

Trefoil Factor 3 – A Potential Inflammatory Marker in Ulcerative Colitis

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the colon and results in disability and reduced quality of life. There is currently no single “gold standard” diagnostic test for UC. Instead, diagnosis is established by a combination of clinical, laboratory, imaging, and endoscopic parameters, including histopathology. Trefoil factors (TFFs) include a family of three mucin-associated peptides secreted by goblet cells in the intestinal mucosa. In the current manuscript, we aim to review the data currently available on the role of TFF3 as a potential inflammatory marker in UC patients.

Key words: Intestinal inflammation, trefoil factor 3, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the colon and results in disability and reduced quality of life.^[1,2] Typically, it shows relapsing and remitting mucosal inflammation, starting in the rectum, and extending to proximal segments of the colon.^[3]

There is currently no single “gold standard” test for the diagnosis of UC. Instead, diagnosis is made by a combination of the following methods: Clinical, laboratory, imaging, and endoscopic parameters, including histopathology.^[4] However, even when the tests are performed by expert physicians, they can lead to diagnostic uncertainty.^[5-7]

The pathogenesis of UC is multifactorial, involving genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors. The best understanding of the UC pathogenesis includes altered epithelial barrier function and a dysregulated immune response in genetically susceptible individuals as a result of multiple interactions between the commensal gut microbiota, the colonic immune system, environmental factors, and the impaired mucosal barrier.^[8,9]

Furthermore, a contributing factor to inflammatory bowel disease pathogenesis could be the alteration in the intestinal mucous components that could impair the barrier function of the mucin layer.^[10] Mucin types and expression are affected by several factors in UC. For instance, the number of mucin-producing goblet cells is reduced in active disease and may remodel the composition and thickness of the mucous gel layer.^[11] There is an increasing pool of evidence that underscores the involvement of trefoil peptides in the protection of mucosal surface and its repair after injury. Trefoil factors (TFFs) involve a family of three mucin-associated peptides (TFF1, TFF2, and TFF3) that are expressed in a tissue-specific manner in the gastrointestinal tract (GIT).^[12] Several tissues that contain mucus-secreting cells express TFFs. However, they are pronouncedly expressed in the GIT.

TFF3 was described in 1991 as a rat cDNA sequence^[13] and 2 years later as a human cDNA sequence.^[14] TFF3 was named intestinal TFF at first. It is secreted mainly by goblet cells of the small and large intestine and defends the mucosa of GIT from insults.^[15] TFF3 is secreted and produced together with mucin (MUC) 2.^[16] An increasing body of evidence has shown the protective function of TFFs in the GIT and their elevated expression at the sites of mucosal damage.^[17-19] Despite the

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growing number of studies and the rising scientific interest in TFF3 over the last few years, its role as a marker of intestinal inflammation in the real-life clinical practice has not been still well defined.

In the current manuscript, we aim to review the data currently available on the role of TFF3 as a potential inflammatory marker in UC patients.

TFF3 AND DISEASE ACTIVITY IN UC

It has been recently suggested that serum levels of TFF3 measured by enzyme-linked immunosorbent assay (ELISA) can predict disease activity in UC patients.^[20,21] Grønbaek *et al.*^[22] found that serum TFF3 levels correlated with disease activity indices in patients with UC and they noted a trend toward reduction in TFF3 levels with clinical improvement after therapy with steroids. In two consecutive studies, Nakov *et al.* showed that the mean levels of TFF3 in active UC were significantly higher than those identified in patients with quiescent UC, which were similar to those of the healthy controls.^[20,21]

Moreover, TFF3 demonstrated a strong correlation with clinical activity Lichtiger index ($r = 0.736$, $P < 0.001$), Mayo endoscopic subscore (MES) ($r = 0.811$, $P < 0.001$), and UC endoscopic index of severity (UCEIS) ($r = 0.820$, $P < 0.001$).^[23] Therefore, TFF3 has a significant potential to be used as a marker for disease activity in UC patients.

TFF3 AND OTHER INFLAMMATORY MARKERS

At present, the best studied and most widely used inflammatory markers are C-reactive protein (CRP) and fecal calprotectin (FC).^[24] TFF3 has been compared with FC and CRP in a recent study of Nakov *et al.*, where TFF3 levels showed significant correlation with FC levels ($r = 0.696$, $P < 0.001$) and CRP levels ($r = 0.405$, $P < 0.001$).^[23] Moreover, FC showed a better correlation with the TFF3 levels, as compared to CRP (Steiger's Z test, $z = 3.209$, $P < 0.01$).^[23]

This strong correlation with FC and CRP makes TFF3 an inflammatory marker with a great potential to be used in the clinical practice for disease activity of UC patients.

TFF3 AND MUCOSAL HEALING (MH) IN UC

Achieving MH has become the target of UC treatment mainly because it leads to better quality of life, minimizes hospitalization rates, and prevents relapses and complications.^[25] Furthermore, MH is suggested as the best predictor of UC prognosis.^[26] Recently, it has been proposed

that serum levels of TFF3 measured by ELISA can reflect MH in UC patients.^[23,27]

Srivastava *et al.*^[27] showed that serum TFF3 could indicate patients with MH in a group of UC patients in clinical remission or with mild activity with acceptable sensitivity and specificity. Nakov *et al.*^[23] demonstrated that a TFF3 cut-off level of 6.74 ng/ml has area under the curve of the ROC curve 0.927, sensitivity of 87.9%, and specificity of 86.9% for predicting complete MH evaluated as both UCEIS and MES values of 0.

Furthermore, it is quite interesting that TFF3 correlates very well with CRP levels in UC patients and the combination of TFF3 and CRP has comparable predictability of complete MH to FC.^[23] This provides an additional opportunity for UC patients – they could be followed up just by blood markers and avoid the unpleasant for some patients fecal material handling.

CONCLUSION

TFF3 is able to predict disease activity and to reflect MH in patients with UC in the real clinical practice. It correlates well with FC levels, CRP levels, and endoscopic activity; hence, it could be used as a non-invasive marker to predict disease activity in UC patients. However, more studies are needed to evaluate the role of TFF3 as a real-life marker of intestinal inflammation.

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