بسم الله الرحمن الرحيم

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Serum IL-22 as a novel non-invasive biomarker in diagnosis and assessment of activity in ulcerative colitis patients

Thesis

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Mohamed Sayed Kortam

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List of Abbreviations

GD	*Graves' Disease*
5-ASA	5-aminosalicylic acid
Ahr	Aryl hydrocarbon receptor
AMPs	Antimicrobial proteins
BaP	benzo (α) pyrene
BCLxl	B cell lymphoma
CD	Crohn's disease
CRP	C-reactive protein
DC	dendritic cell
DNBS	dinitrobenzene sulfonic acid
DSS	dextran sulfate sodium
ER	endoplasmic reticulum
FC	Fecal calprotectin
FMT	fecal micro biota transplantation
FUT2	fucosyltransferase 2
GDNF	glial cell–derived neurotrophic factor
GVHD	graft-versus-host disease
GWAS	genome wide association studies
HS	highly significant
IBD	Inflammatory bowel disease
IBM SPSS	Statistical Package for Social Science

IECs	Intestinal epithelial cells
IFN	interferon
IgA	immunoglobulin A
IL	interleukin
IL-22	Interleukin-22
IL-5	interleukin-5
ILC3	innate lymphoid type 3
ILCs	Innate lymphoid cells
IMID	immune-mediated inflammatory disease
IPAA	ileal pouch-anal anastomosis
ISCs	intestinal stem cells
MAdCAM	mucosal addressin cell associated molecule
MHC	major histocompatibility complex
MLN	mesenteric lymph node
mTOR	mechanistic target of rapamycin
Mϕ	macrophage
NK T cell	natural killer T cell
NS	non significant
OR	odds ratio
PPAR-γ	peroxisome proliferator-activated receptor gamma
S	significant
SES-CD	Simple Endoscopic Score for CD

SNPs	single nucleotide polymorphisms
TCDD	tetrachlorodibenzo-p-doxin
TGF	transforming growth factor
Th	T-helper cell
Th1	T helper type 1
TNF-α	tumour necrosis factor-α
TREG	regulatory T cell
Tyk2	tyrosine kinase 2
UC	ulcerative colitis
UC-CRC	UC-related carcinogenesis

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic inflammatory bowel diseases, characterized by an inappropriate and uncontrolled immune response, stimulated by the gut micro biome in a genetically susceptible host.

Typically, patients with IBD follow a disease course consisting of alternating exacerbations and periods of remission ***(Bourgonje et al., 2019).***

In IBD, the extent of inflammatory disease activity is preferably established by endoscopy, that is translated to validated scoring systems, such as the Mayo endoscopic sub score for UC and the Simple Endoscopic Score for CD (SES-CD) ***(Bourgonje et al., 2019).***

Endoscopic examination is the most reliable approach for diagnosing the presence and extent of IBD disease activity but it has several disadvantages, such as a high patient burden and risks of serious complications, like bowel perforation or bleeding, it is also costly and time-consuming. So, Alternatives for endoscopy are needed ***(Benitez JM., 2013).***

Biomarkers for endoscopic disease activity have been explored to predict the level of mucosal inflammation in IBD.

Fecal calprotectin (FC) and serum C-reactive protein (CRP) levels are now widely used and considered predictive markers for the degree of inflammation, but also show inconsistent correlation with mucosal inflammation when compared to endoscopy; This illustrates the need for better diagnostic measures for IBD exacerbations that can also be also applied to patients with subclinical disease activity ***(Bourgonje et al., 2019).***

The ideal inflammatory marker would be sensitive and specific, easy to perform, non invasive, has a low cost, and has a good prognostic value. It should also be reproducible between individuals and laboratories ***(Yarur et al., 2017).***

The current opinion about IBD pathogenesis is that the disease results from interactions between environmental factors, mainly microbes of the intestinal lumen and their products, and dysregulation of immune responses in genetically susceptible individuals.

Certain harsh environments that may affect barrier integrity (to increase barrier permeability to luminal macromolecular substances, such as protein antigens and microbial products) and over-absorption of luminal microbial products (which has been ascribed to a number of mucosal

pathologies) can lead to an over-activation of immune system, thus resulting in mucosal inflammation.

IL-22 is a member of the IL-10 subfamily, which was identified as T-cell–derived cytokine.

Expression of IL22 is induced in several human inflammatory conditions including IBD.

IL-22 was recently discovered to be mainly produced by both adaptive and innate immune cells.

Several cytokines and many of the transcriptional factors and T regulatory cells are known to regulate IL-22 expression through activation of signal transducer and activator of transcription 3 signaling cascades.

Findings have confirmed the potential role of the IL-22 gene in the pathogenesis of UC and suggest that IL-22 might be involved as a defense mechanism by enhanced mucus production, IL-22 prevents tissue damage and aids in its repair.

IL-22 plays a critical role in the regeneration of damaged epithelial monolayers and stimulates antimicrobial peptide generation. Importantly, the ability of IL-22 to promote intestinal wound healing and proliferation of intestinal epithelial cells in mice and humans has been reproducibly demonstrated by independent groups using different