Cesarean delivery modulate intestinal microbiome and th9 cell asnwer propensity to allergic diseases?

A modulação do microbioma intestinal por influência do parto cesariana possui correlação a resposta das células th9 em doenças alérgicas?

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RESUMO
O tipo de nascimento pode alterar a composição da microbiota intestinal humana e interferir de forma crucial na formação do sistema imunitário inato e adaptativo. Entre os vários grupos celulares que podem ser modulados pelo tipo de parto estão as células T helper (Th). Atualmente, para além do perfil clássico Th1 e Th2, foram identificados outros subconjuntos, incluindo Th17, Th22, Th25 e Th9. Estudos sobre a modulação dos linfócitos T helper associados ao tipo de nascimento estão ainda a emergir. No entanto, sabe-se que a ação das células Th9 é modulada de acordo com a microbiota intestinal. Assim, este estudo visou descrever como o tipo de nascimento, vaginal ou cesariana, pode alterar a microbiota intestinal e colocamos a hipótese de que a forma do parto altera o padrão de resposta ao Th9 nas doenças alérgicas.

Palavras Chaves: Microbiota intestinal. Células T auxiliares. Th9.

ABSTRACT
The type of birth can alter the composition of the human intestinal microbiota and crucially interfere in the formation of the innate and adaptive immune system. Among the various cell groups that can be modulated by the type of delivery are helper T cells (Th). Currently, in addition to the classic Th1 and Th2 profile, other subsets have been identified including Th17, Th22, Th25 and Th9. Studies on the modulation of T helper lymphocytes associated with the type of birth are still emerging. However, it is known that the action of Th9 cells is modulated according to the intestinal microbiota. Thus, this study aimed to describe how the type of birth, vaginal or cesarean, can change the intestinal microbiota and we hypothesized that the form of delivery changes the pattern of response to Th9 in allergic diseases.

Keywords: Intestinal microbiota. Helper T cells. Th9.

1 INTRODUCTION

Since the discovery of the dichotomy between T Helper (Th) lymphocyte profiles in the 1960s, many Th subsets have been discovered, each with a group of cytokines, functional properties and an assumed role in pathologies associated with the immune system (CROTTY et al., 2015; RAPHAEL et al., 2015). Currently, we can list several additional subgroups such as Th17, Th22, TH25 and Th9 that move beyond the two known patterns, Th1 / Th2, and actively corroborate the immune responses (DI GANGI et al., 2020). Th17 cells, for example, recognized within cellular adaptive immunity as a significant subset, are implicated both in the pathology of inflammatory disorders, as well as in the elimination of extracellular infections and maintenance of the microbiota. (SANDQUIST; KOLLS, 2018). They may play central roles in the pathogenesis of severe asthma as they recruit neutrophils, this characteristic being a hallmark of their response pattern (CHESNE et al., 2014; ZHAO et al., 2016). Th22 cells secrete mainly IL-22, IL-13 and tumor necrosis factor-α, which together with Th25 that synthesizes IL-25, are important to initiate and develop allergic reactions of airway inflammation (PASCAL et al., 2018).

Among the discoveries of additional Th cells, we can highlight the Th9 cell, which together with other immune cells produces and secretes Interleukin-9 (IL-9), a protein with pleiotropic action that can act to protect against parasitic infections and immunity antitumor (VARGAS et al., 2017; DEGASPERI et al., 2018). There is also strong evidence that IL-9 acts in pathologies described for allergies, due to the functional capacity to stimulate the production of IgE by B cells Lymphocytes, to accumulate and activate mast cells, to improve eosinophil chemotaxis and to stimulate mucin production

in epithelial cells of the lung. (BADOLATI et al., 2020). In addition, it has recently been discovered that Th9 express H4 histamine receptors that can increase inflammatory potentials during allergic responses (GERHARDT et al., 2020). Therefore, extensive studies have been carried out, in particular, to Th9 as a target for future treatments of allergic diseases, with promising strand in the modulations that the organism's microbiota and some associated factors promote in these pathologies (BADOLATI, et al. 2020). The influence of the microbiota has been a relevant point in studies of the mechanism of action of Th9, since strong associations are being made between the host's immunity and the flora composition of some organs, such as lung, skin and, mainly, intestine, since its flora is able to influence the immune system of the entire organism (ANAND et al., 2018).

