Vaccine Research
ISSN: 2423-4923
eISSN: 2383-2819

The Optimization of *Faecalibacterium prausnitzii* Extracellular Vesicle Concentrations on *PPARγ* and *FIAF* Expression in the Caco-2 Cell Culture Model

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ARTICLE INFO

Research Article

VacRes, 2021
Vol. 8, No. 2, 39- 43
Received: April 04, 2022
Accepted: May 02, 2022
Pasteur Institute of Iran

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KEYWORDS: *F. prausnitzii*, EVs, PPARγ, FIAF, Caco-2 cell line

ABSTRACT

Introduction: *Faecalibacterium prausnitzii* is an important member of human gut microbiota with a critical function in the health of humans through the induction of inflammatory and immune responses leading to intestinal hemostasis. Microbiota-induced extracellular vesicles (EVs) were presented as a novel communication pathway between microbiota and the host that are capable of imposing positive effects on the host. Recently, EV-based treatments have been evaluated in different studies, and using EVs derived from microbiota has been recommended in recent studies as post-vaccination adjuvants. Accordingly, in the present study, the effects of various EV concentrations on the mRNA expression of peroxisome proliferator-activated receptor γ (*PPARγ*) and fasting-induced adipose factor (FIAF) genes were evaluated and optimized in the human epithelial colorectal adenocarcinoma (Caco-2) cell line. **Methods:** The effects of the extracted EVs from *F. prausnitzii* on the *PPARγ* and *FIAF* gene expression were investigated in the Caco-2 cell line via cell culture and quantitative real-time PCR. The obtained outcomes were then compared with those of our previous study (concentrations of 50 and 100 µg/ml). **Results:** It was shown that *F. prausnitzii* EVs (150 µg/ml) significantly increased *PPARγ* and *FIAF* gene expression in the Caco-2 cell line, relative to previous studies conducted by our team. **Conclusion:** Considering the positive impact of *F. Prausnitzii* EVs on the studied genes' expression in the present study, the EVs of the bacterium will be proposed as new post-vaccination adjuvants in people suffering from intestinal barrier disorders such as inflammatory bowel disease patients. However, more studies should be performed in this respect.

INTRODUCTION

All cells can release various types of membranous vesicles such as extracellular vesicles (EVs), which are spherical lipid bilayer membranes and have a diameter of approximately 10-500 nm, including cytosolic and membranous glycolipids, proteins, nucleic acids, phospholipids, and polysaccharides. They are delivered to target cells, leading to induction of important biological responses such as the modulation of cell-mediated immune responses [1, 2]. Probiotics are live microorganisms that have positive effects on the health of the host if used in appropriate amounts. Probiotics could be identified through PRRs (Pattern Recognition Receptores) located on the cell surface of the host which lead to biological events, including strengthening of the intestinal barrier and immunomodulation or more precisely, immune system modulation [3-5]. The modulating effects of the immune system imposed by probiotics-derived EVs have been presented in different *in vivo* and *in vitro* studies [2, 3]. Previous studies have suggested using probiotics-derived EVs instead of the probiotic bacteria where their use should be avoided in high-risk groups such as patients with leaky-gut conditions caused by obesity or inflammatory bowel disease (IBD), in order to improve gastrointestinal diseases [6]. Therefore, many studies are now aiming at the EV-based treatments of probiotics [2, 7]. Recently, it has been shown that such factors (*e.g.*, probiotics) can modulate the gut microbiota and the immune homeostasis [8]. The importance of gut microbiota in modulating signaling pathways, as well as the development and performance of the immune system is well-known. Nowadays, upon quick progress in understanding the role of gut microbiota, there has been increasing interest in searching for those methods by which the

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[DOI: 10.52547/vacres.8.2.39]

composition and performance of gut microbiota could be manipulated, leading to the improvement of the health of patients and/or the prevention of the disease [9].

