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Synthesis of 2'-fucose-based lactose and analysis of the mechanisms regulating intestinal flora

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Abstract: Breast milk has long been recognized as the gold standard for designing infant formulas. Among them, oligosaccharides are the third most important solid component in breast milk and a new class of prebiotics. Among the oligosaccharides, 2'-Fucose (2'-FL) has attracted much attention for its important physiological functions. Numerous studies have confirmed that 2'-FL regulates the infant gut microbiota, inhibits pathogen adhesion, modulates immune responses, supports brain and neural development, and reduces inflammation. This review briefly describes the current synthesis methods of 2'-FL and provides insights into its mechanism of action in regulating the intestinal flora. By mimicking the natural functions of breast milk, 2'-FL has the potential to enhance the quality of infant formulas. Deepening the understanding of its physiological roles and interactions could lay the foundation for its wider application in infant nutrition. The present study provides a theoretical framework for utilizing 2'-FL to promote infant health and development.

1. Introduction

Currently, lack of breast milk is very common and infant formula has become the preferred milk substitute for many families. In the process of formula production, breast milk composition is considered the gold standard. Therefore, it is of great significance to study and analyse the breast milk composition of the Chinese population, and then explore the development of formulas suitable for Chinese infants and young children. Among them, breast milk oligosaccharides (HMOs), as complex sugars with unique structure in breast milk, are one of the important bioactive components of breast milk and the third most abundant solid component in human milk.Given the growing recognition of the critical role of HMOs in infant health and development, there is growing global research and commercial interest in synthetic human milk oligosaccharides and their active analogues as additives in infant formula.

The interaction of a balanced gut and microbiome plays a central role in shaping infant health. It is generally accepted that babies are sterile in the womb and that the microbiome begins to build gradually from birth. There are many factors that determine the establishment of the microbiome, such as mode of delivery, feeding practices, use of antibiotics, and exposure to people and pets.

Among these factors, feeding practices are the most important for the establishment of the microbiome[1].

In recent years, HMOs have gradually become a hot issue in the field of infant formula milk. Their functional roles can be extended from the initial establishment of the infant intestinal flora to the adult stage, covering support for the growth of beneficial bacteria, anti-adhesion of pathogenic bacteria, and so on. Among more than 200 HMOs in human milk, 2'-fucosyl lactose (2'-fucosyllactose, 2'-FL) has the highest content, accounting for about 30%[2]. Therefore, based on the review of the synthesis of 2'-fucosyllactose, this paper focuses on the mechanism of 2'-fucosyllactose regulating intestinal flora. In order to provide theoretical support for the subsequent development of high-quality milk powder that is more suitable for infant growth and development.

2. 2'-Fucose-based lactose synthesis methods

2.1 Chemical synthesis method

The current chemical synthesis of 2'-FL suffers from the use of a large number of organic reagents, complicated steps, harsh reaction conditions and low product yield. Therefore, chemical synthesis of 2'-FL using L-fucose as a starting substrate is costly [3].

2.2 Enzyme-catalysed synthesis

In general, enzyme-catalysed synthesis for the production of 2'-FL requires synthesis by glycosylation reactions involving glycosyltransferases (GTs) or glycoside hydrolases (GHS).GTs are responsible in nature for the formation of glycosidic bonds, catalysing the transfer of monosaccharides from the glycoside donor (Leloir-type GTS) to the acceptor. Fucosyltransferases (Fucts) are a class of enzymes that play an important role in the engineering of glycosylation of complex glycan chain epitopes involved in cell recognition, cell adhesion, immune responses and tumour metastasis, transferring fucosylated GDP-L-fucose donor substrates to oligosaccharide acceptor structures of glycoproteins and glycolipids [4]. Depending on the regional specificity of the fucosylation formed and the type of their receptor, fucosyltransferases can be divided into five classes as α 1,2-Fucts, α 1,3-Fucts, α 1,4-Fucts, α 1,6-Fucts, and O-Fucts [5].Engels et al[6] suggested that WbgL in the GT family 11 of β 1,2-Fucts is unique, and its substrate preference for β4-galactose-containing receptors makes it highly promising for the synthesis of 2'-FL.Albermann et al[7] reported the key work of a two-step enzyme-catalysed in vitro synthesis of 2'-FL, achieving an enzymatic synthesis of 2'-FL in a with a yield of 65%.