The metabolites of the intestinal microbiota guide the hematopoietic pattern of dendritic cells and mainly assist in the maintenance of pulmonary Th2 immunity (DI GANGI et al., 2020). Studies show that the composition of the microbiota of individuals with allergic diseases with that of non-carriers, are different between both, which may represent evidence that there is a relationship between organic flora and the tendency of immediate hypersensitivity in individuals (MELLI et al., 2016). In this sense, the immediate postnatal period is the time when the greatest modulation of the human microbiota occurs, due to the occurrence of the first colonization of the previously sterile intestine (Fuhler, 2020). Studies have revealed that the composition of the intestinal flora of children born by natural birth with that of children born by cesarean delivery, have different constitutions between them, indicating that the type of delivery changes the newborn's microbiota (RUTAYISIRE et al., 2016). This is due to the fact that the intestinal flora of children born from natural childbirth is formed from the mother's vaginal tract, while that of children born by cesarean section will be formed by skin contact with environmental surfaces (Fuhler, 2020).

According to GU et al. (2019), the type of delivery, in addition to altering the composition of the human microbiota, can influence the tendency of children to develop allergies, with those born by C-section having a higher risk of developing them than those resulting from vaginal births. In addition to these investigations, epidemiological studies relating cesarean delivery to increased rates of asthma, allergies, autoimmune disorders and obesity (STINSON et al., 2018). Considering these data, this study aims to describe how the type of birth, vaginal or cesarean, can change the intestinal microbiota, considering the hypothesis that the form of delivery changes the pattern of response Th9 in allergic diseases.

2 DEVELOPMENTAL IMMUNOPHYSIOLOGY

During pregnancy, the immune system undergoes modifications causing an immunoplasticity, because the mother's body produces mechanisms of selective immunological tolerance so that the fetus is not naturally rejected due to the alloantigenic factors present (Barreira et al., 2015). This is due to the paternal-fetal antigen in the dendritic cells that is exposed in the T cells in the uterine lymph nodes, thus there is a peripheral resistance to the fetal antigens mediated by the specific regulatory T cells of the antigen present until the end of the pregnancy (GU et al., 2019). However, at the end of pregnancy, leukocytes migrate to the reproductive tissues, generating a pro-inflammatory response that helps in labor with the release of IL-6 that induces uterine contractions and IL-8 for cervical ripening and aids in the passage of the fetus (HUANG et al., 2017). The work of Petersen et al., (2019), demonstrated that after labor, the production of cytokines is influenced by the delivery routes, with a decrease in IL-6 and IL-8 during cesarean and vaginal delivery within 3 days, however, there was a significant change in IL-7 in parturients who underwent cesarean section. According to maternal serology, patients who evolve to vaginal labor produce more cytokines such as IL-6 and IL-1B and TNF-a, benefiting neonatal immunity through different mechanisms (HAN et al., 2019).

3 THE BIRTH AND THE MODULATION OF THE MICROBIOTA

During delivery, the baby comes into contact with the mother's vaginal and fecal flora, and this contact acts as a thermostat for the baby's immune system (VYAS et al., 2018). It was believed that the fetus was sterile, since the first microbial contact was via vaginal delivery, however, recent studies indicate that through the amniotic fluid displacement of the maternal microbiota occurs. Thus, the mother's immune system can contribute to the development of the infant microbiota (PETERSEN et al., 2019; PERONI et al., 2020).

The composition of the intestinal flora that begins to develop from the first days of life, is shaped by genetic and non-genetic factors. Host immunity and microbiota composition are directly linked, not only in the intestine, but also in organs such as the lungs and the skin (VYAS et al., 2018). Over time, the intestinal flora is established to maintain the homeostasis of the host's immune system, being influenced mainly by the adaptive immune response and the innate immune response (HUANG et al., 2017). Neonates of normal birth have bifidogenic microflora of the mother's vagina in their

intestines, while newborns delivered by cesarean section, as they do not pass through the birth canal, present delayed colonization of the intestinal flora in the first months of life (HAN et al., 2019).

