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Research Article

Pathogenetic Role of Insulin-Like Growth Factor (IGF-I) in Ulcerative Colitis

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Abstract

Aim of Study: Identifying the role IGF-I in ulcerative colitis (UC) pathogenesis.

Materials and Methods: 63 patients were examined who featured various UC severity and endoscopic (Mayo index) activity in the treatment dynamics. The levels of IGF-I in peripheral blood and those of TNF-a, IL-10 in mononuclears under spontaneous and lipopolysaccharide-stimulated conditions were identified with EIA. The inflammation intensity in the colon mucosa (CM) relied on the method by Avtandilov G. G. Implying the calculation of the inflammatory infiltrate (%) in the mucous membrane's own plate. The control group included 20 healthy volunteers. The statistical processing of the obtained data was carried out using SPSS 13.0 software.

Results: The periods of exacerbating ulcerative colitis revealed a lower content of IGF-I in peripheral blood, whereas the synthesis of TNF-a and IL-10 proved to be increased. The IGF-I content in the serum showed an inverse dependence on UC severity as well as on the degree of inflammatory reaction in the CM and the production of TNF-α by MNCs, while there was a direct dependence on IL-10 production. The clinical remission of UC developed along with an increase in IGF-I production, a decrease in TNF-α synthesis, and normalization of IL-10 production.

Conclusion: During the clinical remission of UC, the synthesis of TNF-α decreases naturally, with the production of IL-10 by MNCs normalizes, and the IGF-I growth factor production increases, which ensures regenerative activity of the intestinal mucosa epithelium through this period of the disease.

Keywords: *Insulin-Like Growth Factor; Tumor Necrosis Factor-Alpha; Cytokines; Ulcerative Colitis; Inflammation*

Abbreviations

IGF-I: Insulin-Like Growth Factor; TNF-A: Tumor Necrosis Factor; IL-10: Interleukin 10; MNCs: Blood Mononuclears; CM: Colon Mucosa; IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; EIA: Enzyme Immunoassay; IID: Inflammatory Infiltrate Density

Introduction

Ulcerative colitis belongs to a group of inflammatory bowel diseases, including Crohn's disease, collagen, lymphatic, eosinophilic and indefinite colitis. A typical feature of UC is immuno-inflammatory damage affecting the colon, whereas its development is mediated by immunological mechanisms. Inflammation in case of UC is of a superficial nature and will affect the colon mucous and submucosal membrane only (CM), occurring exclusively in the colon [1,2].

There are more than a few works available nowadays that focus on the etiology of UC. The causes of this pathology, however, remain unknown, while the mechanisms behind its development have not been fathomed [3]. There is description of the disorders in the functioning of immunocompetent cells in case of UC all this being behind the specifics of morphological changes in tissues around the inflammation, as well as the course of the process following the vicious circle principle, which makes it extremely difficult to regenerate damaged tissues and restore homeostasis [4]. There is also no consensus as to the factors triggering and promoting UC progress. The key link in the pathogenesis of UC is believed to be a disturbed T-cell link in the immune system, which results in an imbalance between pro - and anti-inflammatory cytokines.

Recently, there has been an active discussion around the role played by peptide growth factors, which are produced by many types of cells, including the intestinal epithelium, and which are capable of modulating an inflammatory response and proliferative activity in the intestinal epithelium involving various cytokines (IL-10, TNF-α, etc.) [5]. These substances include the family of insulin-like growth factor (IGFs), which are expressed in various parts of the gastrointestinal tract. IGF-1 is one of the most powerful natural stimulators of cell growth and proliferation of various cells in the body. Besides, IGF-1 plays an important role in human physiology through controlling the metabolism of proteins, fats, carbohydrates, as well as it stimulates glucose transport to the muscles [6,7].

Despite a low number of studies focusing on evaluating the biological effects of IGF-I in UC, their role in the immunopathological process is quite obvious [8].

Aim of Study

Identifying the role of IGF-I in UC pathogenesis.

