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Lipid fingerprint image accurately conveys human colon cell pathophysiologic state: A solid candidate as biomarker

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ABSTRACT

Membrane lipids are gaining increasing attention in the clinical biomarker field, as they are associated with different pathologic processes such as cancer or neurodegenerative diseases. Analyzing human colonoscopic sections by matrix assisted laser/desorption ionization (MALDI) mass spectrometry imaging techniques, we identified a defined number of lipid species changing concomitant to the colonocyte differentiation and according to a quite simple mathematical expression. These species felt into two lipid families tightly associated in signaling: phosphatidylinositols and arachidonic acid-containing lipids. On the other hand, an opposed pattern was observed in lamina propria for AA-containing lipids, coinciding with the physiological distribution of the immunological response cells in this tissue. Importantly, the lipid gradient was accompanied by a gradient in expression of enzymes involved in lipid mobilization. Finally, both lipid and protein gradients were lost in adenomatous polyps. The latter allowed us to assess how different a single lipid species is handled in a pathological context depending on the cell type. The strict patterns of distribution in lipid species and lipid enzymes described here unveil the existence of fine regulatory mechanisms orchestrating the lipidome according to the physiological state of the cell. In addition, these results provide solid evidence that the cell lipid fingerprint image can be used to predict precisely the physiological and pathological status of a cell, reinforcing its translational impact in clinical research.

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1. Introduction

Alterations in membrane lipid metabolism are associated to diseases such as cancer or neurodegenerative disorders [1–3]. This coupled with the recent advances in mass spectrometry has boosted the interest to describe complete lipidomes in a diversity of pathological contexts, including colorectal cancer [4], aiming to identify lipid clinical biomarkers [5–7]. However, to fully understand the mechanistic link between a disease and a lipid biomarker, it is necessary to precisely discriminate its cell type origin within the tissue, as well as, its function. While there might be means to assess the cell type, our current knowledge on the specific function of each of the thousands of lipid species comprising a cell lipidome is largely limited [8,9]. It is in this context where emerging imaging mass spectrometry (IMS) techniques may help both lipidomic and the clinical field.

IMS allows visualizing the topographical distribution of hundreds of lipid species across a tissue section with a spatial resolution ranging from micrometers to nanometers (Fig. 1B) [10]. Using this technique, we recently demonstrated how the spatial distribution of a large number of lipid species matches exactly the anatomy of the human colonic mucosa, being possible to clearly distinguish based on their lipid

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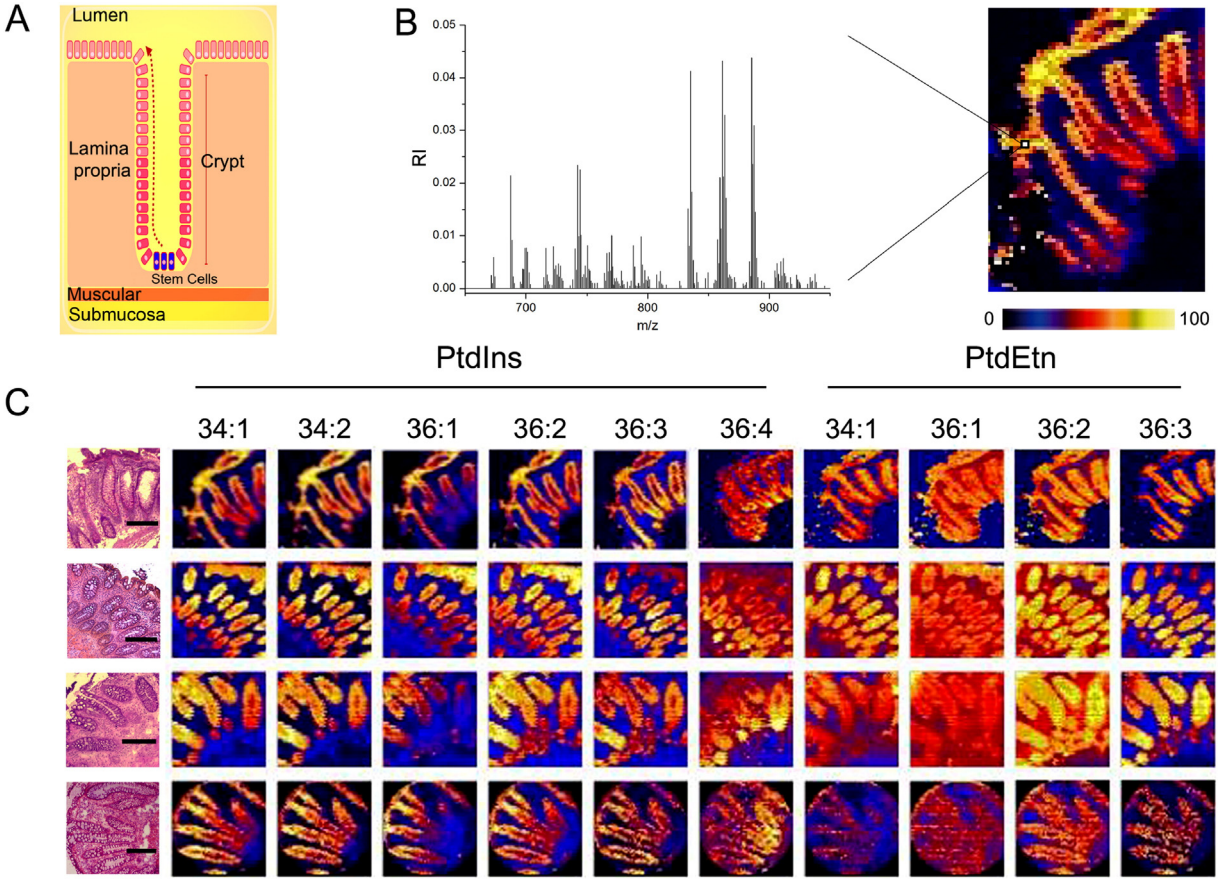