The first bacterial populations that colonize the intestinal tract of neonates are facultative anaerobic bacteria, such as Staphylococcus, Streptococcus, Enterococcus and some species of Enterobacteriaceae (ZHUANG et al., 2019). As the individual develops, the intestine is colonized by strictly anaerobic bacteria of the genus *Clostridium*, *Bacteroide*, *Ruminococcus*, predominant genus *Bifidobacterium* (GU et al., 2019). This type of bacterial establishment in the early stages of life is modulated in addition to the way of birth (cesarean section or delivery), but also by breastfeeding, antibiotic supply, genetics and diet (PETERSEN et al., 2019).

The work by Flaherman et al., (2018), highlighted that 62% of the bacteria isolated in the nasopharyngeal cavity and in the gastric content of newborns, are similar to those found in the mothers' vagina and cervix before delivery. Using the pyrosequencing technique, they found that the bacteria (*Lactobacillus, Prevotella* or *Sneathia*) present in the feces of newborns born by vaginal delivery, were similar to those found in the mother's vagina and skin, while the microbiota in children born by cesarean delivery was composed by bacteria present in the hospital environment (*Aureus*, *Corynebacterium*, *Propionibacterium*) (GHOLIZADEH, et al., 2019; PERONI et al., 2020).

A meta-analysis also showed that individuals who are born by cesarean delivery are 20% more predisposed to developing asthma due to the lack of bifidogenic flora affecting the regulation of immune responses to allergens, making them more prone to allergic diseases (HAN et al., 2019). In addition, children fed with breast milk show a decrease in *Escherichia coli*, *Clostridium difficile* and Lactobacillus populations, compared to those fed with artificial milk, concluding that the type of delivery and maternal feeding are essential factors in intestinal colonization in the early stages of life (GHOLIZADEH et al., 2019).

The reduction in the diversity of the gastrointestinal microbiota in allergic children is dominated by Firmicutes and members of the Bacteroidaceae family and, more specifically, by the increase in the number of Bacteroides fragilis (PETERSEN et al., 2019), *Escherichia coli*, *Clostridium difficile*, *Bifidobacterium catenulatum*, *Bifidobacterium longum* and a lower prevalence of *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and Lactobacillus (ZHUANG et al., 2019). Different studies

suggest that the gastrointestinal microbiota of an allergic individual is different in quantity and composition, compared to that of a non-allergic individual (PASCAL et al., 2018).

Probiotics have become very popular and in most studies one or more strains of lactobacilli or biofobacteria are used to treat or prevent allergic diseases (FLAHERMAN et al., 2018). In this way, the strategy of using probiotics has been used to modulate the immune system by associating with intestinal endothelial cells, originating antimicrobial metabolites, competing with pathogenic microorganisms for nutrients (CUKROWSKA et al., 2020), strengthening the epithelial barrier, acidifying the enteric environment for reducing pathogenic bacterial growth and altering immune responses (SHU et al., 2019).

4 TH1, TH2, TH9 CELLS IN ALLERGIC DISEASES

T helper (Th) lymphocytes express CD4 + molecules on their surface and have the function of secreting cytokines that, in turn, will stimulate the differentiation of B lymphocytes and activation of macrophages. Depending on the secreted cytokines, Th naive lymphocytes generate different subtypes, such as Th1, Th2, Th9 among others (SARAVIA e al., 2019).

The Th1 cell present in the immune response to viruses, bacteria and parasites through the production of interleukins such as IL-2 and Interferon-gamma (IFN-γ). IFN-γ is the main macrophage activating cytokine against intracellular microorganisms (DEGASPERI et al., 2018). IFN-γ acts on B and T cells, NK cells and macrophages, and has an important immunomodulatory role in inhibiting the proliferation of cells that synthesize IL-4, IL-5, IL-6, IL-10, IL-13 and by decreasing the production of some immunoglobulins in certain situations, such as IgG1, IgG4 and IgE (ZHUANG et al., 2019). IFN-γ increases the expression of MHC class I and II genes, and as for IL-2, it demonstrates an important function as a growth and differentiation factor for T cells (SARAVIA et al., 2019). Th1 CD4 + cells participate in the type IV hypersensitivity process, of late onset, by releasing cytokines that promote activation of macrophages generating local damage. Therefore, they do not participate in allergic reactions that, in turn, are mediated by IgE and characterized as immediate response type I hypersensitivity (PETERSEN et al., 2019).