Materials and Methods

The study included 63 patients with various severity and endoscopic (Mayo index) activity of UC through the treatment dynamics. The UC clinical activity and severity were evaluated following the Truelove and Witts criteria. Medication treatment was administered depending on the severity of UC. The control group included 20 healthy volunteers. The detection of IGF-I in peripheral blood was carried out by the EIA method (Mediagnost, Germany). The results were expressed in nmol/l. The level of serum IGF-I in the control group was 120.295 ± 10.723 nmol/l.

The content of TNF-a and IL-10 in peripheral blood mononuclears (MNCs) was identified through the EIA method employing standard Cytokine test systems (Russia). The cells were isolated from heparinized blood on a ficoll-verografin density gradient. After centrifugation, MNCs were extracted alternately, to be washed with medium199, diluted in 1 ml of a special culture medium (RPMI-1640 with glutamine, 2% fetal cattle serum, gentamicin solution 20 mcg/ml). The number of cells was counted in the Goryaev chamber, standardized (2×10^6/ml), incubated for 24 hours at 37°C in an atmosphere of 5% CO_2 without (spontaneous synthesis) and with lipopolysaccharide (LPS), *E. coli* (Sigma, USA) - 10 mcg/ml (stimulated synthesis).

The TNF-a and IL-10 production by MNCs in the control group was, respectively: spontaneous - 1.54+0.9 ng/2 x 10^6 and LPS-stimulated - 2.81+0.21 ng/2 x 10^6 and 5.52 ± 1.39 and 9.17 ± 1.51 pg/2 × 10^6 cells, $P < 0.05$. The CM inflammation intensity was studied relying on the method by Avtandilov G. G. with the calculation of the inflammatory infiltrate (%) of the mucous membrane own plate. The cellular composition of the inflammatory infiltrate was studied, while the statistical processing of the obtained data was performed using SPSS 13.0 software.

Results and Discussion

Through the acute stage of UC, the amount of IGF-I in the blood plasma is reduced (14.06 = 1.30 nmol/l, $P < 0.05$ with control).

A comparative analysis of the IGF-I content in peripheral blood, in view of the UC severity, revealed an inverse relationship - along with an increase in the UC severity, the level of IGF-I in the blood serum would go down (Table 1).

Indicator, nmol/l	Severity		
	Mild (n = 28) (1)	Moderate (n = 25) (2)	Grave (n = 10) (3)
IGF-I	29.50 ± 0.13* P_1< 0.05	14.4 ± 0.081* P_2< 0.05	11.14 ± 0.03* P_3< 0.05

Table 1: *IGF-I level in the peripheral blood in patients with various degree of UC severity* $(\overline{X} \pm m_{\overline{x}})$.

**- P < 0.05 compared to the control group; P_1 - Difference between indicators in groups 1 and 2; P_2 - Difference between indicators in groups 1 and 3; P_3 - Difference between indicators in groups 2 and 3.*

Figure 1 offers a look at the data on the IGF-I level in the blood plasma in patients with UC in view of the activity degree of the inflammatory destructive process (Mayo index) in the CM.

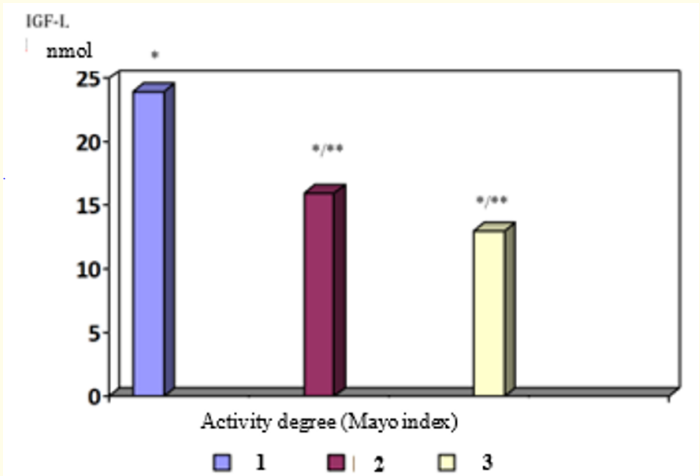

Figure 1: *IGF-I level in blood plasma in view of UC endoscopic activity*

*Note: *- P < 0.05 compared to healthy ones, ** - P < 0.05 compared to Degree 1 of activity.*

There was an inverse dependence identified between the IGF-I contents in peripheral blood and the activity of the inflammatory-dystrophic process in the CM - while there was an increase in the Mayo index, the IGF-I index was going down.

