Pediatric RESEARCH

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COMMENT

The potential use of gene expression profile to identify useful biomarkers for the diagnosis and the treatment of pediatric inflammatory bowel diseases

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Pediatric Research (2020) 87:805–806; https://doi.org/10.1038/s41390-019-0732-x

Inflammatory bowel disease (IBD) are characterized by a chronic course requiring a lifelong treatment, and an overall 25% of cases are diagnosed in the childhood. Both the adaptive and the innate immune systems are involved in the gut inflammation occurring in IBD. Several T helper cell subsets are known to promote inflammatory responses in the gut. Previous studies have reported that T helper(Th)−1 cells secrete key cytokines as interferon(IFN)-γ, tumor necrosis factor(TNF)-α, and interleukin(IL)−12 in Crohn disease (CD), and by contrast, Th2 cells with the production of IL-5, IL-9, and IL-13 are predominant in Ulcerative Colitis (UC).

More recently, it was demonstrated that an additional helper T cell subset, Th17 cells, contributes to chronic intestinal inflammation including IBD.[1] In adult IBD patients, mainly in UC individuals, Th17 cells and their related cytokines, as i.e., IL-17A and IL-22, were found increased in the serum and in the intestinal mucosa compared to control subjects. In addition, a positive correlation was found between the levels of Th17 cytokines or their mRNA expression and disease activity parameters, as endoscopic and histological grading, C-reactive protein and platelet levels.

Though a great progress was reached in the comprehension of the immune mechanisms responsible of gut inflammation in adult subjects with IBD, very few studies focused on the immunological events involved in the development of IBD in pediatric age.[2] Children affected by IBD seem to be a different population with distinctive immunological characteristics and often a more severe phenotype compared to IBD adults, and for this reason, further studies are necessary to better typify the early immune response that develops in pediatric IBD. Moreover, the research of biomarkers to distinguish between pediatric CD and UC could be important to facilitate IBD diagnosis and to establish new specialized approaches for the treatment.

In this context, the study published by the Pediatric Research Journal from Busch and colleagues gives a relevant contribution to better understand the immunological features in the pathogenesis of pediatric IBD, and to propose a new potential diagnostic approach for this IBD cohort.[3] They analyzed by quantitative polymerase chain reaction (qPCR) the expression of 16 target genes, that encode cytokines or transcription molecules in intestinal biopsies taken from fifty-two pediatric IBD and non-IBD individuals. In particular, they observed an overexpression of IL-17 mRNA in the tissues from IBD patients, mainly UC, compared to the control group, and also an increased expression of IL-22 in UC relative to CD intestinal samples. The elevated levels of both cytokines IL-17 and IL-22 produced by Th17 cells in intestinal mucosa highlight the contribution of this cell subset non only in adult but also in pediatric IBD mucosal lesions. Accordingly, previous studies found an increase of Th17 effector cells paralleled by a reduction of Treg cells in the peripheral blood of IBD children.[4] More specifically, the involvement of Th17 cells found by the authors in particular in the tissue specimens of UC compared to CD patients, is probably due to the different molecular pathway at the base of the pathogenesis of the two IBD conditions.[5] The identification of key cytokines unique for UC or CD, could enhance the current understanding of their pathogenesis. As well known, Th17 cells possess a great functional and phenotypical plasticity, and in response to environmental condition they can acquire the ability to produce Th1/Th2 cytokines in addition to IL-17. In particular, in inflammatory states, Th17 cells can change into a Th17/Th1 or Th17/Th2 phenotype, and the "shifted" cells seems to be more pathogenic and aggressive than the "unshifted" cells.[5] The existence of T lymphocytes at the same time producing both IL-17 and IFN-γ identified as Th17/Th1, as well as both IL-17 and IL-4 identified as Th17/Th2, was shown in intestine inflammatory conditions. Th1 cells generated from Th17 cells were defined as non-classical Th1 to discern them from classical Th1, which instead are derived from the direct differentiation of naïve T cells. The transition of Th17 to non-classic Th1 subset could be mediated by different factors including TNF-α, and the same Th17cells produce TNF-α and therefore with autocrine or paracrine mechanism can drive the shifting to Th1.[5] Although it has been demonstrated an inflammatory function of Th17 cells and Th17-related cytokines in the disease activity and in the mucosal damage, Busch et al. proposed also a protective role of this T cell population in IBD. The authors hypothesize that the increased IL-17A gene expression found mainly in UC children, could represent a response to, rather than the cause of bowel inflammation. Most of the experimental data on the regulatory function of Th17 cells has been observed in murine colitis models. The transdifferentiation of Th17 cells into regulatory T cells, a process of global genetic reprogramming, was assessed by a Th17 cell-mediated colitis model in which Th17 cells completed their functional conversion contributing to the resolution of inflammation. However, in humans the antibodies against IL-17A protein or IL-17A receptor have been successfully used in some inflammatory pathologies, such as psoriasis and rheumatoid arthritis, but on the contrary with poor results in IBD.