Previous evidence confirms a change in gut microbiota through probiotics. Classic probiotics mainly belong to the family of lactic acid bacteria, including *Bifidobacterium*, *Lactobacillus* and *Enterococcus*. Some special species of gut microbiota with positive *in vivo* and *in vitro* effects have recently been recommended as the next generation of probiotics for future manipulation methods in gut microbiota, along with health optimization [10, 11]. Currently, the therapeutic applications of probiotics and resulting EVs, including post-vaccination vaccine adjuvants, have been widely taken into consideration [7, 12, 13]. *Faecalibacterium prausnitzii* is one of the important members of intestinal microbiota with proven *in vivo* and *in vitro* anti-inflammatory impacts [14, 15]. It has become clear that its abundance in the intestine of people suffering from IBD, would be highly decreased compared to the healthy group; thus, it has been considered the marker for the recognition of a healthy intestine. Recently, *F. prausnitzii* has been recommended as the next-generation probiotic due to its positive effects on the health of human beings [11, 16]. Therefore, considering the importance of *F. prausnitzii* in the modulation of signaling pathways related to immunity and inflammation, the effects of different EV concentrations extracted from *F. prausnitzii* probiotic on the expression of peroxisome proliferator-activated receptor γ (PPARγ) and fasting-induced adipose factor (FIAF) have been optimized in Caco-2 cell line.

Inflammatory and immune responses are modulated by the interactions between the host and the gut microbiota, and this interactions adjusts signaling pathways to prevent pathogen invasion and intestinal dysbiosis [17]. Microbiota and peroxisome proliferator-activated receptors (PPARs) are closely related in the gut, and one of the most robust connections between gut microbiota and PPARs is through the production of short-chain fatty acids such as butyrate [18]. PPARs as ligand-dependent transcription factors belonging to the hormone-nuclear receptor superfamily are expressed in various tissues and are participated in different functions including metabolism. Three isoforms of PPAR, namely PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C), have already been characterized, each of which is encoded by a specific gene. Despite structural similarities, the identified isoforms have their physiological activities depending on their tissue distribution [19].

PPARγ has a vital role in maintaining intestinal microbial health and involves in the inflammation pathogenesis, tumor progress, and metabolism. Nowadays, PPARγ plays an essential role in maintaining intestinal microbial health and is involved in pathogenesis metabolism, as well as tumor inflammation and progression. It has received extensive attention in the medical field since it is the central transcriptional regulator of glucose and fatty acid metabolism [20]. Currently, researchers through designing natural and synthetic PPAR agonists (including PPARγ), use PPARs as novel therapeutic targets for the treatment of different diseases such as IBDs and obesity [19]. FIAF is one of the critical target genes for PPARγ in intestinal epithelial cells, and the butyrate-PPARγ-FIAF metabolic signaling pathway is the most well-known link between gut microbiota-PPARs [18]. Researchers have investigated FIAF as a multifunctional signaling protein in various tissues. It has been confirmed that FIAF expression in the gut is influenced by microbiota and can affect lipid metabolism. The impact of FIAF on lipid metabolism in the gut is made through the inhibition of the lipoprotein lipase enzyme [21].

The results of several studies have revealed that various bacteria-derived EVs at different concentrations have distinctive effects on the expression of their target genes [22-27]. Tabak *et al*. have demonstrated that the biological impacts of EVs at their target site are relied on their concentration [28]. In our previous study, EVs had additive effects on the gene expression of *PPARγ* and *FIAF* genes in Caco-2 cell line at concentrations of 50 and 100 µg/ml [29]. Previous evidence have confirmed the critical results of *F. prausnitzii* on the health of the host, as well as the importance of PPARγ and FIAF in creating signaling, inducing inflammatory and immune responses, and their impacts on lipid metabolism in the host. Accordingly, the current study investigated whether *F. prausnitzii* EVs can still maintain additive impacts on these genes' expression at concentrations higher than the two above-mentioned previous ones. Finally, the study examined the impacts of *F. prausnitzii* EVs on the expression of *PPARγ* and *FIAF* genes in Caco-2 cell line at the concentration of 150 µg/ml.

