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How and Why Do Lipid Droplets Accumulate in Gastric Epithelial Neoplasms?

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Abstract

Under the endoscopic observation with magnification endoscopy and narrow-band imaging, one of the novel findings in gastric neoplasms is white opaque substance (WOS), which is a manifestation of intracellular accumulation of lipid droplets. To elucidate the significance of this WOS formation, detailed lipid metabolism should be understood in gastric membranes. Recently, expression profiles of lipid-metabolism-associated genes in gastric tumor and non-tumor mucosa were investigated and reported. In this article, we explain the lipid accumulation and disturbance of lipid metabolism in gastric neoplasms.

Introduction

Recently, under practical endoscopic use of magnification endoscopy and narrow-band imaging, several novel findings have been reported especially in gastric epithelial neoplasms. For example, the patterns of micro vascular architecture and micro surface structure of the gastric mucosa provided reliable markers for differentiating between benign and malignant neoplasms [1-6]. Moreover, a white opaque substance (WOS) was found within the gastric neoplastic epithelium (adenoma and carcinoma) using magnification endoscopy with narrow-band imaging and the WOS was histologically verified as intracellular accumulation of lipid droplets [7]. We consider that the morphologic analysis of WOS may represent a useful new optical marker for discriminating between benign and malignant neoplasms [8-10]. Generally, development of lipid accumulation may be the result from disturbance of lipid metabolism. However, the precise process of the absorption, accumulation, excretion, and/or consumption of lipids has been unclear both in the normal and neoplastic gastric mucosa. Therefore, our group has analyzed and reported the expression profiles of lipid-metabolism-associated genes in paired gastric tumor and non-tumor mucosa to elucidate the mechanism of WOS/lipid droplet accumulation in gastric neoplasms [11].

Expression Analysis of Lipid-Metabolism-Associated Genes

Our group analyzed lipid-metabolism-associated genes, which have already been well characterized in enterocytes, because gastric intestinal metaplasia is considered to have high risk to develop into gastric adenoma and carcinoma [12-15]. Paired biopsy samples, which were supplied for assessing expression levels of lipid-metabolism-associated genes, were obtained endoscopic ally from neoplastic and adjacent non-tumor areas from 34 patients with gastric epithelial neoplasms (0-I, 0-IIa, 0-IIb, or 0-IIc according to the Paris endoscopic classification). The background characteristics of the participants are shown in Table 1 [11]. Expression levels were analyzed by real-time reverse-transcription polymerase chain reaction. Expression profiles in gastric adenomas and carcinomas were compared with those in adjacent background mucosa. Gene expression profiles in gastric neoplasms are summarized in (Figure 1). Characteristic expression patterns were as follows 1) Expression levels of genes associated with fatty acid synthesis, sterol regulatory element-binding protein 1c (SREBP-1c), acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FAS), and acyl-CoA:diacylglycerol acyltransferase 2 (DGAT2), were up-regulated in gastric neoplasms, though the difference was only significant for SREBP-1c and DGAT2. 2) Those of genes associated with lipid droplet degradation, adipose triglyceride lipase (ATGL) and comparative gene identification-58 (CGI-58), were down-regulated with significant differences. 3) Those of genes associated with chylomicron assembly, acyl-CoA: cholesterol acyltransferase 2 (ACAT2), microsomal triglyceride transfer protein (MTP), apoB, acyl-CoA: diacylglycerol acyltransferase 1 (DGAT1), and intestinal fatty acid-binding protein (I-FABP), were significantly decreased. 4) Those of genes associated

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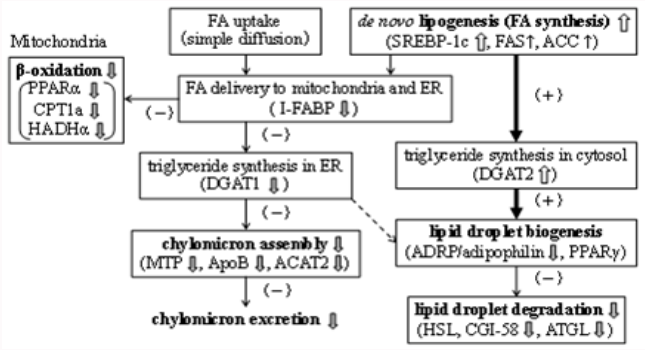

Figure 1: Scheme of changes in expression levels of lipid-metabolism-associated genes in neoplastic cells (modified from ref. 11). Arrows indicate increased or decreased expression compared with adjacent non-tumor mucosa. (+) positive change, (−) negative change.

Table 1: Background characteristics of the patients.

Age (years) mean ± SD (range)	69.11 ± 8.83 (49–87)
Gender male/female	23/11
Tumor type differentiated carcinoma/adenoma	28/6
Paris endoscopic classification 0-I/0-IIa/0-IIb/0-IIc	1/15/2/16
Positivity of WOS positive/negative	20/14

with mitochondrial β-oxidation, peroxisome proliferator-activated receptor α (PPARα), carnitine palmitoyltransferase 1a (CPT1a), and hydroxyacyl-CoA dehydrogenase (HADH), were also significantly decreased.

Lipid Accumulation and WOS in Gastric Tumors

Lipid metabolism in gastric mucosa has not been investigated well and still unclear. Functions of estimated genes in Figure. 1 are conformed to those in enterocytes. Perhaps, gastric mucosa acquire fatty acid from diet-derived triglycerides and *de novo* lipogenesis. These obtained fatty acids may either be used for consumption or storage, and an imbalance between storage factors (fatty acid uptake, *de novo* lipogenesis, and lipid droplet biogenesis) and consumption factors (mitochondrial β-oxidation, chylomicron assembly, and lipid droplet degradation) may result in triglycerides/lipid droplets accumulation in the cytoplasm. As shown in Figure. 1, compared with non-tumor mucosa, lipid consumption was attenuated and conversely, lipid storage was promoted in gastric neoplasms, consequently reading to accumulation of lipid droplets and WOS formation. In our endoscopic estimation, WOS was evident in 74.2% of tumor tissues and in 12.9% of non-tumor tissues. It remains unclear whether WOS is associated with carcinogenesis and/or development of gastric tumors. However, we consider that WOS may be a result of the development of gastric cancer, but not a cause. Occasional positivity in gastric intestinal metaplasia [16,17] may indicate the process of carcinogenesis through adenoma to adenocarcinoma. However, further investigations are needed to clarify the association between WOS and carcinogenesis.

Conclusion

Many lipid-metabolism-associated genes in enterocytes are also active in gastric cells. Lipid accumulation and WOS formation in gastric neoplasms is largely caused by a deterioration of lipid consumption (β-oxidation/excretion/lipolysis) and an acceleration of lipogenesis. Further investigation of lipid metabolism in gastric tumors may lead to significance of WOS to be a useful new optical marker for the detection/diagnosis of early gastric cancer.

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