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Th17 immune response in inflammatory bowel disease: Future roles and opportunities for lactic acid bacteria and bioactive compounds released in fermented milk

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ABSTRACT

Background: Evidence have shown that Th1- and Th17-related cytokines are often elevated in inflammatory bowel diseases (IBD). Hence, targeting Th17 cells or their effector cytokines represents an attractive alternative for treatment IBD. In this context, recent evidence have indicated that fermented dairy products, with specific lactic acid bacteria, selectively targeting the Th17 lineage, suggesting their effectiveness in preventing and treating IBD.

Scope and approach: This review aims to present an overview of the available information on the role of Th17 in inflammatory bowel diseases, and on the potential of fermented milk in the prevention and management of IBD, by modulating this response.

Key findings and conclusions: Recent evidence has shown that fermented milks may contain specific bacteria and/or bioactive compounds (e.g., peptides, exopolysaccharide, free amino acids, organic acid and vitamins) released during fermentation, capable to downregulate the production of pro-inflammatory cytokines related to Th17 cells, including IL-17, IL-10, IFN, IL-6, IL-23, and TGF-β, by modulating TLR signaling and differentiation of native Th cells into Th1, Th2 or Th17 effector cells. Hence, such fermented milks represent a promising alternative for the treatment of IBD. However, further studies are required to elucidate the molecular mechanisms of bacteria and bioactive components responsible of such anti-inflammatory effects.

1. Introduction

Over the last decade, the production of fermented milk products has increased, and according to some statistics (https://www.alliedmarketresearch.com/fermented-milk-market-A05952) (Allied Market Research, 2020), this production will growth dramatically by 2026, especially for those products that provide health benefits, including preventive effects against cardiovascular disease and enhancement of the immune system (Bordoni et al., 2017; Coqueiro, Raizel, Bonvini, Tirapegui, & Rogero, 2018; Guo et al., 2017).

Such fermented milk products, in addition to having dairy minerals and vitamins with important metabolic roles, may also contain specific lactic acid bacteria (LAB) capable to produce different compounds with health effects, such as peptides, free amino acids (Korhonen, 2009), and exopolysaccharides (Santiago-López et al., 2018). Hence, research has focused on the screening of new LAB able to produce such bioactive compounds in fermented milk (Beermann, & Hartung, 2013). In this sense, the production of bioactive peptides by *Lactococcus lactis* strains (NRRL B-50571 and NRRL B-50572) has been documented; these compounds have demonstrated antihypertensive (Beltrán-Barrientos, Hernández-Mendoza, Torres-Llanez, González-Córdova, & Vallejo-Córdoba, 2016; Marcone, Belton, & Fitzgerald, 2017), antimicrobial,

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antioxidative (Balakrishnan & Agrawal, 2014), immunomodulatory (Foligné et al., 2016), opioid, and anti-inflammatory effects (Lordan & Zabatakis, 2017). Additionally, the production of exopolysaccharides, free amino acids, and organic acids (Santiago-López et al., 2015; Wang et al., 2012) have been also reported for other LAB. These compounds have shown to modulate the immune system and improve inflammatory bowel diseases (IBDs), as ulcerative colitis and Crohn's disease (Matsumoto, Watanabe, Imaoka, & Okabe, 2001; Santiago-López et al., 2018; Yoda et al., 2014).

IBDs are related to an excessive and uncontrolled immune response mediated by Th1, Th2 or Th17 cells and their related cytokines. Particularly, Th17 cells infiltrating the inflamed intestine secrete IL-17 and other cytokines such as (e.g., TNF-α, IL-1β, IFN-γ, GM-CSF, and IL-22), which can, in turn, trigger and amplify the inflammatory process on mucosal surface (Okada, Puel, Casanova, & Kobayashi, 2016). On the other hand, Th17 cells have also been associated with some diseases mediated by immune system, as the multiple sclerosis and arthritis (Kempski, Brockmann, Gagliani, & Huber, 2017; Ruiz de Morales et al., 2020). Th17 cells may enhance the expression of some neutrophilic chemokines such as CXCL1, CXCL2, and CXCL5 (Griffin et al., 2012). On the other hand, the activating transcription factors STAT3 and IL-23 is required for the proliferation and survival of Th17 cells (Ruiz de Morales et al., 2020). Besides, Th17+ cells activation also promote the expression of IL-10, an important regulatory cytokine in the inflammatory processes (Ahern et al., 2010; Cosmi et al., 2010; Evans et al., 2014). Recently, the role of theTh1/Th17 axis and Treg/Th17 cells has also been documented in the pathogenesis of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis as well as hypertension, atherosclerosis, and IBD (Bunte & Beikler, 2020).

Despite several studies have shown that consumption of some fermented milk products can improve Th1/Th2 immune homeostasis in IBD, a few studies have been conducted to determine the role of fermented milk on Th17 response (Coqueiro et al., 2018; Lee, Yin, Griffey, & Marco, 2015; Santiago-López et al., 2018; Ueno et al., 2017), even though, the potential role of Th17 cells in the pathogenesis of inflammatory bowel disease. Therefore, the aim of the present work was to provide an overview of the available evidence supporting the potential role of fermented milk in the prevention and management of inflammatory bowel diseases by modulating the Th17 response.

