FIBROGENESIS BIOMARKERS AND RISK FACTORS OF GASTROINTESTINAL TRACT STRICTURES IN CROHN'S DISEASE

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INTRODUCTION

Inflammatory bowel disease (IBD), such as Ulcerative Colitis (UC) or Crohn's Disease (CD) are characterized by chronic inflammation and damage of intestinal tissue, which leads to local expansion of mesenchymal cells and excessive deposition of extracellular matrix components, such as collagen or fibronectin. Inflammatory and fibrotic changes together contribute to progressive bowel wall thickening, stricture development and subsequent obstructing complications. The lifetime risk of stricture formation is about 24,9-50% among patients with CD. A major group of these patients require surgery at least once in the lifetime. Drug development over the last decades has led to better control of the inflammation, however anti-inflammatories do not specifically target or reverse fibrosis. Currently, there are no biomarkers which could be useful in early detection of fibrosis and improvement of patient outcomes.

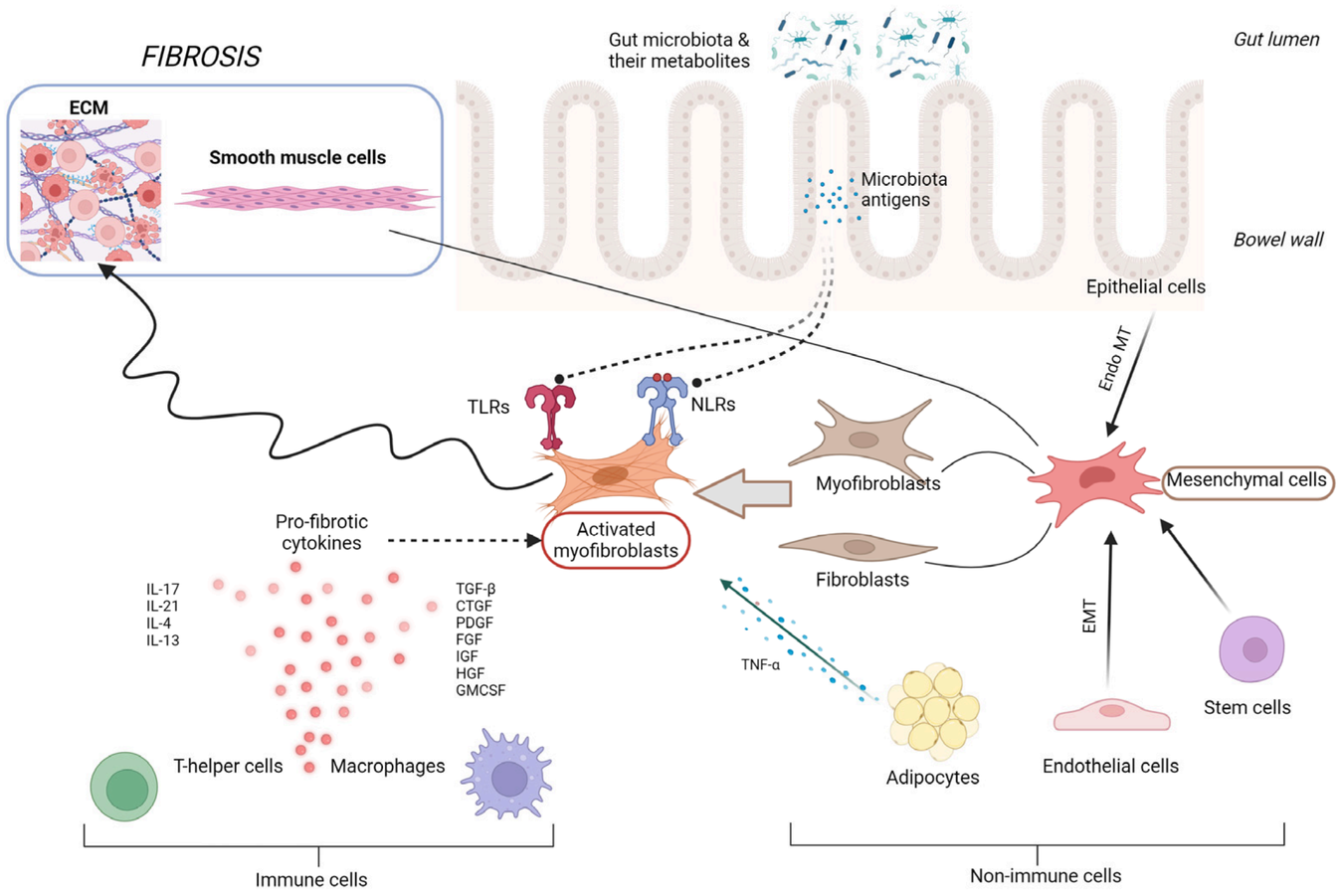

Figure 1. Pathophysiology of intestinal fibrosis. CTGF, connective tissue growth factor; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; Endo MT, endothelial-mesenchymal transition; FGF, fibroblast growth factor; GMCSF, granulocyte-macrophage colony stimulating factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IL, interleukin; NLRs, NOD-like receptors; PDGF, platelet derived growth factor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α. Źródło: Dudek P, Talar-Wojnarowska R. Current Approach to Risk Factors and Biomarkers of Intestinal Fibrosis in Inflammatory Bowel Disease. Medicina (Kaunas). 2024 Feb 10;60(2):305. doi: 10.3390/medicina60020305.

AIM OF THE STUDY

Our study aims to assess the clinical importance of potential biomarkers of gastrointestinal tract fibrosis, as well as to determine the significance of risk factors for stricture formation among patients with CD. By identifying reliable biomarkers, we hope to stratify patients according to their risk of intestinal strictures development or identify early stages of fibrosis prior to clinical symptoms. This proactive approach could revolutionize the management of CD, offering targeted interventions to high-risk individuals and potentially averting the progression of debilitating complications.

MATERIALS AND METHODS

