat gastrointestinal diseases and bacterial infections

Studies in using probiotics as a treatment for a diverse set of diseases ranging from colorectal cancer, traditional gastrointestinal diseases (i.e. IBS/IBD/RCDI), as well as non-gastrointestinal diseases such as arthritis, autism, multiple sclerosis, and Parkinson's among others [99] has been undertaken. In this chapter, we will focus mainly on the effect probiotic and/prebiotic treatments on gastrointestinal diseases.

The therapeutic potential of prebiotics has been investigated for some gastrointestinal disorders. Irritable bowel syndrome (IBS) is a gastrointestinal disease characterized by chronic pain and altered bowel movements with no clear cause. Crohn's disease, a chronic relapsing inflammatory bowel disease (IBD), can affect any part of the gastrointestinal tract. For both conditions, it has been speculated that a shift in the gut microbiota population lays at the foundation of these diseases. It has been shown that the *Bifidobacteria*, *Faecalibacterium prausnitzii*, *Bacteroides* to *Firmicutes* population ratio were decreased [100, 101].

Therefore, prebiotics were hypothesized as a potential therapeutic because of its known properties to stimulate the growth of beneficial bacteria. In regards to IBS, the results were unclear for 4 clinical trials. Two clinical trials had no improvement [102, 103] whereas two studies using FOS and GOS showed an improvement in IBS symptoms [104, 105]. In the case of Crohn's disease, one study showed improvement [106] while two did not [107, 108]. As reviewed in [109], their analysis of available studies indicated that generally, the conclusions were supportive of probiotic treatment for IBS, however, the exact beneficial strains to be used were unclear. The caveats from these studies were the variabilities in the type of prebiotic(s) used, the dosage, time of supplementation, and patient disease stage. As has been used in the treatment of recurrent *C. difficile* infection (RCDI), fecal microbiota transplantation (FMT) has also been used with success in the treatment of IBS and IBD (i.e. Crohn's disease) [99].

The recurrent infection in humans with recurrent *Clostridium difficile* infection (RCDI) in hospitalized patients treated with antibiotics is a severe problem. Studies have successfully used the transfer of healthy gut microbiota to the infected individuals as a treatment [110, 111]. As reviewed in [99], an amazing success rate of ≈92% of RCDI patients was found after FMT therapy.

Another area of medical use that prebiotics may impact is on the health of preterm neonates. These babies are at significant risk of developing the severe gastrointestinal condition necrotizing enterocolitis (NEC), a life-threatening condition. Studies have shown that FOS and GOS prebiotics can help prime the growth of gut bacteria such as *Bifidobacteria* and reduce pathogenic organisms in preterm babies [112–114] thereby preventing NEC. Additionally, SCFAs from prebiotic fermentation enhances both gastric emptying and bowel motility [115, 116]. A systemic analysis of four randomized controlled trials showed elevated concentrations of fecal *Bifidobacteria* if babies were given FOS, GOS, or their mixture, but there was no significant risk reduction or progression to NEC [117]. In a review of several studies regarding probiotics and their effectiveness in preventing necrotizing enterocolitis (NEC) in preterm infants [13, 118], the authors concluded a beneficial effect of using probiotics but this benefit decreased over time. However, since the studies varied in age, doses, and duration of treatment, this observation has probably very little effect on NEC.

The successful use of probiotics in treating acute infectious diarrhea (AID) in children is well documented and accepted treatment therapy [119]. It has beneficial effects for children at risk (i.e. hospital acquired diarrhea) and should be used early after onset of symptoms. Its usage, however, in healthy populations as a preventive measure to prevent diarrhea in day care centers and communities is currently unknown and not advised.

It has been shown that *E. coli Nissle* 1917 can outcompete *Salmonella* for iron leading to reduced *Salmonella* colonization and inflammation [120]. *E. coli Nissle* 1917 also can prevent *L. monocytogenes* entry into cell lines [121]. Probiotic treatment against *Listeria* infections has best been shown in the poultry industry. Competitive exclusion (CE) cultures have been developed and used successfully. Pre-treatment with CE prevented the expansion of *Listeria monocytogenes* in young chickens [122].

The development of synthetic oligosaccharide-based mimics such as Synsorb (inert silica particles-linked to synthetic oligosaccharides) have been developed against a variety of toxins including: Stx1/2-Gb_3, Stx2e-Gb_4, Ctx-GM1, LT-GM1, epsilon toxin–GM2, TcdA-Lewis X and Lewis Y, botulinum neurotoxin- GD1a, GT1b, *E. coli* K88 ad fimbriae-nLc4, *E. coli* P pili- Gb_3 and Gb_4 [98]. However, the results for these synthetic oligosaccharide conjugates have been mixed. Synsorb-PK was designed as a mimic for Gb_3, receptor for Stx1/2, to prevent intoxication with Shigella and STEC strains but failed to prevent the progression of children to hemolytic uremic syndrome (HUS) in a clinical trial [123]. However, there could be at least two reasons as to the failure of this compound, (1) treatment given late in the onset of disease and (2) potential steric hindrance of the size of the compound. Synsorb-90 was developed in the treatment of severe colitis due to *C. difficile* infection. This compound was able to bind TcdA *in vitro* as well as decrease toxin-mediated fluid secretion in a rat-ileal loop model [124]. However, phase III clinical trials for Synsorb-90 was abandoned after promising results from both phase I and phase II trials so we still do not know its efficacy [125].

STEC gastroenteritis has not been traditionally treated with probiotics/FMT as has been seen with acute gastroenteritis and RCDI. There has been a plethora of evidence suggesting the role of probiotic strains in having an antimicrobial effect

on STEC but the effects were dependent on the strain(s) used as reviewed in [126]. Additionally, recombinant receptor mimics have been targeted against STEC [98].

In the three studies that mimicked human digestive conditions, *S. cerevisiae* CNCM I-3856 was implicated in having antagonistic effects on STEC including downregulating Stx expression and how the resident microbiota regulates infectivity [126–129].

Though there have been many successful and safe uses of probiotics for treatment of multiple conditions, there have been reported side effects linked to their usage especially in vulnerable populations [130]. As reviewed in [131], there has been movement toward using extracellular vesicles (EVs) derived from probiotic strains (both Gram-negative and Gram-positive) to deliver the same beneficial effects as from using the probiotic strains themselves. There are many different pathways that EVs utilize including bacteria-bacteria communication, affecting host microbial interactions, host immune system, increasing tight junction function, and decreasing inflammatory responses from TLR signaling [131].

6. Future works and perspectives

It has been shown that the development of gastrointestinal disease is due to an imbalance in the host response (physical, commensal microbiota, adaptive/innate immune systems) to bacterial infections. There has been an increasing accumulation of evidence (*in vitro*, *in silico*, and some *in vivo*) supporting the key role that the resident microbiota in the gut plays in mitigating bacterial infections as well as metabolic and physical diseases. There has been development of novel therapies all designed to replace/regenerate the lost beneficial commensal strains in a variety of diseases such as IBS, IBD, acute gastroenteritis, NEC, RCDI, etc. There has been tremendous success in the treatment of RCDI, IBS, and IBD using FMT therapy. However, it is still unclear from all the evidence that giving probiotics and/or prebiotics will mitigate all gastrointestinal diseases [13]. The beneficial effects of a probiotic(s)/prebiotic mixture is utterly dependent on many factors including: time of dosage in relation to disease, probiotic strains used, prebiotics given, dosage, time of treatment, pre, post, and the pre-existing health and/or the microbiota of the host. Additionally, the clinical trials should also be developed with statistical power to clearly answer the question at hand.

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Conflict of interest

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