We studied the dependence of the IGF-I index on the severity of the inflammatory response in the CM. To do so, a morphometric study of CM recto biopsies was carried out in the examined patients along with the calculation of the inflammatory infiltrate density (IID). Depending on the said density index, the patients were divided into two groups - one group with a weak inflammatory reaction (35.8 ± 1.7%), and the other - with a significant infiltrate intensity (67.1 ± 2.3%, P < 0.05 with Group 1).

In order to find out any possible dependence between the intensity of the inflammatory process in the CM and the level of serum IGF-I in patients with active UC, a correlation analysis was performed (Table 2).

Relation	Correlation index (rs)	
	Weak	Significant
Inflammation infiltrate density		
IGF-I (nmol/l) and IID	- 0.326*	- 0.646*

Table 2: *Link between IGF-I index and inflammation infiltrate density in CM in patients with UC.*

*Note: * - P < 0.05.*

Mild (weak) inflammatory infiltrate intensity in the CM was found to feature a negative interrelation between the IGF-I index and the infiltrate density in the CM. In case the IID was significant, though, the relation was strong.

Given the fact that the expression of IGF-I has a certain dependence on the production of certain cytokines [9], we tried to identify possible connection between the studied peptide growth factor in the examined group of patients and the synthesis of the pro-inflammatory cytokine TNF-α and anti-inflammatory-IL-10 by peripheral blood mononuclears.

We found that the initial spontaneous and stimulated synthesis of TNF-a by MNCs (1. spontaneous - 5.9 ± 0.8 and 2. stimulated - 8.2 ± 0.9 ng/2 x 10^6) and IL-10 (1. spontaneous - 9.57 ± 1.22 and 2. stimulated - 15.9 ± 0.79 ng/2 x 10^6) in patients with active UC was significantly above the control values (P1, 2 < 0.05 with control).

A correlation analysis was caried to match the production of TNF-α, IL-10 by MNCs and IGF-I in the peripheral blood of patients with active UC.

As table 3 shows, we identified a reliable inverse relationship between the synthesis of TNF-α by MNCs under spontaneous and LPS-stimulated conditions, as well as a positive relationship between the production of IL-10 by MNCs under spontaneous and stimulated conditions, on the one hand, and the level of IGF-I in peripheral blood, on the other.

Indicator	Rank correlation coefficient (rs)	
	TNF-α synthesis by MNCs	IL-10 synthesis by MNCs
IGF-I	-0.422* -0.614*	0.611* 0.453*

Table 3: *Relationship between the IGF-I level in peripheral blood and the MNC production of TNF-α and IL-10 in patients with active UC.*
*Note: numerator - spontaneous production; denominator - LPS-induced * - p< 0.05.*

During the formation of UC clinical remission (on average - 8 weeks after), the level of the peptide went up to 96.115 ± 26.08 nmol/l, P < 0.05 along with the acute phase, yet not to reach the control values (P < 0.05). The induction of UC clinical remission was accompanied with a decrease in the synthesis of TNF-α by MNCs, both under spontaneous (3.6 ± 0.4 ng/2 x 10^6) and LPS-stimulated conditions (5.2 ± 0.08 ng/2 x 10^6, P1, 2 < 0.05 with exacerbation and control). IL-10 production by MNCs got back to normal by that stage of the disease (5.61 = 0.21 and 9.42 = 0.31 ng/2 x 10^6, P1, 2 > 0.05 with exacerbation and control).

The regularities we detected in the content of the studied IGF-I peptide growth factor in the blood serum observed in patients with various clinical UC types, when viewed in connection with the inflammation mediators of the CM, are not accidental and serve an indirect proof to their involvement in pathophysiological processes affecting the colon.