2. Th17 response in inflammatory bowel disease

The gastrointestinal system is protected by a thick luminal mucin layer, a single epithelial cell barrier, and immunological molecules such as IgA and cytokines (Macpherson, Koller, & McCoy, 2015). However, the inflammatory processes, during several gastrointestinal disorders, can modify the intestinal barrier, that directly or indirectly, promotes the production of anti-inflammatory cytokines, which are crucial for protecting the intestinal epithelium and for suppressing the development of T-cells, thus contributing to maintain the homeostasis of the gastrointestinal tract (Ueno et al., 2017).

Previous studies have shown that a specific pattern of immune response is involved in the development of IBD. In ulcerative colitis, there is a pronounced Th2 response characterized by the presence of the cytokines IL-5 and IL-3, which may be mediated by the activation of the transcription factor GATA3. On the other hand, Crohn's disease is characterized by a Th1 response along with the presence of cytokines (e.g., IFN-γ, IL-6, and IL-12) and the activation of T-bet (Strober & Fuss, 2011). Interestingly, the Th17 response is involved in both pathologies, ulcerative colitis and Crohn's diseases; as well as Treg cells play an important role in anti-inflammatory and immunoregulatory responses (Omenetti & Pizarro, 2015).

A close relationship has been reported among the Th17 response Th1, Th2 and Treg responses. For the activation of Th17/Treg, some specific conditions must be present, as the expression of the transcription factor for Treg cells (FoxP3+) and the retinoic acid-related orphan receptor γ (RORγ) for the Th17 cells (Ueno et al., 2017). Particularly, epithelium, innate lymphoid cells, antigen-presenting cells (APCs), and T and B cells are involved in the regulation of homeostatic enteric microbiota to generate adaptive antigen-specific responses (Blander, Longman, Iliev, Sonnenberg, & Artis, 2017). Similar to Th1 and Th2, Th17 cells have their own distinct set of differentiation factors. For instance, a combination of cytokines, namely transforming growth factor (TGF)β and IL-6 are required for differentiation *in vitro*, but IL-23 is required for stabilization (McGeachy et al., 2009). This observation was taken up again in human studies, where these cytokines were indispensable for the activation of *RORC,* which encodes for RORγt, a key master regulator in the development of T helper 17 cells (Manel, Unutmaz, & Littman, 2008).

On the other hand, it has been reported that patients with intestinal diseases, such as Crohn's disease, express IFNγ + and IL-17A + cells cytokines. Specially, IFNγ has been associated with Th1 cells in inflammatory lesions of colitis. Harbour, Maynard, Zindl, Schoeb, and Weaver (2015) confirmed these observation by using a Th17 transfer model of colitis. Authors found that IFNγ-deficient Th17 cells retained an IL-17A + phenotype and were unable to induce colitis in recipients. These findings reveals the key role of Th17 cells as mediators of colitis pathogenesis by either directly transitioning to Th1-like cells and by supporting the development of classic Th1 cells (Harbour et al., 2015).

A clinical assay showed an extensive Th17 cells and IL-23 in the intestinal mucosal of IBD patients, compared to healthy subjects. Besides, the production of IFN exhibited the relation between Th1/Th17 cells (Maggi et al., 2010). However, in some cases the production of IL-17 has opposite contribution, for instance, in a model of inflammation, IL-23, TNFα and GM-CSF where involved in pathogenesis, while IL-17 was protective (Komuczki et al., 2019).

In this sense, the activation of antigen-presenting cells (APCs), including dendritic cells and macrophages, promote the secretion of IL-1β and IL-6, which are important for the differentiation and maintenance of Th17 cells (Ueno et al., 2017). Additionally, the presence of IL-23 is required to maintain RORγ; then, Th17 may be stabilized (Gaffen, Jain, Garg, & Cua, 2014).

In particular, IL-17A and IL-17F have a powerful inflammatory effect on the mucosal surfaces in combination with TNF-α, IL-1β, IFN-γ, GM-CSF, and IL-22 (Okada et al., 2016). Besides, the expression of IL-12 and IL-23 may enhance T-bet and promote the Th1 response. Furthermore, under above mentioned conditions, Th17 may drive IL-10 expression and have regulatory properties (Ahern et al., 2010; Cosmi et al., 2010; Evans et al., 2014). Additionally, the enhancement of IL-23 by APCs, or granulocytes, has been reported in murine models of colitis and colitis-associated cancer. The suppression of IL-12/IL-23 p40 or IL-23 p19 and IL-23R could diminish inflammatory processes at the gastrointestinal level; thus, all of them could be considered target molecules (Neurath, 2019).

Overall, the microbiota, and some probiotics strains, have a specific role as regulator of IL-17A production by interacting with immunological and non-immunological cells, including macrophages/lymphocytes and epithelial cells, respectively (Luzza et al., 2000). In this regard, the IL-17A plays a protective dual role by inducing the immune response against the intestinal microorganism and by protecting against inflammatory based diseases, including IBD (Douzandeh-Mobarrez & Kariminik, 2019; Kumar et al., 2016). Specifically, IL-17A regulates intestinal pIgR expression and IgA production; and induces secretion of antimicrobial peptides such as calprotectin, lipocolin, β-defensin, and α-defensins (Cao et al., 2015; Rizzo, Losacco, Carratelli, Domenico, & Bevilacqua, 2013). These mechanisms are involved in some other diseases, e.g., rheumatoid arthritis, oral antibiotic treatment leads to skin microbiota dysbiosis, obesity and insulin resistance diabetes (Douzandeh-Mobarrez & Kariminik, 2019).

