

Potential diagnostic biomarkers of Ulcerative colitis-associated colorectal dysplasia

A. MERLI (1), C. MASSOT (2), N. BLÉTARD (3), F. QUESADA CALVO (1), D. BAIWIR (4), G. MAZZUCHELLI (5), N. SMARGIASSO (5), L. SERVAIS (6), C. OURY (6), M. DE PAUW-GILLET (7), E. DE PAUW (5), C. COIMBRA MARQUES (8), A. COLARD (9), A. VIJVERMAN (10), P. DELVENNE (3), M. MEUWIS (2), E. LOUIS (2) / [1] GIGA-R, University of Liège, Liège, Belgium, Translational Gastroenterology, [2] CHU de Liège -GIGA-R, Liège, Belgium, Hepato-Gastroenterology and Digestive Oncology and Translational Gastroenterology, [3] CHU de Liège, Liège, Belgium, Pathological anatomy and cytology, [4] GIGA facility Uliège, Liège, Belgium, GIGA-proteomics, [5] University of Liège, , Belgium, Laboratory of Mass Spectrometry, Chemistry dep., [6] GIGA-R, University of Liège, Liège, Belgium, Laboratory of Thrombosis and Hemostasis, [7] University of Liège, , Belgium, Mammalian Cell Culture Laboratory, [8] CHU de Liège, Liège, Belgium, Abdominal Surgery Department, [9] CHC de Liège, Liège, Belgium, Gastroenterology, [10] CHR Citadelle de Liège, Liège, Belgium, Gastroenterology and Digestive oncology

Introduction

In Ulcerative Colitis (UC), dysplasia can develop in areas that are or have been affected by chronic inflammation and are identified as Dysplasia Associated to Inflammation (DAI). Dysplasia may also develop independently of chronic inflammation and be defined as Sporadic Dysplasia (DSp). Anatomopathological diagnosis of DAI remains difficult, especially when tissue inflammation is present, as mucosal regenerative remodeling impairs dysplasia confirmation.

Aim

The aim of this study is to highlight specific proteins of UC-DAI.

Methods

We performed a study on Formalin-Fixed Paraffin-Embedded (FFPE) samples from UC-DAI (n=5). To compare the proteomes of dysplastic (DAI), inflammatory (I) and normal (NL) paired tissues, we collected epithelial cells by Laser Capture Microdissection (LCM) before differential analysis using label free proteomics. Confirmation of tissue distribution of one selected protein differentially distributed between DAI and I or NL was done by Immunohistochemistry (IHC) on UC-DAI (n=11). Colonic tissues of a colitis-associated cancer mouse model (AOM/DSS)(Thaker AI et al, J Vis Exp 2012) were evaluated by IHC encompassing Low Grade Dysplasia (LGD - n=39), High Grade Dysplasia (HGD - n=12), Adenocarcinoma (ADC - n=6), I (n=30) and NL (n=6) tissues.

Results

Proteomic analysis enabled confident identification of 1070 proteins. Nineteen proteins showed differential abundance between DAI and I or NL, among which Solute Carrier Family 12 member 2 (SLC12A2) that was only detected in DAI. SLC12A2 IHC on UC cases confirmed significantly different distributions with DAI>I ($p=0.0001$ for bordering epithelium and $p=0.002$ for crypts epithelia) and DAI>NL ($p<0.0001$ for bordering epithelium and $p=0.001$ for crypts epithelia). In the AOM/DSS model, SLC12A2 was significantly increased in dysplasia and ADC compared to I and NL tissues (LGD>I with $p<0.0001$, LGD>NL with $p=0.004$, HGD>I with $p<0.0001$, HGD>NL with $p=0.007$, ADC>I with $p=0.0002$ and ADC>NL with $p=0.009$). SLC12A2 was significantly higher in advanced lesions (HGD>LGD with $p=0.012$ and ADC>LGD with $p=0.038$).

Conclusions

SLC12A2 could be a potential marker of DAI in UC as being able to identify dysplasia from surrounding tissues with inflammation. It requires proper validation to evaluate its power as a specific IHC marker that could be used to clarify difficult cases diagnosed as “indefinite for dysplasia”.