As stated earlier, the biological effects of IGF-I in case of UC have been poorly studied, while the currently obtained research outcomes are ambiguous. Growth factors, including IGF-I, perform numerous functions and often have opposite actions in cases of ulcerative colitis and Crohn's disease. We found that during the exacerbation stage of UC, the level of IGF-I in the blood serum was low, while it was so proportionately to the severity of the next attack. Similar outcomes were reported by Thayu M., *et al* [10]. In other studies, the authors found no significant deviations in the IGF-I content in patients with active UC, in contrast to patients with CD, where the levels of the peptide in question were much above the control parameters [11].

An undeniable proof to the importance of the role played by the insulin-like growth factor IGF-I in case of UC can be seen from its certain relation to the severity of the inflammatory response in the CM and the synthesis of cytokines by peripheral blood mononuclears.

Being one of the central links in the human immune system, the cytokine system can respond to almost any pathological processes occurring within the intestine. In this case, we have activated immunocytes here, which ultimately, as has been proven through respective studies, leads to a sharp increase in the level of not only pro- yet also anti-inflammatory cytokines in the peripheral blood cells in patients with IBD [4].

For instance, we found an inverse relationship between the IGF-I level and the TNF-α synthesis, and a positive relationship between the studied peptide and IL-10. Low IGF-I growth factor production is known to potentially have a negatively impact on the trophism of the intestinal epithelium in the active stage of inflammation, as well as during the recovery period [12]. It has been proven that a prolonged decrease in the IGF-1level in case of UC can lead to a disturbed bone metabolism with an increased risk of osteoporotic fractures, which is a frequent case for this category of patients [13]. On the other hand, excessive accumulation of growth factors can cause aberrant proliferation of the mucosal epithelium, which will increase the risk of developing intestinal carcinoma, a common complication of IBD [14].

The experiment has shown that cytokines can regulate the IGF-I expression in the intestinal epithelium through inhibiting the somatotropic hormone. TNF-α, for instance, reduced the IGF-I secretion in macrophages [15], while the exogenous insulin-like factor associated with protein-3 (IGFBP-3) suppressed the TNF-α cytokine production induced by the NF-kB nuclear factor [16]. The protective role of IGF-I against the degradation of cartilage proteoglycans induced by interleukin-1 or TNF-α has been demonstrated *in vitro* [17].

We believe that in the active phase of UC, pro-inflammatory cytokines can suppress the IGF-I production, thus prolonging the immunoinflammatory process in the CM. During that, excessive production of anti-inflammatory IL-10 by blood immunocytes through acute UC is due to high production of various pro-inflammatory mediators by Tx1-clone lymphocytes and is apparently aimed at their suppression. However, the regulatory effect this cytokine has on the IGF-I expression cannot be excluded. IL-10 has been shown to have potential to inhibit the cellular inflammatory response (whether the cells involved in it belong to a particular subpopulation of helper T-lymphocytes or not) and to restore the mucosa tolerance to proper intestinal flora. Moreover, an experiment carried out on mice, showed that the introduction of IGF-1 will increase the expression of the IL-10 anti-inflammatory cytokine [18].

We have found that during the formation of UC clinical remission, against the background of immunomodulatory treatment, the TNF-α synthesis decreases naturally, the production of IL-10 by MNCs gets to normal, while the production of IGF-I growth factor increases, which ensures regenerative activity of the intestinal mucosal epithelium through this period of the disease [19].

Advances in understanding the processes associated with intestinal inflammation progress, the role of certain biological agents in the development of a pathological immune response, in particular, have led to the development of the targeted biological treatment concept. We believe that studying the role of bioregulatory peptides, IGF-I in case of UC in particular, may be essential in terms of searching for new treatment targets.

Conclusion

1. During acute attacks of UC, the level of IGF-I is reduced, and the synthesis of TNF-α and IL-10 cytokines by MNCs is increased.
2. The production of IGF-I revealed an inverse dependence on the severity of UC, on the degree of inflammatory reaction in the CM, on the production of TNF-α, and a direct one - on the IL-10 synthesis by MNCs.
3. Clinical remission of UC was accompanied with an increase in IGF-I production, a decrease in the TNF-α cytokine synthesis, and with normalized production of IL-10 by MNCs.