Therefore, the evidence suggests that the activation of Treg/Th17 and/or Th1/Th17, plays a kye role in the development of inflammatory diseases (Bjaumik, & Basu, 2017). On the other hand, the reduction of

the Th17 response decreases inflammation, at a systemic level, which may be caused by hypertension, obesity, diabetes, multiple sclerosis, or IBDs (Bunte & Beikler, 2020).

Considering that evidence points out that the Th17 response can be modulated by specific components present in fermented milks, there is growing interest in the beneficial effects of such fermented milks, including their anti-inflammatory properties and the effect on the immune system/response.

3. Role of lactic acid bacteria and bioactive compounds in inflammatory processes

The interaction of bacteria and the immune system has been established as essential factor for the development of the gastrointestinal system and tolerance to specific antigens. Milk and dairy products have received special attention in recent years due to their nutritional value and the physiological impact of their bioactive components (Granier, Goulet, & Hoarau, 2012). Several *in vitro*, *in vivo*, and clinical studies have documented the beneficial health effects of LAB, bioactive peptides, and exopolysaccharides, either isolated or contained into fermented milks (Matar, Goulet, Bernier, & Brochu, 2000; Rodríguez, Medici, Rodríguez, Mozzi, & Font de Valdez, 2009; Santiago-López et al., 2015).

3.1. Effect of lactic acid bacteria

In recent years, the search for new treatments to reduce IBD has grown. LAB have potential applications in this regard because of their anti-inflammatory effect either by the bacteria *per se* or by the bioactive metabolites produced during milk fermentation (Owaga et al., 2015). Several studies have demonstrated the effects of LAB at different concentrations in animal models and clinical assays (Coqueiro et al., 2018). The anti-inflammatory effect of specific LAB, including probiotics, has been attributed to different mechanisms, such as antagonism against pathogens, improvement of epithelial barrier function, and immunomodulation of Th1, Th2, Treg, and Th17 cell production (Miyauchi et al., 2013; Tanabe, 2013).

For instance, *Lactobacillus casei* Shirota has been reported to mitigate the inflammatory processes by downregulating the production of IL-6 and IFNγ in lamina propria mononuclear cells derived from mice with chronic colitis and in peripheral blood mononuclear cells from patients with ulcerative colitis. These results suggest that *L. casei* Shirota can potentially be used to downregulate the inflammatory process of IBD (Matsumoto et al., 2005). Furthermore, the administration of live *L. casei* Shirota (1×10^9 CFU/mL) in rats, with indomethacin-induced inflammation, shown to prevent the enhancement of myeloperoxidase activity and expression of TNFα mRNA, and led to the inhibition of NF-kB in THP-1 cells, suggesting an anti-inflammatory effect via the LPS-TLR4 (Toll like Receptor) signaling pathway (Watanabe et al., 2009). These cytokines are important defense mechanisms, but their over-production can contribute to an enhancement of the inflammatory processes in several diseases.

In contrast, *Lactobacillus rhamnosus* GG (LGG) (1×10^8 CFU/mL) and *Bifidobacterium lactis* Bb12 (1×10^9 CFU/mL) shown to increase myeloperoxidases, ulceration, and cells proliferation; and to decrease crypt cell apoptosis compared to the control group (inflammation induced by indomethacin) (Kamil, Geier, Butler, & Howarth, 2007). On the contrary, the administration of a dairy product with LGG (1×10^7 CFU/mL) for 5 days, shown to protect the gastric mucosal barrier of 16 healthy volunteers that ingested indomethacin (Gotteland, Cruchet, & Verbeke, 2001). These results are contradictory; hence, the expression and production of cytokines, the administration time or dose, the food matrix, and the signaling pathways associated with the anti-inflammatory effect should continue to be evaluated.

In this regard, Lee et al. (2015) suggested that *Lactobacillus casei* BL23 (2×10^7 CFU/mL), in combination with milk, protects against the development of colitis in mice. Authors noted less weight loss and reduced diarrheal stool in treated group than the control group. Additionally, there was observed a decrement in neutrophil infiltration, and the cytokines IL-1α, IL-6, IL-17, KC, G-CSF, and MCP-1 with respect to the control group (Lee et al., 2015). Hence, authors conclude that the efficacy of LAB was influenced by the food matrix.

In another study, a commercial product (VSL#3), containing *Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve*, *Bifidobacterium infantis*, *Lactobacillus acidophilus, Lactobacillus plantarum*, *Lactobacillus casei*, and *Lactobacillus bulgaricus,* was administrated for 7 days to a rat model of induced colitis by DSS. Results showed a decreased myeloperoxidase activity, and reduced levels of iNOs, COX-2, NF-kB, TNFα and IL-6. Moreover, enhancement of IL-10 was recorded, suggesting that the anti-inflammatory effect observed may be due to inhibition of P13k/Akt and NF-kB pathways (Dai, Zheng, Meng, Zhou, Sang, & Jiang. 2013).

