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Diet modulates host health through gut microbiota derived extracellular vesicles: A short review

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ABSTRACT

Gut microbes are involved with many host physiological processes including digestion, metabolism, immune response, gut function and behavior. Among all the factors, diet is being considered the most important one to modulate gut microbiota composition, metabolism and their metabolites. Extracellular vesicles (EVs) are secreted to the intestinal environment by gut microbes and play an essential role in gut microbe-host communication. This paper aims to review how diet affects gut microbial EVs and its composition as well as how this change further affects host health. This review summarizes the latest research progress of interaction among diet, gut microbial EVs, and host health. Through the microbiota-gut axis, gut microbial EVs involve in many physiological activities, including brain function, metabolism, gut function and immune response. It has been verified that diet composition has direct changes on gut microbial morphology and internal molecules within gut microbial EVs. Overall, studies investigating the effects of diet through gut microbial EVs on host health are very limited. Future research regarding axis of diet-gut microbial EVs-host health is recommended.

Introduction

The resident bacteria in the gut have significant effects on host's physiology and pathology. Colonizing the gastrointestinal tract, gut microbiota is involved in many host essential processes, such as digestion, metabolism, immune system development, gut function and behavior (Diez-Sainz *et al.*, 2022; Sommer and Backhed, 2013). Numerous diseases are related with gut microbiota dysbiosis (Durack and Lynch, 2019). For example, gut microbiota dysbiosis may play a role in the onset and progression of obesity and diabetes (Cuevas-Sierra *et al.*, 2019). Manipulation of gut microbiota is considered a possible way to treat microbiota related diseases. Many factors, including diet, the use of antibiotics and probiotics, age, stress, and host genotype, could modulate gut microbiota composition, their metabolism as well as their metabolites (Sommer and Backhed, 2013; Yadav *et al.*, 2018). Among all the factors, diet is being considered the most important one (Kim *et al.*, 2013). Thus it is necessary to understand how to best manipulate gut microbiome through diet regulation (Liu *et al.*, 2016).

As crucial players in inter-kingdom communications, extracellular vesicles (EVs) are being studied by many scientists recently. EVs are heterogeneous, phospholipid membrane-enclosed structures and can be secreted by all kinds of organisms, including eukaryote, bacteria, and archea (Woith *et al.*, 2019). Bacterial EVs, discovered in both Gram-negative and Gram-positive bacteria, share many common traits with eukaryotic EVs, such as size, morphology, physical and chemical properties. Microbial EVs contain nucleic acid, protein, metabolites and other biomolecules as cargo and are essential in inter-kingdom communication (Badi *et al.*, 2017). EVs are present in biological fluids and are involved in multiple physiological and pathological processes. They are now considered as an additional

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mechanism for intercellular communication, thus allowing the exchange of internal contents. Unlike gut microbes, microbial derived EVs can pass through the mucus layer to reach the host. Gut microbe derived EVs can be considered as biomarkers of certain disease (Tulkens *et al.*, 2020). How gut microbial EVs affect host health has been reviewed by many researchers (Badi *et al.*, 2017; Cuesta *et al.*, 2021; Diez-Sainz *et al.*, 2022; Macia, Nanan *et al.*, 2019; Sultan *et al.*, 2021). EVs were originally considered diet-independent metabolites (Shen *et al.*, 2012). However, recent studies have shown that gut microbial EVs are affected by diet (Choi *et al.*, 2015; Lagos *et al.*, 2020; Tan *et al.*, 2022). This review aims to summarize the existing studies on how diet shapes gut microbial profiles and how this affect host health. Hopefully this paper can bring the consideration of promoting host health through modulating gut microbial EVs by diet.