The study will include a group of 120 patients over 18 years of age with CD, hospitalized in the Department of Digestive Tract Diseases. The study group will consist of patients with diagnosed stenosis of the gastrointestinal tract, while the control group will include patients without evidence of strictures in the gastrointestinal tract. Diagnosis of gastrointestinal strictures will be confirmed using radiological and/or endoscopic criteria. To meet the radiological criteria, the gastrointestinal tract must show segmental stenosis with a thickened wall at the site and widened lumen before it. The endoscopic criterion is the inability to pass the narrowed section without prior dilation. We selected four types of the most promising potential biomarkers of fibrostenosis: cartilage oligomeric matrix protein COMP, hepatocyte growth factor activator HGFA, antibodies against granulocyte-macrophage colony stimulating factor GM-CSF Ab, isoform ED-A of fibronectin. Peripheral blood samples (5 ml) will be collected from subjects and concentration of candidate biomarkers will be measured in the obtained serum samples by ELISA technique. To elucidate risk factors of fibrostenosis, questionnaires completed by subjects and medical charts will be analyzed. The study was approved by the Bioethics Commitee- consent number RNN/69/23/KE from 18.04.2023.

Table 1. Potential biomarkers of fbrogenesis in Crohn's disease.

Category	Biomarkers
Extracellular matrix proteins	Collagen I Collagen III Collagen IV Collagen degradation products (fragments of type I (C1M), III (PRO-C3, C3M), IV (PRO-C4, C4M, C4G) and VI (C6Ma3)) Fibronectin isoform ED-A Cartilage oligomeric matrix protein (COMP
Growth factors	Transforming growth factor β (TGF-β) Hepatocyte growth factor activator (HGFA
Cytokine antibodies	Anti-TGF beta antibodies, Anti- IL-10 antibodies, Anti GM-CSF antibodies
Antimicrobial antibodies	Anti- Saccharomyces cerevisiae antibody (ASCA) Anti- zymogen granule membrane glycoprotein 2 (GP2) antibodies Anti- flagellins: A4-Fla2, anti Fla-X, anti-CBir1 Anti- Escherichia coli outer membrane porin C (anti-OmpC) Anti-CD associated bacterial sequence (I2) Cathelicidin (LL-37)
Genetic variants	Caspase activation recruitment domain (NOD2/CARD15) L-selectin (CD62L) Micro-RNA (miR-19a-3p, miR-19b-3p) Genetic variation of cytokines: IL-12B, IL 10 Tumor necrosis factor (TNF) ligand superfamily member 15
Histhopathology/ Tissue based markers	Mast cell density TGF-β activated kinase 1 (TAK1) Ovarian cancer G-protein coupled receptor 1(OGR1) mRNA Cholesterol 25 hydroxylase (CH25H) mRNA
Other	fecal calprotectin (FC) fecal lactoferrin (FL) a2-Heremans-Schmid glycoprotein (AHSG/fetuin A) Elafin Mannan-binding lectin (MBL) C-reactive protein (CRP)

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