Therefore, several studies have demonstrated not only the anti-inflammatory effects of LAB, specifically of probiotic bacteria, but also their beneficial effect on disease activity markers, e. i, body weight loss, stool consistency, rectal bleeding, and overall conditions (Geier, Butler, Giffard, & Howarth, 2007; Herias, Koninkx, Vos, Huis, Veld, & van Dijk, 2005; Kawahara et al., 2015). However, further studies are needed to evaluate the immune system response and mechanisms involved.

Several studies have demonstrated the potential role of some LAB in decreasing the inflammatory response through affecting the Th17 response. For instance, administration of different concentrations (10^4–10^8 CFU/mL) of *Lactobacillus acidophilus* in mice with DSS-induced inflammation, shown to decrease IL-17 production. Besides, a downregulate IL-23 and TGF-β1, downstream phosphorylation of pSTAT3, and regulation of IL-23/Th17 cells was observed (Chen et al., 2015). In another study, a reduction of IL-6, TNF-α, IL-1β, and IL-17 concentration, and an increase of Foxp3, Treg, and IL10 were observed, suggesting that the administration of *L. acidophilus* (8×10^{10} CFU/kg) to treat IBD, could be achieved by modulating the balance between Th17 and Treg (Park et al., 2018). Meanwhile, *Lactobacillus fermentum* KBL374 and KBL375 (5×10^8 CFU/mL) enhanced IL-10 and CD4+Cd25+Foxp3+Treg in mesenteric lymphoid nodes (Jang, Kim, Han, Lee, & Ko, 2019). Based on these findings, the capacity of new strains alone or in fermented milk to decrease the Th17 response should continue to be evaluated.

3.2. Bioactive components

Milk is the most important source of bioactive peptides. These peptides can be released through different mechanisms, such as enzymatic hydrolysis, fermentation, or gastrointestinal digestion (Mohanty, Mohapatra, Misra, & Sahu, 2016). On the other hand, it has been reported that the sequence and structure of amino acids may influence their potential health effects (Pessione & Cirrincione, 2016).

Cyto-chemical studies have documented the capacity of bioactive peptides, derived from casein and whey protein, to promote macrophage phagocyte activity, human lymphocytes, antibody synthesis, and cytokine production (Anusha & Bindhu, 2016). In a previous study, the hydrolysates of milk whey were found to suppress the IL-8 cytokine on the epithelial cell, and reduced LPS binding to surface of TLR4, suggesting the potential anti-inflammatory effect via TLR4 pathway (Iskandar, Dauletbaev, Kubow, & Mawji, 2013). In a related study, authors evaluated the administration of pasteurized fermented milk with *Lactobacillus* strains and peptide fractions (<10 kDa) in a murine model with LPS-induced inflammation. The findings showed a decrease in IL-6 and TNF-α and enhancement of IL-10 at the systemic level (Reyes-Díaz et al., 2018). These results suggest that fermented milk and peptides have a potential anti-inflammatory effect, although the mechanisms were not evaluated.

In another study, the anti-inflammatory effect of casein-derived peptides was evaluated in a murine model of trinitrobenzene sulfonic

acid-induced Crohn's disease. The results showed a decrease in mortality rates. Besides, a faster recovery of initial body weight, a decrease in myeloperoxidase activities in the gastrointestinal system, enhanced production of IL-10, and decreased production of IFNγ were also observed (Turbay, De Leblanc, Perdigón, De Giori, & Hebert, 2012).

In a related work, glycomacropeptide (GMP) and milk-derived peptides, produced by a simulated gastrointestinal digestion, were able to enhanced the proliferation of splenocytes *in vitro*, and induced the expression and production of nitric oxide synthase, cyclooxygenase, IL-10, and Foxp3+. Additional studies have also evaluated the effects of GMP. For instance, GMP in human peripheral blood monocytes was found to up-regulate the secretion of TNF, IL-1β, and IL-8, inhibit the signaling of MAPK or NF-kB, and induce the phosphorylation of NFkB (Requena et al., 2009; Sánchez de Medina et al., 2010). Recently, the protective effect of GMP was evaluated in an indomethacin-induced enteropathy model in Wistar rats. Interestingly, GMP administration for seven days prevented weight loss and decreased neutrophil infiltration, CXCL1, IL-1β, and inducible iNOS expression. Additionally, NO and lipid hydroperoxide levels decreased. These results suggest that GMP has both a protective and antioxidant effect (Cervantes-García et al., 2020).

As previously mentioned, exopolysaccharides (EPSs) are metabolites produced by LAB during milk fermentation. In general, EPSs are used as emulsifying agents in the food industry (Fernandez, Picard-Deland, Le Barz, Daniel, & Marette, 2016). However, recent studies have demonstrated that they possess immunomodulatory, antitumor, and cholesterol-lowering effects (Al-Dahi, Esmail, Duraipandiyan, & Valan, 2019; Al-Dahi, Esmail, Duraipandiyan, Valan Arasu, & Salem-Bekhit, 2016; Almalki, 2020). Although few reports exist, an acidic heteropolysaccharide of glucose, galactose, and glucosamine secreted by *Lactobacillus fermentum* RS20D may stimulate macrophage RAW264.7 cells and release nitric oxide, similar to the group with LPS, in addition to increasing the mRNA expression of TNF-α and IL-6. These results suggest that this EPS produced by *Lactobacillus fermentum* RS20D has an immunostimulant effect (Zhu et al., 2019).