Conflict of Interest

The authors declare that they have no conflict of interest.

Bibliography

1. Pravda J. "Can ulcerative colitis be cured?" *Discovery Medicine* 27.149 (2019): 197-200.
2. Hart AL., *et al*. "What Are the Top 10 Research Questions in the Treatment of Inflammatory Bowel Disease?" *Journal of Crohn's and Colitis* 7 (2017): 204-211.

3. Fakhoury M., *et al*. "Inflammatory bowel disease: clinical aspects and treatments". *The Journal of Inflammation Research* 21 (2014): 113-120.

4. Fonseca-Camarillo G and Yamamoto-Furusho JK. "Immunoregulatory Pathways Involved in Inflammatory Bowel Disease". *Inflammatory Bowel Disease* (2015): 1-6.

5. Jacob N., *et al*. "Cytokine and anti-cytokine therapies in prevention or treatment of fibrosis in IBD Received: 21 January 2016". *United European Gastroenterology Journal* (2016): 1-10.

6. Sanderson IR. "Growth problems in children with IBD". *Nature Reviews Gastroenterology and Hepatology* 11.10 (2014): 601-610.

7. Zatorski H., *et al*. "Is insulin-like growth factor 1 (IGF-1) system an attractive target inflammatory bowel disease?" *Benefits and Limitation of Potential Therapy* (2016): 809-815.

8. Falvey JD., *et al*. "Disease Activity Assessment in IBD: Clinical Indices and Biomarkers Fail to Predict Endoscopic Remission". *Inflammatory Bowel Disease* 21 (2015): 824-831.

9. Theiss AL., *et al*. "Growth factors in inflammatory bowel disease: the actions and interactions of growth hormone and insulin-like growth factor-I". *Inflammatory Bowel Disease* 10.6 (2004): 871-880.

10. Thayu M., *et al*. "Determinants of changes in linear growth and body composition in incident pediatric Crohn's disease". *The Journal of Gastroenterology* 139.2 (2010): 430-438.

11. Li P., *et al*. "Resveratrol inhibits collagen I synthesis by suppressing IGF-1R activation in intestinal fibroblasts". *World Journal of Gastroenterology* 20.16 (2014): 4648-4661.

12. Sanderson IR. "Growth problems in children with IBD". *Nature Reviews Gastroenterology and Hepatology* 11.10 (2014): 601-610.

13. Eivindson M., *et al*. "The insulin-like growth factor system and markers of inflammation in adult patients with inflammatory bowel disease". *Hormone Research* 64.1 (2011): 9-15.

14. Underwood LE. "Growth hormone treatment, acromegaly, and relationship to cancer and leukemia. In Bercu BB and Walker RF (eds) Growth Hormone II: Basic and Clinical Aspects, New York: Springer Verlag (2010): 259-268.

15. Emmerson E., *et al*. "Insulin-like growth factor-1 promotes wound healing in estrogen-deprived mice: new insights into cutaneous IGF-1R/ER[alpha] cross talk". *Journal of Investigative Dermatology* 132.12 (2012): 2838-2848.

16. Lee KW., *et al*. "Rapid apoptosis induction by IGFBP-3 involves an insulin-like growth factor-independent nucleomitochondrial translocation of RXRalpha/Nur77". *Journal of Biological Chemistry* 280.17 (2009): 16942-16948.

17. Tyler JA. "Insulin-like growth factor I can decrease degradation and promote synthesis of proteoglycan in cartilage exposed to cytokines". *The Journal of Biochemistry* 260 (2012): 543-548.

18. Johannesson B., *et al*. "Insulin-like growth factor-1 induces regulatory T cell-mediated suppression of allergic contact dermatitis in mice". *Disease Models and Mechanisms* 7.8 (2014): 977-985.

19. Steven JB and Lloyd M. "The Immune Response in Inflammatory Bowel Disease". *The American Journal of Gastroenterology* 102 (2007): 2058-2069.

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