As for the Th2 cell, it has a role in the response, especially against extracellular parasites and has production of IL-4, IL-5 and IL-6. (DEGASPERI et al., 2018). It is worth mentioning that the Th2 lymphocyte participates in humoral immunity by producing the cytokines IL-4 and IL-13 that induce the production of IgE by B cells and,

thus, activate the protective immune response against helminths and in type 1 hypersensitivity reactions (ZHU et al., 2010). Th2 cells play an important role in the pathology of allergic inflammations, as is seen, for example, in the production of memory Th2 by IL-5 that induces allergic inflammation, including eosinophilic airway inflammation and chronic skin inflammation (SHINODA et al., 2017). Thus, it is visible that the cytokines produced by the Th2 lymphocytes demonstrate important functions, so that IL-5 is responsible for eosinophilia, IL-13 promotes mucus production and IL-4 is involved in changing the class of antibodies and in the production of IgE (GURRAM; ZHU, 2019).

Regarding TH9 cells, their activity occurs from the activation of virgin T cells in the presence of TGF-β 1 and IL-4 that induce the production of IL-9 secreting helper Th cells (MALIK; AWASTHI, 2018). Th9 cells play a role in parasitic defense, tumor suppression and allergic responses. IL-9 is produced by several immune cells in addition to Th9 cells, such as mucosal mast cells, type 2 innate lymphoid cells (ILC2) and CD8+ T cells (DEGASPERI ET AL., 2018). Its function is to act as a growth factor for mast cells and enhance the production of cytokines by these cells (PERONI et al., 2020). In B lymphocytes, it induces the production of IgG and IgE and the production of mucus by pulmonary epithelial cells and expression of the IL-5 receptor in eosinophils (JIA et al., 2017).

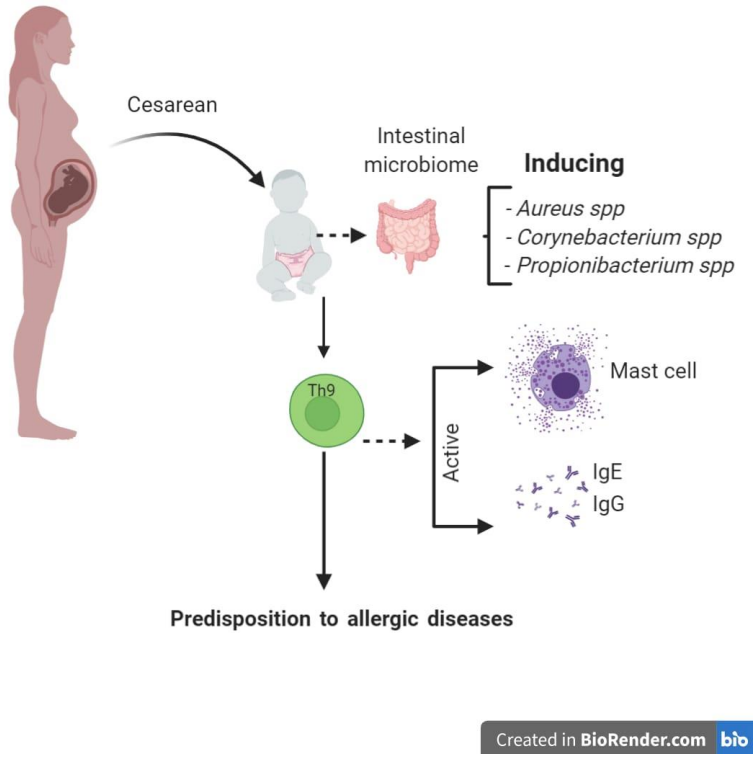
The transcription factors that regulate Th9 cells have been elucidated. However, it is known that there is not only one main factor involved in the Th9 response, since several factors are expressed simultaneously by other strains of T helper (HAMILTON, 2019). Transcription factors such as PU.1, FOXO1 and BATF were found in Th9 cells, and their inhibition significantly reduces the expression of IL-9 in CD4 T cells (DEGASPERI ET AL., 2018). Interferon-4 (IRF4) is part of the factors that promote the development of Th9 cells by binding with the IL-9 promoter. It also has the function of regulating Th2 and Th17 cells (SARAVIA ET AL., 2019). It was observed that for the induction of IRF4 it was necessary downstream of the IL-4 signaling pathway called STAT6, being important for the initial development of Th9 cells. Likewise, genes like IL-4RA and IL-33 are related to Th9 and also participate in the mechanism of allergic inflammation in human pathologies (MALIK; AWASTHI, 2018).