Other LAB metabolites, such as gamma aminobutyric acid (GABA), may also be present in fermented milk. *In vivo* studies have showed that GABA can reduce the production of inflammatory cytokines and proliferation of T cells (Bjurstom et al., 2008; Mendu et al., 2011; Tian et al., 2004). Additional studies have demonstrated the role of GABA receptors in ulcerative colitis (Aggarwal, Ahuja, & Paul, 2017; Ma et al., 2018). In this sense, the exposure of mice to early-life stress was found to significantly alter $GABA_A$-mediated contractility and impair barrier function. Furthermore, colon tissue showed increased levels of Gabra3 mRNA. Overall, the results show that stress increases colon inflammation and is mediated by $GABA_A$ receptors (Seifi, Rodaway, Rudoplh, & Swinni, 2018). Accordingly, this metabolite could confer anti-inflammatory properties to GABA-rich fermented milk. However, more studies are needed to confirm this hypothesis.

4. Future trends in dairy fermented and the th17 response

As mentioned before, there are several studies addressing the anti-inflammatory properties of fermented milks and their bioactive components (e.g., bacteria, peptides, EPS). However, little is known about the effect of these components and fermented milks on the Th17 response involved in IBD (Santiago-López et al., 2018; Yoda et al., 2014).

Continuous administration of yoghurt to BALB/c mice, with acute inflammation induced with trinitrobenzene sulfonic acid (TNBS), has shown to decrease the IL-17, and IL12 levels and enhance IL-10 in the intestinal tissues. Besides, changes in the intestinal microbiota were observed (de Moreno de LeBlanc, Chaves, & Perdigón, 2009). In the same way, female BALB/c mice were induced to inflammation with TNBS. Then, yoghurt prepared with eight *Lactobacillus delbrueckii* subsp *bulgaricus* (CRL 861, 863, 864, 866, 869, 871, 872 and 887) strains and two *Streptococcus thermophilus* (CRL 806 and 807) strains, was administered to mice by 14 days. Results showed an overproduction of Th1 cytokines. The main mechanism of activation of this response may be mediated by regulation of TLR4, which was observed to be markedly decreased in those groups treated with TNBS and yogurt (Chaves, Perdigon, & de Moreno, 2011). In this sense, a strategy for decrease the inflammation process may be regulated by suppressing the TLR4 expression or TLR9.

Furthermore, there is evidence that the administration of fermented milk with *Lactobacillus rhamnosus* GG to C57BL/6 mice for six days, before and during the DSS-induced intestinal inflammation, decreased ($p < 0.05$) colon shortening, stimulated the epidermal growth factor receptor (EGFR), and suppressed apoptosis and H_2O_2 production. These finding were attributed to the soluble proteins p40 and P75 (Yoda et al., 2014), which have previously shown protective effect on the intestinal barrier through the p40 EGFR pathway (Seth, Yan, Polk, & Rao, 2008; Yan et al., 2018).

Plé et al. (2016) performed a preventive intervention study using a chemical-induced colitis model. Mice received, by oral gavage, experimental fermented dairy products, i. e, a single-strain fermented milk (*Lactobacillus* subsp. *lactis* CNRZ327), a two-strain pressed cheese (*Lactobacillus* + *Propionibacterium freudenreichii* CIRM-BIA 129), during five days. The results showed that consumption of fermented dairy products decreased the effect of induced colitis by modulating the local and systemic inflammation. Particularly, the expression of IL-10, an important anti-inflammatory cytokine, in addition to the activation of MyD88, an important protein in the process of NF-kβ activation, was observed. Decreased oxidative stress and epithelial cell damage was also registered.

The effect of the administration of fermented milk with *Bifidobacterium breve* strain Yakult (1.0×10^{10} CFU/mL), *Bifidobacterium bifidum* strain Yakult (5.0×10^9 CFU/mL), and *Lactobacillus acidophilus* strain Yakult (1.0×10^9 CFU/mL) on the development of IBD was evaluated in SAMP1/Yit strain mice (Matsumoto et al., 2001). The results showed a significant reduction in the histological injury score and myeloperoxidase activity in mice treated with fermented milks. Moreover, IgG1 and IgG2 were significantly lower in the inflammatory regions, and the production of Th1 cytokines (IFNγ and TNFα) and IL-10 in extracts of mesenteric lymphoid nodes was also significantly lower. Overall, these results demonstrate that these effects may be modulated via mucosal immunity (Matsumoto et al., 2001), and suggest that fermentation products, regardless the evaluated bacteria, may modulate the mucosal immune response and induce Th1 or Treg cells.

Commonly, most studies have linked the anti-inflammatory effect of fermented milks to probiotic bacteria, which have been shown to reduce the systemic inflammatory response (Wu et al., 2019). However, evidence described above, suggest that administration of fermented milks may be used as coadjuvant therapy for treatment of inflammatory diseases via Th17 response. In this sense, some *in vivo* studies have documented that components produced during milk fermentation decreased the intestinal inflammatory process (Santiago-López et al., 2018; Yoda et al., 2014).