Diet affects host health through gut microbial EVs

Bacteria produce EVs to improve their survival by releasing misfolded proteins or toxic materials to remove surface-attacking agents (Macia *et al.*, 2019). Increased microbial stress could increase microbial EV production (Macia *et al.*, 2019). EVs lipid bilayer protects the internal molecules such as enzymes, toxins, nucleic acid, antigenic determinants, and metabolites from degradation in the gastrointestinal tract (Shen *et al.*, 2012). miRNAs within EVs can both directly act on RNA and at the DNA level to affect gene expression by aligning to either the plus or minus target strand (Liu *et al.*, 2016). Other than the common contents from mammalians and plants EVs, microbial EVs can also include harmful molecules such as lipopolysaccharide (LPS), peptidoglycan, toxins etc. Gut microbial EVs can cross the intestinal and brain barriers (Diaz-Garrido *et al.*, 2021). The interaction of gut microbes and the host rely on translocation of gut microbial components entering the systemic circulation (Zhou *et al.*, 2018). The interaction mechanisms between gut microbes and the host are not fully understood.

Brain Function

Through the microbiota-gut-brain axis, the gastrointestinal microbiota is involved with neurodevelopmental processes and brain functions regulations. *Paenalcaligenes hominis* derived EVs can cause cognitive disorders by penetrating the brain through the blood and the vagus nerve (Lee *et al.*, 2020). Many studies have proven that microbial EVs play a role in gut-brain interaction (de, Forlenza *et al.*, 2018; Filipovic and Filipovic, 2014; Fung *et al.*, 2017). A more thorough discussion on role of microbial EVs in gut-brain communication can be found in the review by Cuesta *et al.* (2021). However, how diet induced EVs changes affect brain function has not been reported.

Metabolism

Gut microbe derived EVs move more freely than microbe as they can pass through the intestinal barrier and enter the systemic circulation. Gut microbe-derived EVs play a key role between gut microbes and host, such as in glucose metabolism and pathogenesis of T2D (Diez-Sainz *et al.*, 2022). Choi *et al.* (2015) reported that size of EVs from high fat diet-fed mice stool were much smaller than EVs from regular diet-fed mice stool. EVs from high fat diet-fed mice also had more LPS but less lipoteichoic acid. The gut microbe-derived EVs can infiltrate through the gut barrier and interfere insulin signaling in the liver, adipose tissue and skeletal muscle (Choi *et al.*, 2015). In vitro study, the authors showed that EVs from high fat diet-fed mice can induce insulin resistance and glucose intolerance in murine skeletal muscle. Compared to gut microbe, diet induced more drastic changes in the composition of gut microbial EVs in their study. The authors concluded that LPS-expressing EVs from gut microbes are the main mediator of insulin resistance in both skeletal muscle and adipose tissue and glucose intolerance caused by high fat diets (Choi *et al.*, 2015).

The composition and amount of gut microbial EVs are related to the environmental conditions such as available carbohydrate sources. Lagos *et al.* (2020) reported β-mannan can modulate porcine gut microbiota derived EVs. EVs from control group had an average diameter of 105 nm whereas EVs from β-mannan supplementation group were larger with an average size of 165 nm. The authors observed that most proteins from EVs isolated from culture grown on β-mannan are mapped to MAG53, MAG272 and MAG 343, belonging to the orders *Clostridiales*, *Bacilli* (phylum *Firmicutes*), and *Enterobacteriales* (phylum *Proteobacteria*), respectively. These proteins were involved in translation, energy production, amino acid, carbohydrate, and metabolism. The authors pointed out that EV proteins are reflecting how specific microbe are reacting to the available carbohydrate source β-mannan. 55% of the proteins identified were only detected from the EVs isolated from the β-mannan cultures not the control group.