MATERIALS AND METHODS

Cell Culture and Treatment

As previously described, after the preparation of *F. prausnitzii* and the extraction of its EVs, Caco-2 cell line (ATCC® HTB-37) was cultured in a Dulbecco's modified Eagle's medium (DMEM)/high glucose medium enriched with 1% penicillin/streptomycin and 10% FBS (fetal bovine serum; Gibco BRL) in 5% CO_2 at 37 °C. The Caco-2 monolayer was treated with *F. prausnitzii* (at the multiplicity of the infection ratios of 10) and its EVs (at the concentration of 150 µg/ml). The phosphate-buffered saline (PBS) and sucrose were utilized as a control. Eventually, cell viability was checked following treatments [29].

Table 1. The sequence of primers utilized in the qRT-PCR [29].

Name of Gene	Anticipate Size (bp)	Symbol of Gene	Primer Pair Sequence (5' 3')
Glyceraldehyde-3-phosphate dehydrogenase	166	*GAPDH*	Forward: CAAGATCATCACCAATGCCT Reverse: CCCATCACGCCACAGTTTCC
Fasting-induced adipose factor	64	*FIAF*	Forward: CGTACCCTTCTCCACTTGGG Reverse: GCTCTTGGCGCAGTTCTTG
Peroxisome proliferator activated receptor gamma	159	*PPARγ*	Forward: GAGCCCAAGTTTGAGTTTGC Reverse: CAGGGCTTGTAGCAGGTTGT

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[DOI: 10.52547/vacres.8.2.39]

Statistical Analysis

The ΔΔCT was used to analyze the relative gene expression, and the GAPDH was considered as the internal control. Finally, gene expression changes were calculated using GraphPad Prism 8.0 for the value analysis of the cycle threshold.

RESULTS

***F. prausnitzii* EVs increased *PPARγ* and *FIAF* expressions in Caco-2 cell line**

F. prausnitzii significantly decreased *PPARγ* expression at the mRNA level (Fig. 1A), but its EVs elevated *PPARγ* expression at the mRNA level at the concentration of 150 µg/ml (Fig. 1B). Moreover, FIAF expression was significantly decreased by *F. prausnitzii* (Fig. 1A), while its EVs (150 µg/ml) increased at the mRNA level (Fig. 1B).

Our data indicated that unlike *F. prausnitzii* which markedly decreased *PPARγ* and *FIAF* expression, its EVs notably, increased the expression of *PPARγ* and *FIAF* in Caco-2 cell line at the concentration of 150 µg/ml. These findings were consistent with the results of a previous study evaluating the impact of *F. prausnitzii* EVs (at the concentrations of 50 and 100 µg/ml) on *PPARγ* and *FIAF* expression [29]. Comparison of the results of this study with those of the previous research (Fig. 2), indicated that *F. prausnitzii* EVs could increase *PPARγ* and *FIAF* expression in a dose-dependent fashion in Caco-2 cell line [28].