The administration of fermented milk by *Lactobacillus fermentum* J20 and J28 (800 μL/day/mouse at 10^9 CFU/mL) to DSS-induced chronic inflammation model. DSS was intragastrically administered to C57Bl/6 mice (200 μL/day/mouse) during four cycles. The administration of fermented milk during 60 days decreased the serum levels of IL-17 and IFN-γ, whereas IL-10 was increased (Santiago-López et al., 2018). Conversely, data showed that the administration of the same milk to mice C57Bl/6 with indomethacin-induced inflammation reduced the concentration of proinflammatory cytokines, particularly IL-17 was reduced at serum and intestinal levels and fewer inflammatory cells were observed to infiltrate epithelial cells. These results suggest that viable cells prevent indomethacin-induced intestinal injury by decreasing pro-inflammatory markers (Santiago-López et al., 2019). However, further studies are needed to elucidate the potential role of the

bioactive components in fermented milk and LAB and their mechanisms of action.

In a related work, it was observed that fermented soymilk with *Lactobacillus plantarum* CRL2130 was able to attenuate inflammation markers in a model of colitis with TNBS. Besides, the administration of fermented soymilk with *Lactobacillus casei* rifoflavin-producing strain, and unfermented soymilk supplemented with commercial riboflavin (1.6 mg/mL), to mice during seven days (three days before inflammation and four days post-infection), reduce weight loss of treated mice, and reflected lower intestinal damages and minor microbial translocation to liver. Intestinal cytokine profiles in fermented soymilk and supplemented soymilk groups showed lower concentration of TNF, MCP-1 and IL-10, compared to mice that received unfermented milk (Levit et al., 2017). These findings exhibited the role of vitamin B2 as an anti-inflammatory compound, capable to alleviated oxidative injuries by scavenging the free radicals, lipid peroxidation, leukocytes infiltration and cytokine production (Iwanaga et al., 2007).

These same results were observed by Levit, de Giori, de Moreno de LeBlanc, LeBlanc, (2017), when administrated individual suspension of several riboflavin-producing strains (10^8 CFU/mL), namely *Lactobacillus plantarum* CRL2130, *Lactobacillus paracasei* CRL76, *Lactobacillus bulgaricus* CRL871, and *Streptococcus thermophilus* CRL803. Authors induced the inflammation in female mice with TNBS. Then either individual bacterial suspension, saline solution or commercial vitamin were administrated intragastrically. The groups receiving riboflavin-producing strains showed lower inflammation, lower microbial translocation to liver, and presence of iNOS + cells in the large intestine. Regarding to cytokines, *Lactobacillis paracasei* CRL76 increase IL-10 levels, similar to group that received the commercial riboflavin. Although the study was not focused on IL-17 production, it was observed that this cytokine was markedly decreased in the groups administered with CRL871 and CRL2130 strains. Besides a marked decrease of IL-6 and IFN was observed (Levit et al., 2017). These findings provide evidence that vitamin-producing strains or even the Persian vitamins could regulate this response.

An open-label randomized control, single-center, prospective trial was performed from May 2015 to December 2016. In this study, kefir, a sour carbonated and fermented milk product was used. kefir was administrated (400 mL/day) twice a day during four weeks. The results showed a decrease in erythrocyte sedimentation rate and C-reactive protein (Yilmaz, Dolar, & Özpinar, 2019). Although this study shows evidence of the use of fermented products, the study was limited to only biochemical markers and analysis of the microbiota, but no immunological markers were evaluated that could give evidence of regulation in Th17 response cytokines.

Overall, these results provide feasible evidence regarding the key role of fermented milks on Th17 response modulation. However, more studies are needed to confirm these findings and to possibly extrapolate these effects to other diseases in which the Th17 response is implicated, such as multiple sclerosis (Fletcher et al., 2009; Álvarez-Sánchez et al., 2019), rheumatoid arthritis (Kuca-Warnawin et al., 2011; Liu et al., 2016), hypertension (Madhur, Lob, McCann, Blinder, & Guzik, & Harrison, 2010; Zhang et al., 2016), obesity, and diabetes (Wang et al., 2018).

5. Mechanistic pathway for the activation of the Th17 response

As mentioned above, the Th17 response is involved in various inflammatory processes, including IBDs. Due to some studies have been controversial, research in this pathology has been increasingly growing at present in order to define the actual role that Th17 response plays to attenuate inflammatory process. In this sense, it has been emphasized is that lactic acid bacteria and/or their metabolites present in fermented dairy may have a key role in regulation of Th17 response on IBDs (de Moreno de LeBlanc et al., 2017; Santiago-López et al., 2018).

Several potential strategies for the treatment of IBD have been recommended, including the blockage of pro-inflammatory cytokines related to Th17 cells. Specifically, IL-6, IL-21, and IL-23 may increase Th17 cell differentiation; thus, the blockage of their receptors may be an alternative IBD treatment (Stolfi et al., 2011), as well as the anti-TNFα antibodies, which have been used in the clinical assay. However, the role of Th17 in the gastrointestinal tract is not completely clear, and two specific cytokines (IL-17A and IL-17F) may also exacerbate inflammation. Thus, additional studies on the inflammatory response must be undertaken with caution (Fitzpatrick, Small, Doblhofer, & Ammendola, 2012; Hueber et al., 2012). Another strategy may be blocking the transcription factors associated to Th17 cells, specifically (ROR)γt and STAT3, which are essential for the regulation of Th17 cells (Lee, Kwon, & Cho, 2018). The inhibition of NFk-B and STAT3 reportedly reduced intestinal inflammation (Fitzpatrick, 2013; Fitzpatrick et al., 2012; Hontecillas et al., 2011; Klotz et al., 2009).