Studies show that inflammatory bowel diseases stimulate the secretion of IL-9 which, in turn, recruit mast cells, cytokines and pro-inflammatory proteases (VYAS; GOSWAMI, 2018). These cells are capable of altering the permeability of the intestinal

barrier and subsequently causing a rupture, which facilitates entry of antigens and leads to activation of immune cells of the mucosa, thus increasing the risk of allergic responses (GERLACH ET AL., 2015). It was observed that the lamina T cells of patients with inflammatory bowel disease have a high amount of TCD4+, PU1, IL-9 and CD4+, IRF4, IL-9 cells, suggesting the association of IL-9 with the severity of the inflammatory disease intestinal (MALIK; AWASTHI, 2018).

Regarding dermatological pathologies, the constant presence of Th9 cells can activate innate immune cells such as mast cells, in order to contain pathogens after skin infection (JADALI, 2019). When a fungal infection occurs, IL-9 induces the production of IL-8 from keratinocytes, which promote the influx of neutrophils (MALIK; AWASTHI, 2018). The literature suggests that IL-9 potentially contributes to different types of skin diseases, such as atopic dermatitis, allergic contact dermatitis, delayed allergen-induced hypersensitivity, psoriasis and cutaneous T-cell lymphoma (CLARK; SCHLAPBACH, 2017). The immunological mechanisms associated with the response of Th9 cells and their role in allergic diseases are listed in table 1 and also shown in figure 1.

Figure 1. Immune mechanisms associated with Th9 responses and allergic diseases



Source: Authorial drawing

Tabela 1. Immune mechanisms associated with Th9 responses and allergic diseases

Authors	Kind of study	Outcome	Mechanism of action
Schaper-Gerhardt et al., (2020)	Human peripheral blood	Stimulation of Th9 cells with histamine generates increased expression. Of mRNA and protein for IL-9. This stimulation is mediated by H recpetors, and this association with th9 cells can amplify the pro-inflammatory potency of these cells.	Transcription pathway mRNA for H_1, H_2 and H_4 histamine recpetors.
Schwartz et al., (2019)	Human peripheral blood	The expression. Of th9 cells, associated with a pro-inflammatory profile, can be suppressed by retinoic acid in allergic diseases.	Signaling pathway RA-RARα.
Jia et al., (2017)	Human peripheral blood	The levels of IL-9, IL-4 e PU.1 are increased in children with allergic asthma, while IFN- γ is reduced. IL-9 upregulates CD69 and CD25 expression in B cells and the combination of IL-9 e IL-4 increases IgE production.	Transcription pathway Overexpression of PU.1 increases IL-9 production and decreases IL-4 production Stimulation with PMA associated with ionomycin in the presence of BFA.
RENGA et al. (2018)	Murine model and human duodenum biopsies	Candida albicans in human intestinal diseases can transition between pathogenesis and commensal nature under the regulation of IL-9 (produced by Th9 and other cells) and mast cells (MCs). When IL-9 and MC deficiency was observed, inflammatory dysbiosis was diagnosed, thus suggesting a role beyond host immunity, such as regulation of the microbiota. By inducing TGF-β in stromal MCs, IL-9 contributes decisively to mucosal immune tolerance through the enzyme indoleamine 2,3-dioxygenase. However when induced by C. albicans and mucosal MCs IL-9 contributes to inflammation and barrier loss and in patients with celiac diseas	By inducing TGF-β in stromal MCs, IL-9 contributes decisively to mucosal immune tolerance through the enzyme indoleamine 2,3-dioxygenase. However when induced by C. albicans and mucosal MCs IL-9 contributes to inflammation and barrier loss and in patients with celiac disease.
		The gut microbiota can modulate the action of Th9 profile cells. Given that T cell receptors are reactive to	It occurs through GATA3+ Th2 responses and T