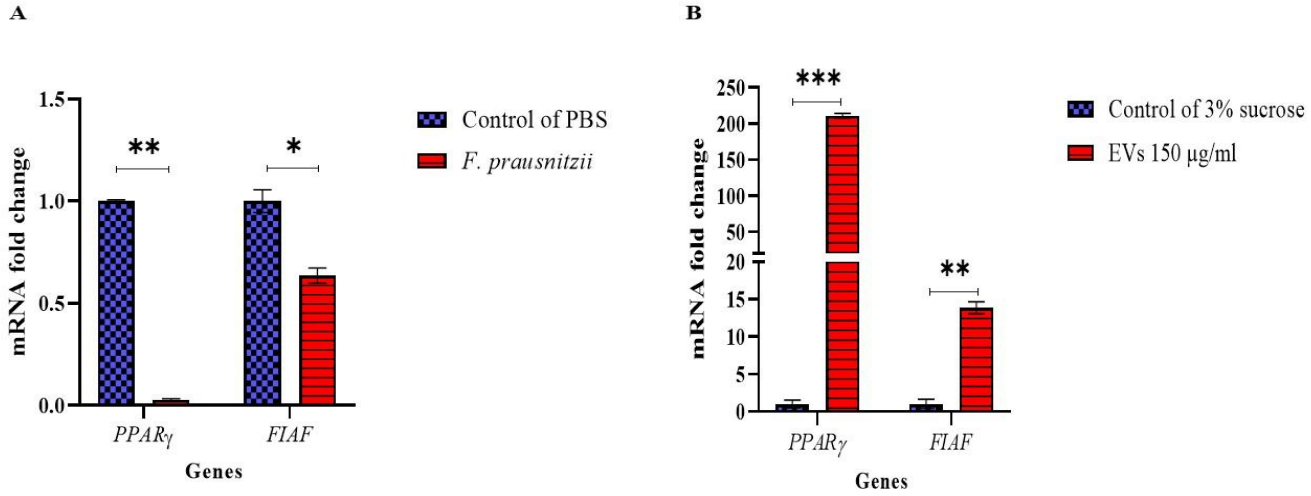

Fig. 1. The impact of *F. prausnitzii* and related EVs on *PPARγ* and *FIAF*: (A) *F. prausnitzii*-treated Caco-2 cells (MOI=10) and (B) Caco-2 cell treatment with *F. prausnitzii*–derived EVs at the concentration of 150 µg/ml. EV: extracellular vesicle; MOI: Multiplicity of infection. *** $P < 0.001$, ** $P < 0.01$, and * $P < 0.05$, were statistically significant. We applied *GAPDH* as the internal control.

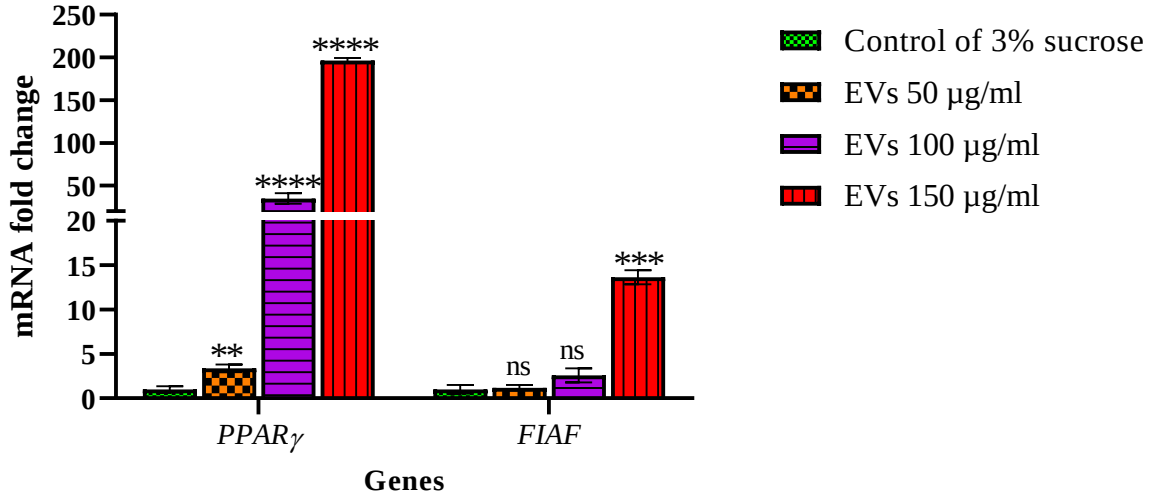

Fig. 2. Comparison results of the previous and current studies on the impact of EVs on the expression of *PPARγ* and *FIAF* genes in the Caco-2 cell line at 50 and 100 µg/ml concentrations. EV: extracellular vesicle; *$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$ are statistically significant. We used GAPDH as the internal control.

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DISCUSSION

Probiotic bacteria, including *F. prausnitzii*, are crucial for human intestinal health. Nonetheless, the utilization of probiotics-derived EVs, compared to the probiotic bacteria, is probably more critical for "leaky-gut" conditions. These EVs can induce different signaling pathways to improve various diseases, including IBD, caused by the disruption of the intestinal epithelial barrier. The pathophysiological processes of inflammatory bowel diseases (IBDs) are not fully understood yet; however, it is well known that inflammatory lesion pathogenesis is due to an irregularity or disorder in the regulation of the intestinal immune system and the overproduction of proinflammatory cytokines. The evidence highlights the role of genetic and environmental factors in IBD. Regarding the environmental factors, the microbiota seems to perform a vital role. PPARs as nuclear receptors affect lipid metabolism, glucose homeostasis, immune/inflammatory processes, fibrosis, and cell proliferation. In addition, they interact with various environmental factors such as microbiota and can modulate them. Through observing the flawed expression of PPARγ in the colon epithelial cells of ulcerative colitis patients, it has been suggested that impaired PPARγ signaling could be a critical step in the pathogenesis of IBD [31].