The anti-IL-17/IL-23 antibodies have been poorly reported. However, a recent study showed the possibility of cloning them in *Lactobacillus salivarius* in order to bind IL-17A, IL-23 and TNFα thus reduce the inflammation in IBD patients. Modified bacteria had the ability to remove cytokines in solution, in addition to showing an efficient union with different concentrations of cells and cytokines in solution, even after the bacteria was subjected to simulated gastric conditions (Kosler, Strukelj, & Berlec, 2017). In this way, administration of this bacterium could be an alternative to counteract the effects of IBD, once it can be established what could be the limits of inhibiting the production of Th17 response cytokines. This is an interesting line of research for the use of molecular tools.

Although there is no single mechanism through which fermentation metabolites or LAB exert anti-inflammatory effects, some studies suggest that bioactive peptides may suppress the NF-kB pathway through PPAR-γ, which is a transcription factor that, when activated, antagonizes the pro-inflammatory capability of NF-κB (Marcone, Haughton, Simpson, Belton, & Fitzgerald, 2015). Other possible activation pathways have been explored, including the involvement of NF-κB and activation of c-Jun N-terminal kinases (JNK) (Santiago-López, Gonzalez-Cordova, Hernandez-Mendoza, & Vallejo-Cordoba, 2017).

Vitamins perform an important role in cell growth and differentiation of immune cells. Specifically, the vitamin A displays a critical role in the mucosal immune response, by promoting Foxp3 of Treg and IgA, as well as in the activation of dendritic cells promoting the differentiation of effector T cells and protection of the mucosa (Oliveira, Teixeira, & Sato, 2018). Hence, vitamin-producing strains have been used to reduce the inflammation process in IBD. Despite the mechanisms of vitamin activation have not been fully understood (Levi et al., 2017), the supplementation of vitamin A to obese women decrease IL-17 and TGF-β (Farhangi, Saboor-Yaraghi, & Keshavarz, 2016); meanwhile the vitamin D counteracts an IL-23-dependent IL-17A$^+$ IFN-γ$^+$ (Mann et al., 2017).

In regard to the differentiation of Th17 cells, molecules are processed by APC cells, MHC-II cells, and the TCR of T cells, leading to either Th1, Th2, or Th17 differentiation (Stahdouders, Lubberts, & Hendriks, 208). The release of IFN-γ and the increase in TGF-β cause naive cells to initiate their differentiation process and with the presence of IL-6 and IFN-γ, naive CD4$^+$ cells can differentiate into Treg and in return produce IL-1β and IL-6. The combination of TFG-β from APCs and IL-21 from Th0 would then lead to the differentiation of Th17 cells. Moreover, it has been suggested that Th0 cells and IL-23 secreted by APCs may together lead to the differentiation of Th17 cells, and when Th0 cells differentiate into Th1, these may in return release IL-10, IFN-γ, and TNF-α.

Some studies have suggested that lower concentrations of IFN-γ and higher concentrations of IL-23 may lead to the differentiation of Th17 and, consequently, the production of IL-21, IL-17A/F, and IL-22 cytokines (Chehimi et al., 2019; Ligfoot and Mohamadzadeh 2013; Owaga et al., 2015). These cytokines play an important role in the elimination of harmful microorganism; however, the unregulated expression of these cytokines may contribute to the pathogenesis of autoimmune diseases, diabetes, hypertension, and IBD (Coqueiro et al., 2018; Madhur

et al., 2010).

6. Future perspectives

Based on the results of different investigations, it is hypothesized that Th17 response may be mediated by different components present in fermented milk. When they are present in the gastrointestinal system, they may be recognized by dendritic cells in the intestinal lumen by TLRs, specific receptors of epithelial cells, or M cells (Fig. 1). Once recognized by TLRs, they could mediate the response by activating of TLR4 and inducing changes in $CD4^+$ and $CD8^+$ T lymphocytes.

In a model of colitis with TNBS, the $CD4^+$ T lymphocytes increased, but the administration of yoghurt regulated the T-cell expansion, as well as the IFNγ and TNFα regulated the expression of TLR4 and myeloid differentiation protein 2 (Chaves, Perdigon, & de Moreno de LeBlanc, 2011; Fukata & Abreu, 2007). TLR9 has been associated with the beneficial effect of probiotics in IBD models. Specifically, the DNA derived from such bacteria may contributes in reduce the inflammation process (Lee, Rachmileitz, & Raz, 2006; Obermeier et al., 2005). These results suggest that the beginning of the activation of the immune response can be mediated by the activation of TLRs, which recognize bacterial components and thus lead to an adaptive response to differentiate among Th1, Th2, Th17, or even Treg cells.

More studies are needed to prove this hypothesis and to elucidate mechanistic activation pathways, as these bioactive compounds, including LPS, bacterial lipoprotein, bacterial components, unmethylated CpG DNA, and metabolites of fermentation, may generate individual or synergistic effects, activating either the NFk-B (Zhang & Ghosh, 2001). The more precise establishment of these mechanisms would help to explain how fermented milk products can be used as treatments to decrease the inflammatory response via Th17 cells.