2.3 Whole-cell biosynthesis

Whole-cell biosynthesis is currently the main method for the industrial production of 2'-FL. The keys to reducing the cost of whole-cell biosynthesis of 2'-FL are to reduce the cost of L-fucose, to regulate the balance between the level of guanosine diphosphate-L-fucose (GDP-fucose) in the synthesis pathway and the growth of the bacterium, and to explore new highly active α-1,2-fucosyltransferases. , and 2-fucosyltransferases.The construction of the synthetic pathway of 2'-FL in some of the safer expression hosts (e.g., antibiotic-free Escherichia coli, Bacillus subtilis, and Saccharomyces cerevisiae, etc.) has also been challenging[8].

2.4 Microbial fermentation

Considering green, efficient and sustainable production strategies, in recent years, biological expression systems with high substrate consumption rates and rapid growth have been gradually discovered, such as Escherichia coli, Bacillus subtilis, Saccharomyces cerevisiae, Saccharomyces cerevisiae and Corynebacterium glutamicum, etc., and the production of FL through cell factory strategies can effectively increase the efficiency of product synthesis in the fermentation process and contribute to the development of the breast milk oligosaccharides biotechnology [9].

3. Mechanism of intestinal flora regulation by 2'-fucose-based lactose

Studies have shown that the flora regulation mechanism of 2'-FL mainly includes regulating intestinal microecology, resisting the adhesion of pathogenic bacteria, and regulating immune function[10].

3.1 Regulation of intestinal microecology

2'-FL is able to act as a metabolic substrate for bacterial flora and selectively promote the growth and reproduction of specific beneficial bacteria in the infant intestine, thus increasing the number of beneficial bacteria.2'-FL has an important impact on the establishment of the intestinal flora in early infancy, and it can significantly improve the adhesion of bifidobacteria to the intestinal mucosa [11].2 '-FL has the ability to promote the growth of beneficial bacteria while selectively promoting the growth of bifidobacteria, which mainly include Bifidobacterium longum, Bifidobacterium bifidum and Bifidobacterium infantis. In addition, 2'-FL can also stimulate the growth of some bacillus mimetic species[12]. Studies have shown that the intestinal flora of breastfed infants is predominantly Bifidobacterium. Numerous Bifidobacteria are able to efficiently recognise 2'-FL with the help of fucosyl lactose transporter proteins and use it as a carbon source for growth.He et al[13]evaluated 151 strains of Bifidobacteria for their ability to utilise the 2'-FL by genotypic analysis. Among these strains, 37 had the ability to utilise 2'-FL, including Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium longum ssp. longum, and Bifidobacterium dentium. Hirvonen et al[14]monitored the bacterial growth using the Bioscreen C Growth Curve Analyser, which determines the growth of the fermentation capacity of Lactobacillus, Bifidobacterium and Bacteroides bacteria. It was found that almost all the bacteria studied were able to utilise oligogalactose, lactose and glucose, but B. longum ssp. infantis, B. bifidum, Bacteroides fragilis, Bacteroides vulgatus, Bacteroides thetaiotaomicron, and other bacteria can only use breast milk oligosaccharides (HMOs) as their sole carbon source. Other studies have shown that Bifidobacterium longum infantum subspecies, the dominant strain in the intestinal tract of breastfed infants, is able to utilise 2'-FL to sustain its own growth and produce metabolites such as lactic acid, acetic acid, and 1,2 - propanediol[15][16][17]. In vitro simulations have shown that 2'-FL is capable of full-length fermentation in the colon. As 2'-FL was continuously fermented, the relative abundance of Bifidobacteriaceae increased, accompanied by an increase in Actinobacteria, as well as an increase in Proteobacteria and Enterobacteriaceae. Enterobacteriaceae[18][19][20]. The use of 2'-FL as a carbon source not only promotes the growth of Bifidobacterium, but also enhances the adhesive properties of Bifidobacterium. When 2'-FL was used as a carbon source, the adhesion performance of B. bifidum DNG6 was significantly improved, and the expression level of genes related to Caco-2 cell adhesion was significantly higher than that when oligogalactose and glucose were used as carbon sources[21] as shown in Figure 1.