Several studies have confirmed the positive effect of *F. prausnitzii* EVs relative to the bacterium using Caco-2 and A549 cell lines, [22, 25, 26], which were in line with our findings. For example, Yaghoubfar *et al.* have shown that, unlike the bacterium, *F. prausnitzii* EVs increased the expression levels for serotonin in Caco-2 cell line [26]. Given the previous findings, the gut microbiota performs as a metabolic organ through interactions with the human metabolic system. First, the gut microbiota probably improves the energy efficiency of the host via fermenting indigestible food. Moreover, fatty acid flux and its storage in the adipose tissue are controlled by FIAF expression, which depends on the gut microbiota [32]. In our work, *F. prausnitzii* had no impact on the expression of *PPARγ* and *FIAF* genes in Caco-2 cell line.

According to the obtained data from this research and other studies, although FIAF expression depends on the existence of microbiota in the intestine, its expression differs in several bacterial species. Recent investigations have represented that diverse bacterial species in different intestinal cell lines may have different influences on FIAF expression [33-37]. For instance, the Aronsson team have revealed that the probiotic bacterium *Lactobacillus paracasei* ssp. *paracasei* F19 increases PPARγ transcription factor and its target gene (FIAF) in HCT116 cell line, which contradicts the results of the present work. Additionally, Couvigny et al. have found that Streptococcus salivarius strains reduce the expression of *PPARγ* and *FIAF* in HT-29 cell line [38], which conforms to the results of the current study regarding the impact of *F. prausnitzii* on expressing these genes in Caco-2 cell line.

The gut microbiota possibly applies its effect on the activation of transcription factors and induction of gene expression through interactions with each other in the gut. For example, in a reported research by Mennigen group, a probiotic mixture consisting of diverse probiotics (*e.g.*, *Bifidobacterium* and *Lactobacillus* species) induces protective effects on the intestinal barrier function in colitis-induced mice [39]. Therefore, probiotic bacteria alone may not induce gene expression in the host, and some probiotic bacteria require the presence of other probiotic bacteria to induce signaling pathways, leading to gene expression in the host. Several studies have reported that natural and synthetic PPARγ agonists can improve intestinal inflammation and lipid and glucose metabolism in the host. For instance, the Bassaganya-Riera group have obtained molecular evidence through which colitis inflammation reduces with a PPARγ-dependent mechanism using *in vivo* IBD models [21, 40, 41]. The roles of probiotics bacteria and their related EVs have been recently studied as new post-vaccination adjuvants [7, 12, 13]. Recent research has demonstrated that adjuvant priobiotics and intestinal barrier microbiome can increase immunogenicity resulting from vaccines, especially in high-risk groups, including elderly people [13]. Clinical studies and those performed on animal models have suggested the essential role of activities and composition of human gut microbiota in the adjustment of safety responses to vaccination. Therefore, considering the useful effects of *F. Prausnitzii* EVs in the present study, EVs from this bacterium can be recommended as post-vaccination adjuvants in people suffering from intestinal disorders such as IBD.

In conclusion, according to previous data and the beneficial impact of *F. prausnitzii* EVs on the expression of *PPARγ* and *FIAF* in present study, *F. prausnitzii* EVs have probably a dose-dependent impact on the studied gene expressions. The EVs of this bacterium can be suggested as a new PPARγ agonist suitable for regulating inflammatory pathways and lipid metabolism in "leaky-gut" conditions. However, further evaluations are suggested in future studies, including confirming the investigated gene expression in this study and examining the impacts of *F. prausnitzii* EVs in animal models.

ACKNOWLEDGEMENT

We highly appreciate the staff of Mycobacteriology and Pulmonary Research Department and Microbiology Research Center of Pasteur Institute of Iran for their support in the present study.

CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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