Currently, the importance of functional foods has increased worldwide, mainly due to the rise of metabolic diseases, such as cardiovascular disease, obesity, diabetes (Chehimi, Vidal, & Eljaafari, 2017; Wang et al., 2018), and hypertension (Kologrivosa, Suslova, Koshel'skaya, Vinnitskaya, & Trubacheva, 2014; Liu et al., 2014; Zhang et al., 2016). The latest evidence on the inflammatory processes in individuals with cardiovascular diseases has confirmed that Th17 cells play a role. It is important to continue to study the bioactive components present in foods that could be used as a strategy to mediate the inflammatory processes (Pacha, Sallman, & Evans, 2020; Wu & Yang, 2020; Zabetakis, Lordan, Norton, & Tsoupras, 2020).

7. Conclusions

Several studies have been dedicate on mediating the Th1 and Th2 inflammatory responses. However, recent studies have also been focused on combined immune responses, including those of Treg/Th17 and Th1/Th17. These combined responses may be mediated by different components present in fermented milks. Studies specifically on the Th17 response are still scarce; however, this represents an opportunity for future research. It is important to continue to explore how the Th17 response is mediated given its important role in different systemic inflammatory processes.

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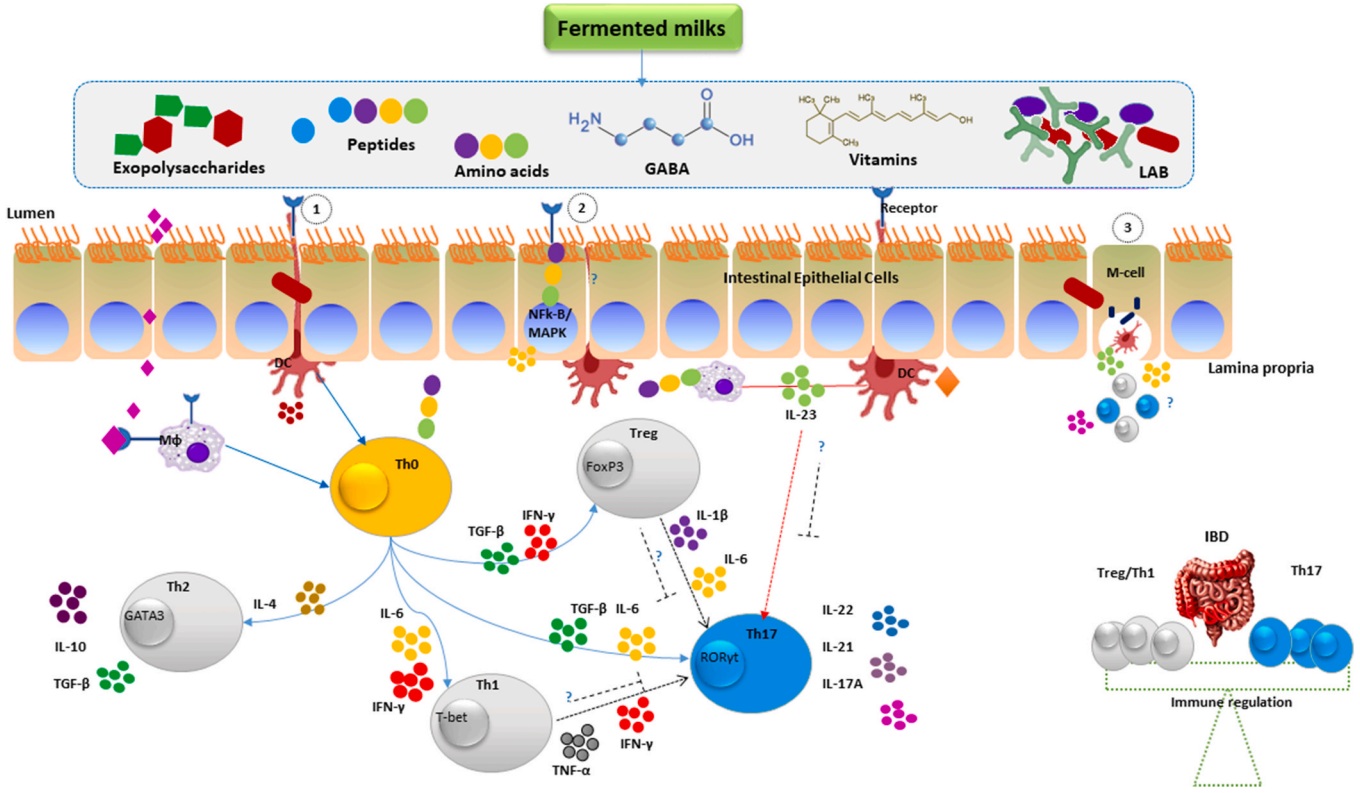

Fig. 1. Hypothesis of the possible activation pathway of fermented milk components and their regulation in Th17 response. The fermented milk-derived compounds which are present in the gastrointestinal tract, might be recognized by: 1) dendritic cells (DC) (localizated in the intestinal lumen) or macrophages; 2) specific receptors (present in epithelial cells; TLRs); or 3) M cells. After recognition, the Th0 is activated and releases IFN and TGF to conduct to Treg differentiation; however, in presence of IL-6, IL-23, and TGF-β it could derivate to Th17 cells. On the other hand, the components released during the fermentation might decrease IL-23, IL-6, IL-1β, and IFN cytokines content; this event could inhibit the proliferation of Th17 response and thus, display an anti-inflammatory activity.

Declaration of competing interest

The authors declare no conflict of interest regarding the publication of this paper.

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