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WORD COUNT	972	TIME SUBMITTED	04-JUL-2022 07:14PM
		PAPER ID	88002255

Urotensin II level is elevated in inflammatory bowel disease patients

Zhang Y *et al*. Urotensin II and IBD

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Abstract

Alicic *et al* reported that the Urotensin II (U-II) levels in inflammatory bowel disease (IBD) patients are significantly higher than that in the controls. To provide future guidance for the management of cardiovascular risks in IBD patients, the sample size of the current study appears to be limited, and more clinical samples to compare U-II levels in IBD patients and control subjects are needed. This will clarify the possible roles of inflammation factors and related signaling pathways (like EPK1/2, NF-κB and Rho/ROCK) in the pathophysiology of IBD. Therefore, more studies with a large sample size and multi-centers should be done to confirm the findings and underlying mechanisms in the future.

Key Words: Inflammatory bowel disease; Urotensin II; Inflammatory factors; High sensitivity C reactive peptide

Zhang Y, Chen GX. Elevation of Urotensin II level in patients with inflammatory bowel disease. *World J Gastroenterol* 2022; In press

Core Tip: Attracted by Alicic D's observational report, we learned that the levels of Urotensin II (U-II) in inflammatory bowel disease (IBD) patients were significantly increased compared with that in the controls. In addition, the authors also reported that the blood U-II level is positively correlated with high sensitivity C reactive peptide, and severe endoscopic features of the disease. This study provides us with a brand-new role of U-II in IBD, which warrants future larger scale multicenter clinical and basic studies

to determine the mechanisms by which U-II triggers inflammatory responses and activate signaling pathways (EPK1/2, NF-κB and Rho/ROCK).

TO THE EDITOR

We had read the observational study reported by Alicic *et al*[1], who have convincingly shown the roles of elevated Urotensin II (U-II) levels in patients with inflammatory bowel disease (IBD).

IBD comprising of Crohn's disease (CD) and ulcerative colitis (UC) is a multifactorial condition of relapsing chronic inflammation in the gastrointestinal tract with an unpredictable course[2]. In addition, extra-intestinal manifestations of IBD cardiovascular risks occur frequently and contribute to morbidity and reduced quality of life[3-5].

U-II is a peptide ligand that acts as a potent vasoconstrictor, which was originally discovered four decades ago. The vasoconstriction activity of U-II is more potent than endothelin-1 (10-fold stronger)[6]. Majority of U-II studies have been conducted to understand its role in the development of cardiovascular diseases[7]. A growing number of scholars have recognized the links of U-II levels with malignant lesions associated with liver, pancreas and gut[8]. Whether U-II participates in the start and progress of IBD has always intrigued contemporary gastroenterologists. This observational study reported the potential relationship of U-II and IBD, which provides the field with new knowledge and attracts our attention.

In this article, the authors compared the blood levels of U-II in IBD patients and healthy controls, and investigated the associations of U-II levels with the anthropometric, clinical and biochemical parameters. The study included 50 adult patients with pre-diagnosed IBD (24 patients with UC and 26 patients with CD) and 50 healthy, age and gender matched controls. IBD patients had significantly higher U-II levels than control subjects. Significant positive correlations between serum U-II levels and high sensitivity C reactive peptide (hsCRP) levels, UC Endoscopic Index of Severity and Simple Endoscopic Score for CD were observed. Whether these clinical data imply

the involvement of U-II in the inflammatory responses and disease outcomes of IBD patients remains to be confirmed.

The action of U-II is mediated by U-II receptor (UTR). UTR is also called GPR14, which is a G-protein-linked receptor[9]. Both U-II and UTR can be found in various of cells cardiovascular, pulmonary, central nervous system, kidney, and other metabolic organs and tissues. The biding of U-II as a ligand activates UTR, which mobilizes calcium in cytoplasm, induces proliferation of smooth myocytes, and triggers inflammation[10,11]. As expected, the level of inflammatory factor hsCRP in IBD patients is significantly higher than the healthy controls.

The article is the first clinical study to investigate blood UII levels in both UC and CD patients. However, limitations can be seen, which can potentially bolster the authors' conclusions if resolved: (1) The single center study only has 50 subjects each in the IBD and control groups, which is a small number. If more institutes are included in a multicenter investigation and more human subjects are recruited, the conclusions will become more convincing and relevant. Therefore, more studies with a large sample size and multi-centers are anticipated in the future; and (2) the research results show that the elevation of the blood U-II level is associated with the disease development and progression, and attributed to the inflammation mediated by hsCRP. However, the levels of other inflammatory factors were not measured (interleukin-6, interleukin-8, tumor necrosis factor-α and so on). Their levels and involvements in the elevated U-II concentration and inflammatory responses in those patients should be clarified. Regarding the mechanisms, it is possible that U-II as a ligand activates pathways that may stimulate the releases of inflammatory effectors such as cytokines stated above. These cytokines may potently activate signaling pathways consisting of EPK1/2, NF-κB and Rho/ROCK, which regulate a variety of downstream inflammatory responses[12-14]. Whether those cytokines and U-II act among each other or in concert to form a system influencing the host inflammation status remains to be answered. In the future, gastroenterologists should continuously put efforts in unravelling how U-II interacts with other inflammatory mediators, and how U-II modifies those signal pathways to

potentiate the IBD severity in various *in vivo* and *in vitro* systems. In so doing, more results could be collected and analyzed, which are needed to form theoretical and practical evidence to guide prevention and treatment of cardiovascular complications in IBD. Additionally, antagonists to the UTR activation system can also be developed, which may counteract any detrimental effects due to the U-II elevation in patients with IBD.

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