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Received: 12 August 2019 Revised: 7 October 2019 Accepted: 6 November 2019
Published online: 2 January 2020

In addition, Busch et al. found IL-23A overexpressed in intestinal tissues of both UC and CD patient groups, in agreement with recent studies that supports the involvement of the IL-12/IL-23 axis in the pathogenesis of IBD. IL-23 enhances IL-17 production in vivo and it is considered a maintenance factor for the Th17 phenotype. In adult IBD, IL-23 is mainly produced by dendritic cells and macrophages, instead in pediatric IBD a further source of IL-23 is represented by granulocytes, suggesting that the type of cell producing IL-23 may change in the disease progression playing a key role in the pathogenesis. Differently from the therapy with anti IL17A protein/receptor, the treatment with antibodies that bind and neutralize IL-12/IL-23 and IL-23A, Ustekinumab and Risankizumab, respectively, induced clinical remission in patients with active CD during clinical trials. Interestingly, in the intestine of adult CD patients treated with neutralizing anti-TNF antibodies and without clinical response to the therapy, it has been observed an induction of IL-23 mRNA expression, suggesting that IL-23 may cause molecular resistance to such therapy. The treatment with the inhibitors of TNF-α is widely used in IBD, but within one year up to 40% of IBD patients treated with anti-TNF drugs lose response, therefore it is necessary a therapy optimization. Moreover, there are IBD patients that do not respond to these biological agents. The interactions between IL-17, IL-23, and TNF-α and their mutual influence, in addition to their increased levels in inflamed IBD mucosa, suggest that anti IL-17 and/or anti IL-23 could be an additional and/or an alternative therapeutic target for these IBD patients, also in UC subjects. Moreover, in the context of pediatric IBD, the authors demonstrated that a high expression of other inflammatory cytokines such as TNF-α, IFN-γ, and IL-6 characterizes both the inflamed UC and CD mucosa. In particular, IFN-γ and IL-6 mRNA expression were observed enhanced in both UC and CD patients without differences among IBD groups, while TNF-α was abundantly expressed mainly in CD children. At the same time, they found a slight increased level of TGF-β1, a cytokine with regulatory activity, in CD inflamed mucosa compared to the normal intestinal tissue of non-IBD group.

Therefore, considering the differential expression of some peculiar inflammatory or protective cytokines found in IBD biopsy samples, Busch et al supported the hypothesis that is possible to cluster patients on the basis of gene expression patterns differentiating IBD from non-IBD children, and in particular UC from controls, and also UC from CD. They conclude that genetic panels can be used as a diagnostic approach for pediatric IBD, as well as a tool to monitor the success of the treatment.

In accordance, in a previous study, Rosen et al analyzed rectal tissues from treatment-naive pediatric patients with IBD, observing that UC children were characterized by an increased mucosal expression of genes involved in type 2 and type 17 immune responses, compared to subjects with CD. They also evaluated clinical outcome and they found a good response to the therapy in UC pediatric patients with high expression of type 2 genes at diagnosis.[5] In spite of certain differences, pediatric UC and CD share overlapping genetic and clinical features, making it challenging to diagnose and distinguish between them. Indeed, to date there are still few and contrasting data reported on the gene expression profile as diagnostic/monitoring tool and further studies are needed to optimize it.

In conclusion, targeting Th17cells in the management of other autoimmune diseases is already showing promising results, thus a better understanding of this T cell subset and the related cytokine pathways, i.e., IL-17 and IL-23, could lead to development of novel therapeutic strategies for IBD. Moreover, genes differentially expressed in UC and CD could be used as new diagnostic biomarkers for pediatric IBD and their identification could improve the therapeutic strategies for these two distinct pediatric IBD forms.

AUTHOR CONTRIBUTIONS

S.V. and C.S. participated equally in this study; They contributed to conception and intellectual content of the study, and they drafted the article.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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