3.2 Prevention of pathogen adhesion to the gut

The first step in pathogen colonisation, invasion and biofilm formation is surface adhesion[22]. Many breast milk oligosaccharides (HMOs) have been shown to act as receptor analogues for pathogenic bacteria, and in this way inhibit the adhesion of pathogenic bacteria to the intestinal mucosa, thereby reducing inflammation[23][24]. A correlation was found between the intake of 2'-FL in breastfed infants and the incidence of Campylobacter jejuni induced diarrhoea[25]. 2'-FL, as a soluble ligand, inhibits Campylobacter jejuni binding to intestinal H (O) antigens, attenuates the release of pro-inflammatory factors and signals from the intestinal mucosa and thus reduces the infection risk[26]. Breast milk oligosaccharides (HMOs) can prevent pathogenic infections of the organism. Some bacteria, fungi and viruses invade host cells by attaching to the glycocalyx of intestinal epithelial cells, thus harming the organism. And HMOs can act as decoy receptors because of the similarity between HMOs and surface glycans of pathogenic species[27], HMOs will bind to the glycocalyx of the intestinal epithelium first, compete for the binding site with other pathogens, and encapsulate the pathogens so that they can not adhere to the intestinal epithelial cells. This effectively prevents harmful bacteria, fungi and viruses from adhering to the intestinal epithelium, thereby reducing the risk of host disease. Studies have shown that Campylobacter jejuni can cause diarrhoea in infants, which in severe cases can lead to infant death. 2'-FL can act as a decoy receptor to reduce the colonisation of the intestinal epithelium by Campylobacter jejuni; El-Hawiet et al[28] showed that Campylobacter jejuni causes diarrhoea in infants, which in severe cases can lead to infant death. 2'-FL can act as a decoy receptor to reduce the colonisation of the intestinal epithelium by Campylobacter jejuni; He et al[29]found that 2'-FL can directly inhibit the inflammation caused by the invasion of enterotoxin-producing Escherichia coli, and that in addition to reducing the adherence of pathogenic bacteria, HMOs can also alter the gene expression on the surface of bacteria and inhibit the inflammation of the organism. In addition to reducing the adhesion and invasion of pathogenic bacteria, HMOs are also capable of altering gene expression on the bacterial surface and inhibiting the growth of harmful bacteria. For example, the growth and biofilm formation of group B streptococci can be regulated by HMOs, which can delay the growth of group B streptococci, with lacto-N-tetrasaccharide (LNT) showing the highest inhibitory ability. HMOs also inhibit fungal infections, and it has been shown that HMOs down-regulate genes encoding the expression of Candida albicans hyphae-specific adhesion and neo-histone, leading to the inhibition of Candida albicans hyphal expression, and thus to the inhibition of the growth of Candida albicans [30]. It has been shown that HMOs can down-regulate genes encoding Candida albicans hyphae-specific adhesion and neoflagellate expression, which leads to a reduction in adhesion between Candida albicans and epithelial cells, and the binding sites between Candida albicans and intestinal epithelial cells are also blocked by HMOs[31].HMOs can also resist the infections of some infantile lethal viruses, such as rotaviruses and noroviruses [32].2'-FL and 3'-SL HMOs such as 2'-FL and 3'-SL have been shown to have strong antiviral activity against specific rotaviruses [33]. By mimicking receptor sites, HMOs prevent viruses from binding to the host and stimulate the body to increase the expression of interferon and inflammation-suppressing factors in the cells, activate immunity, and reduce the viral attack on the organism. However, specific HMOs can also increase the infectivity of certain neonatal rotaviruses, such as neonatal rotavirus G10P[34], which becomes more infectious with increasing concentrations of LNT and lacto-N-neotetraose (LNnT), and the mechanisms involved need to be further investigated. HMOs have also been shown to have a strong norovirus HMOs have also been shown to have a strong inhibitory capacity against norovirus. HMOs are structurally similar to the key binding sites of norovirus, the histological blood group antigens (HBGAs), which prevent norovirus from binding to the HBGAs, thus reducing norovirus infection. In addition to viruses that infect the neonatal gut, HMOs have also

been found to inhibit respiratory viral infections[35], and it has been shown that 2'-FL reduces the viral load of respiratory syncytial virus and enhances the body's innate and acquired immunity [36], as shown in Figure 2.