DI GANGI et al. (2020)	Murine model and Intestinal microbiota	microbiota-derived antigens that are required for proper maturation of the immune system and to ensure proper colonization of the intestinal lumen.	regulatory lymphocytes (Tregs), and bacterial metabolites such as short chain fatty acids (SCFAs) are directly detected by G protein-coupled receptors (GPCRs).
Schlapbach et al. (2014)	Human peripheral blood and skin tissue.	IL-9 is transiently and selectively produced by Th skin-tropic cells after stimulation with Candida albicans.	T-cell cytokine production after stimulation with monocytes pulsed with autologous antigen was measured in cell culture using bead-based multiplex assay. IL-9 was selectively produced by skin-tropic T cells in response to Candida albicans
GOSWAMI, R. e VYAS, S. P. (2018)	Murine model and intestinal microbiota.	The role of Th9 cells in inflammatory bowel disease is related to the secretion of the cytokine IL-9, involved in the pathogenesis of the disease.	Activation and migration of various immune system cells, such as mast cells, to the site of inflammation by inducing the production of chemokines, such as RANTES, CCL19 and CCL21.
Gerhardt, et al. (2018)	Human peripheral blood mononuclear cells	histamine H4 receptors amplify the proinflammatory potency of Th9.	During differentiation, the cells were additionally stimulated with histamine receptor agonists or left untreated. Histamine receptor expression as well as IL-9 production was measured.
Hoppenot et al., (2015)	Human peripheral blood	Serum IL-9 levels and peripheral blood Th9 cell counts are elevated in patients with allergic asthma. In contrast, eosinophil apoptosis is inversely related to IL-9 concentration.	Peripheral eosinophils and CD4 cells were isolated by high-density gradient centrifugation and magnetic separation. Th9 cells and apoptotic eosinophils were estimated by flow cytometer and serum IL-9 and IL-5 concentration was determined by ELISA.

5 CONCLUSION

As described, the microbiota is capable of modulating several immune responses in the human organism, being able to potentiate anti-inflammatory mechanisms, improving the defense against invading pathogens, as well as pro-inflammatory pathways, exacerbating inflammation mediators and, thus, predisposing the organism allergies (GU et al., 2019). This modulation in turn varies according to the state of balance and composition of the intestinal flora. Since the mode of delivery alters the constitution

of the microbiota in neonates, it can crucially interfere in the formation of the immune system (KATAOKA, 2016; FRANCINO, 2018).

As highlighted, Th9 cells have an exacerbation of inflammatory response in the presence of *Staphylococcus aureus* and *Candida albicans*, microorganisms present on the skin, mucous membranes and even on environmental surfaces, being an important source in the intestinal colonization of neonates from cesarean sections (Renga et al., 2018). Thus, as there is evidence that the fetal and neonatal phase plays an important role in the development of the immune system, it is possible to infer that cesarean delivery may corroborate the development of allergies in their babies, since in addition to providing delayed colonization of intestinal flora in the first months of life, still contaminates it with a pro-inflammatory microbiota (GU et al., 2019; HAN et al., 2019). As highlighted in addition to the flora composition of neonates from cesarean sections being pro-inflammatory, it is still deficient in Bifidobacteria whose lack affects the regulation of immune responses to allergens, making them even more prone to allergic diseases (HAN et al., 2019). Finally, studies have highlighted that allergic children have a low concentration of Bifidobacteria and high *Staphylococcus aureus* and Enterobacteria when compared to normal children, favoring the hypothesis that cesarean delivery predisposes allergic diseases to corroborating the mechanisms that intensify the Th9 pro-responses inflammatory (Gholizadeh et al. 2019).

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