Gut Function and Immune Response

The outer mucus layer of the intestine is where the commensal microbiota resides. The inner mucin layer prevents bacteria from accessing the epithelial cells (Wang *et al.*, 2019) indicating that the direct interaction of gut microbiota and the intestinal epithelium is not how this works. Among bacterial metabolites, food derivatives, and bacteria EVs in the luminal environment, only bacterial EVs can activate TLR4 with the contained bacterial motifs (Tan et al., 2022). Shen *et al.* (2012) reported by stimulating of TLR, *Bacteroides fragilis* derived EVs are able to promote regulatory T-cell differentiation. As a membrane associated PAMP (pathogen-associated molecular pattern), LPS can be released through bacterial EVs. As the bacterial EVs enter the systemic circulation, LPS can be delivered to different organs and elicit a variety of immunological and metabolic responses (Wispelwey *et al.*, 1989). Increased levels of systemic LPS-positive bacterial EVs were observed in patients with intestinal barrier dysfunction (Tulkens *et al.*, 2020). Evidenced by proteomic analysis of feces-derived EVs, the authors calculated that there are approximately 10^{14} bacterial EVs in the human gut and these EVs may serve as a substantial source of PAMP. The bacterial EVs can stimulate the peripheral blood mononuclear cells to secret pro-inflammatory cytokines such as IL-6, IL-8, MCP-1 and MIP-1α (Tulkens *et al.*, 2020).

Zakharzhevskaya *et al.* (2017) pointed out nontoxigenic and toxigenic *Bacteroides fragilis* represent different metabolic activities whereas the outer membrane vesicles (OMVs) play an important nutrition role. The OMVs of nontoxigenic *B. fragilis* exert beneficial effects on the intestine, such as anti-inflammatory effects on immune cells. However, their toxic counterparts contribute to bowel disease, such as colon cancer. *Lactobacillus paracasei*-derived EVs reduced the expression of LPS induced pro-inflammatory cytokins and increased the expression of the anti-inflammatory cytokins. This might be because that *Lactobacillus paracasei*-derived EVs induced the expression of ER stress associated proteins which promote the anti-inflammatory effects of the EVs (Choi *et al.*, 2020). Diverse proteins packed in microbial EVs can influence the host-pathogen interaction. Detoxified cytolysins from EVs purified from a genetically engineered *A. aureus* mutant are immunogenic in mice. These EVs can elicit cytolysin-neutralizing antibodies and protect the animals in a lethal sepsis model (Wang *et al.*, 2018). Zhang *et al.* (2018) reported the abundance of microbial proteins related to oxidative stress responses are altered in isolated free EVs from mucosal-luminal interface samples of a pediatric IBD inception cohort. The authors concluded that the aberrant host-microbiota interaction is highly correlated with alterations of microbial EVs in IBD patients. Chelakkot *et al.* (2018) observed *Akkermansia muciniphila*-derived EVs enhanced tight junction function, reduced body weight gain and improved glucose tolerance in diabetic mice induced by high-fat diet. In vitro, *Akkermansia muciniphila*-derived EVs also decreased the gut permeability of LPS treated Caco-2 cells compared to the control group (Chelakkot *et al.*, 2018).

As described above, we would expect that diet, by affecting microbial EVs, could indirectly affect the host health status. Studies on role of diet in shaping gut microbial EVs are limited. Tan *et al.* (2022) observed EVs isolated from the small intestine luminal content of mice had similar size distribution among high fat, high carbohydrate, and high protein diets. However, EVs from mice on high protein diet has a 2-fold increase in concentration compared the other two diets. The authors concluded dietary protein is the major driver of secretory IgA production which is a key mucosal component ensuring host-microbiota mutualism. Dietary protein mediates the secretory IgA production through gut microbiota derived EVs, not the T-cell-dependent pathways or changes in gut microbiota composition (Tan *et al.*, 2022). The gut microbial EVs activate Toll-like receptor to increase the epithelial expression of IgA-inducing cytokine. Succinate produced by high dietary protein is the middle player promoting gut microbial EV production. Furthermore, EVs from mice on high protein diet stimulated TLR4 to the highest extent (Tan *et al.*, 2022). Although studies regarding gut microbial EVs on gut function and immune responses are scarce, it is clear that manipulation of gut microbial EVs by regulating diet could affect host health to some extent.

Conclusions

Further studies are required to understand how diets affect gut microbial EVs profiles and how these changes affect host health systematically, thus making diet regulation a potential strategy to improve host health. All the possible bioactive molecules associated with gut microbial EVs (such as lipids, proteins, miRNAs etc) need to be identified and the mechanism behind the biological effects needs further investigation. In addition, future studies should not only focus on pure culture of bacteria but complex microbial community which is similar to gut microbial communities.

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