Fig. 1. Colonocyte differentiation status dictates its lipid composition in healthy epithelium. A — Schematic representation of a colon crypt. B — Representative MS spectra associated to one of the pixels defining an IMS image. Each *m/z* peak is integrated and the value is represented according a color scale vs. the coordinates where the spectra was recorded; C — First column: hematoxylin and eosin staining of colonoscopy biopsies included for comparison, the rest of columns show the distribution of some of the lipid species displaying a gradient in intensity. Scale bar = 150 μm. All spectra were recorded in negative-ion mode and at 10 μm of spatial resolution.

composition, the epithelial layer, lamina propria and muscularis mucosae [11]. Colon mucosa provides a fine arrangement in which it is easy to follow cells at different developmental stages. Thus, a single layer of epithelial cells lines the mucosa with insertions into the lamina propria forming the colon crypt (Fig. 1A). In addition to the inherent polarization of any epithelial cell, there is a second polarization axis along the crypt: pluripotent adult stem cells reside at the base, proliferate, expand and gradually differentiate while ascending toward the intestinal lumen. It is becoming clear that different signaling pathways, as Wnt, BMP, Hedgehog and Notch, orchestrate this complex process [12,13] and that any alteration in them may lead to pathogenesis [14–18].

Here, we investigated, how sensitive the cell lipidome was to the physiological state of the cell, testing whether it was possible to classify colonocytes according to their differentiation state or to identify cells undergoing a malignant transformation based on data generated from their lipid fingerprint image.

2. Material and methods

2.1. Human sample collection

2.1.1. Ethics statement

The sample collection for this study was specifically approved by the Ethics Research Committee of the Balearic Islands (IB 2118/13 PI). Informed consent was obtained in written form from each patient before performing each endoscopy. Human colon biopsies were obtained in the Endoscopic Room of the Hospital Universtari Son Espases (Palma, Spain) or of the Hospital Comarcal de Inca (Inca, Spain). Endoscopic biopsies were resected using a Radial Jaw Standard Capacity Biopsy Forceps (Radial Jaw™ 4, Boston Scientific, USA) and immediately snapped frozen in liquid nitrogen and saved at −80 °C until sample preparation. Sections of ~10 μm thickness were prepared using no crioprotective substances and no embedding material in cryostat (Leica CM3050S) at −20 °C and placed on plain glass microscope slides. A consecutive section was stained with hematoxylin and eosin (H&E) for structure identification.

2.2. Sample preparation for MALDI-imaging and data analysis

2.2.1. Reagents

2-Mercaptobenzothiazole (MBT) and 1,5-diaminonaphtalene (DAN) matrices, as well as hematoxylin and eosin for histological staining were purchased from Sigma-Aldrich. Water, methanol, acetonitrile, 2-propanol and formic acid (Fisher Scientific, Fair Lawn, NJ, USA) were of Optima® LC/MS grade. Leucine enkephalin acetate hydrate, ammonium acetate and sodium hydroxide solution were purchased from Sigma-Aldrich Chemie (Steinheim, Germany).

Detailed information regarding the MALDI-imaging and data analysis can be found in Garate et al. [11]. Briefly four sections of control and four sections of AD colon from different individuals were scanned in negative-ion mode, while four sections of control and another three sections of AD colon were scanned in positive-ion mode, using the orbitrap analyzer of an LTQ-Orbitrap XL (ThermoFisher), equipped with an N_2 laser (100 μJ max power, elliptical spot, 60 Hz repetition rate). Mass resolutions of 30,000, 60,000 and 100,000 at $m/z = 400$ Da were used to record the data, and the scanning range was 480–1000 Da in positive-ion mode and 550–1200 Da in negative-ion mode. Lipid assignment was based on the comparison between the

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