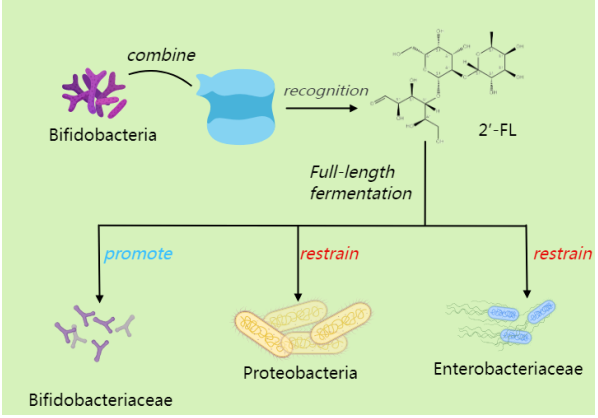

Figure 1 The Effect of 2'-FL on Gut Bacteria

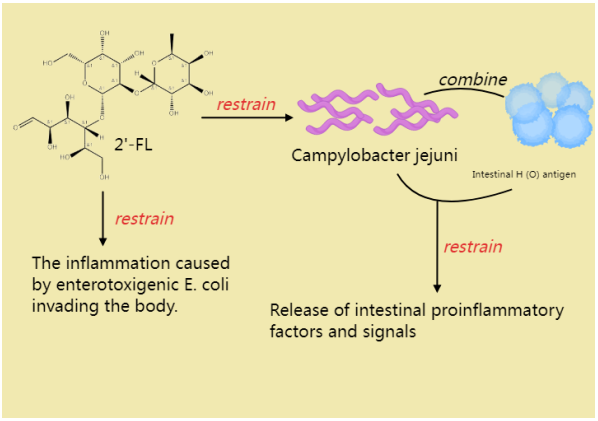

Figure 2 A diagram illustrating the mechanisms for reducing the risk of Campylobacter infection.

3.3 Regulation of the immune system

2'-FL can promote the maturation of the immune system and enhance the immune function. 2'-FL can act directly on intestinal epithelial cells, regulate the gene expression of intestinal epithelial cells, change the cell surface polysaccharides as well as the cellular response, which has a significant immunomodulatory effect [37]. Meanwhile, a multicentre study conducted by Bosheva et al[38] found that the group using standard milk infant formula supplemented with HMOs had higher levels of secretory immunoglobulins and lower levels of α-1 - antitrypsin in the former compared to the group using standard cow's milk infant formula without HMOs. Whereas, Bifidobacterium bifidum as one of the most active species in the infant intestinal flora in metabolising HMOs is also one of the most important health related species[38].Azagra-Boronat et al[39] administered 2'-FL daily to rats from birth and after 16 d, the rats demonstrated higher levels of plasma IgG and IgA as well as mesenteric lymph nodes, etc.[40] It was found that 2'-FL could promote mucosal immune development by supporting the action of microbial CpG-DNA, which was associated with the regulation of epithelial galactoglucan lectin and TGF-β1 secretion. Mao et al.[41] found that thymus index of mice fed 2'-FL-containing formulated milk, lymphocyte proliferation rate were significantly increased ($P<0.05$), while natural killer cell activity and the degree of delayed allergic reaction were significantly improved ($P<0.05$) in mice fed milk containing 2'-FL formula.

In addition, clinical studies have shown that infants fed 2'-FL formula are similar to those fed regular formula in terms of body weight, digestion, and behavioural patterns; however, plasma concentrations of inflammatory cytokines such as interleukins (IL-1α, IL-1β, IL-6), interleukin-1 receptor antagonist (IL-1ra), tumour necrosis factor-α (TNF-α), etc. are 29-83% lower; and there is a significant reduction in bronchitis, lower respiratory infections, and the use of antipyretics and antibiotics.

The results of this series of studies suggest that 2'-FL has a positive effect in promoting immune function, reducing inflammatory response, and decreasing the risk of disease in infants. Formulas supplemented with 2'-FL can mimic the advantages of breastfeeding to a certain extent, providing better protection for the healthy development of infants [42][43]. 2'-FL can also improve chronic immune-mediated inflammatory skin diseases such as psoriasis.Lei et al [43]conducted experiments using imiquimod (IMQ)-induced psoriasis mice as a model, and found that mice administered with 2'-FL showed significant reduction in erythema and thickness of the skin, as well as reduced skin damage and inflammation. Further mechanistic studies showed that 2'-FL could inhibit the immune response of Th17 cells and the secretion of Th17-associated cytokines by regulating the STAT3 signalling pathway, thus improving psoriasis.

4. Conclusion

As the most abundant breast milk oligosaccharide in breast milk, 2'-FL has been supported by a growing body of evidence for its physiological efficacy in regulating infant intestinal microecology, preventing pathogens from adhering to the intestinal tract, and modulating the immune system. Meanwhile, as a new type of nutritional agent, 2'-FL has a promising future development. At present, realising the localised production of human milk oligosaccharides (HMOs) and applying them in infant formula is of strategic significance to serve the healthy growth of infants and young children as well as the healthy development of the nation. The synthesis technology is also gradually upgrading. However, 2'-FL has not yet been approved as a food additive in infant formula in China, and there is a lack of relevant standards. Therefore, while promoting the development of 2'-FL synthesis technology, it is also necessary to actively promote the declaration and approval of 2'-FL as a new food ingredient in China, as well as the development of relevant industry standards.

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