Common Fatty Markers in Diseases with Dysregulated Lipogenesis

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Abstract

Recent studies have reported the upregulation of a subgroup of triacylglycerides as markers of different diseases with dysregulated lipogenesis, which means that these markers are not selective. This observation has a deep impact on their use as diagnostic tools in clinical practice (*e.g.* markers of risk of type II diabetes).

Text

Dysregulated lipogenesis in the liver has been associated with the risk and status of different diseases, *e.g.* type II diabetes, non-alcoholic fatty liver disease, and hepatocellular carcinoma. This increase of lipogenesis in the liver is reflected in both liver tissue and very-low-density lipoproteins in plasma [1]. Consequently, recent studies have used lipidomics as a new diagnostic tool for these diseases. In these studies, we have found a common pattern of markers that carries meaning in the biochemical interpretation. This pattern has also implications in their use as predictors of disease risk and status.

Razquin *et al.* have recently reported a unique lipid profile in plasma in relation to type II diabetes: among triacylglycerides, TG(50:1) was the one that best correlated with disease risk [2]. From this starting point, we searched in the literature if other lipidomics studies have found specific upregulation of triacylglycerides in relation to type II diabetes. Suvitaival *et al.* have reported that, among triacylglycerides, TG(50:0), TG(48:0), TG(52:0), and TG(54:1) presented the highest levels in progressors [3]. By using different cohorts, Mamtani *et al.* have selected the upregulation of TG(52:1) (with palmitic, stearic, and oleic acids) as predictor of type II diabetes risk [4]. Mousa *et al.* have also found in plasma that TG(48:0) with palmitic acid, TG(50:0) with stearic acid, TG(50:1) with oleic acid, and TG(52:1) with stearic acid are inversely associated with insulin sensitivity in overweight or obese nondiabetic individuals [5]. In addition, other

diseases associated with dysregulated lipogenesis present a similar profile of triacylglycerides. Regarding non-alcoholic fatty liver disease, Orešič *et al.* have found that TG(52:2) and TG(50:1) (with palmitic and oleic acids) were the most upregulated triacylglycerides in serum [6]. In relation to cardiovascular incidents, Stegemann *et al.* have found that TG(50:1), TG(50:2), TG(52:1), and TG(54:2) in plasma were positively correlated with disease risk [7]. Respecting hepatocellular carcinoma, Yang *et al.* have reported the upregulation of TG(50:2) in plasma as disease marker [8]. In addition, Li *et al.* have studied the triacylglyceride profile in liver tissue of hepatocellular carcinoma and have found that TG(52:0), and TG(50:0) presented the highest increases in abundance [9]. From this bibliographic search, we observed a new pattern. All these triacylglycerides have two common structural characteristics: 1) the sum of the acyl carbons is between 48 and 54; and 2) the sum of the acyl unsaturations is between 0 and 2. While some of these studies did not identify the fatty acids esterified in the triacylglycerides, all of them are commonly associated with combinations of palmitic, palmitoleic, stearic, and oleic acids [10]. We coin this ensemble of triacylglycerides as the *common fatty markers*.

At this point, we wondered: does enzyme selectivity explain why the *common fatty markers* are more upregulated than other triacylglycerides in dysregulated lipogenesis? The answer is affirmative. Dysregulated lipogenesis affects the synthesis of triacylglycerides by increasing the *de novo* synthesis of fatty acids and by regulating the acyltransferases involved in the *de novo* synthesis of triacylglycerides. Regarding the *de novo* synthesis of fatty acids, fatty acid synthase (FAS) preferentially synthesizes palmitic acid, but it also yields stearic acid. In addition, stearoyl-CoA desaturase 1 (SCD-1) synthesizes palmitoleic and oleic acids from palmitic and stearic acids –which are the main products of FAS. Consequently, the upregulation of FAS and SCD-1 increases the availability of palmitic, palmitoleic, stearic, and oleic acids for the acyltransferases in the *de novo* synthesis of triacylglycerides. Among these acyltransferases, glycerol-3-phosphate acyltransferase 1 (GPAT-1) shows strong preference for saturated fatty acids, especially palmitic acid [11]. While dysregulated lipogenesis in the liver affects other enzymes and other lipids, the combined upregulation of FAS, SCD-1, and GPAT-1 explains the profile of triacylglycerides in these diseases: those with palmitic, palmitoleic, stearic, and oleic acids (the *common fatty markers*) show the highest increases.

We wondered again: is there a signaling pathway relating the upregulation of FAS, SCD-1, and GPAT-1 and the diseases that present dysregulated lipogenesis? Again, the answer is affirmative. At a transcriptional level, sterol regulatory element-binding protein 1c (SREBP-1c) upregulates FAS, SCD-1, and GPAT-1; and carbohydrate-responsive element-binding protein (ChREBP) upregulates FAS and SCD-1. Furthermore, the upregulation of liver X receptors (LXRs) upregulates both SREBP-1c and ChREBP [12,13]. In addition, LXRs directly upregulate SCD-1 and FAS [12]. Extensive research in the last years has associated the upregulation of LXRs, SREBP1-c, and ChREBP with the risk and status of the diseases that we reviewed (type II diabetes, fatty liver disease, cardiovascular incidents, and hepatocellular carcinoma) [1,12,13]. At a ligand level, other lipids and hormones (*e.g.* insulin) regulate the LXR pathway. Consequently, the LXR pathway is influenced in a very complex manner by diet, exercise, hormonal state, and genetic predisposition to induce dysregulated lipogenesis in the liver. Figure 1 schematically summarizes the biochemical relationships among lipogenesis, LXRs, SREBP-1c, ChREBP, GPAT-1, SCD-1, FAS, and the *common fatty markers*. Because of this common pathway of signaling and synthesis, the *common fatty markers* appear statistically associated with the risk and status of the diseases that present dysregulated lipogenesis in their onset and/or development. This common synthetic regulation has an important consequence in their use as markers of disease risk and status. We cannot consider them as selective markers of a specific disease, but markers of the dysregulated lipogenesis in the liver, which is common to many diseases.

Finally, regarding the regulation and enzyme selectivity of the lipogenesis in the liver, we wondered: can we think of a specific triacylglyceride as preferred marker of lipogenesis in the liver? To answer this question, we considered the *de novo* synthesis of triacylglycerides, which is initiated by glycerol-3-phosphate acyltransferases (GPATs) [11]. These enzymes transfer a fatty acid to the sn-1 position of glycerol-3-phosphate. While other GPATs do not seem to be regulated and do not show preference for palmitic acid, GPAT-1 is upregulated in the LXR pathway and shows preference for palmitic acid [11]. Hence, the upregulation of the lipogenic LXR-pathway is expected to increase the content of palmitic acid in the sn-1 position of triacylglycerides. Consequently, we propose that TG(sn-16:0/16:0/18:1) is of special interest (Figure 1). The palmitic acid in the sn-1 position can be related to the activities of FAS and GPAT-1 [11]. The palmitic acid in the sn-2 position can be related to FAS through the activity of

acyl-CoA:1-acylglycerol-3-phosphate acyltransferase (AGPAT) [11]. Finally, the oleic acid in the sn-3 position can be related to SCD-1 through the activity of diacylglycerol transferase (DGAT) [11]. Many lipid profiling studies only identify the total number of carbons and unsaturations (*e.g.* TG(50:1) for TG(sn-16:0/16:0/18:1), despite that the type of fatty acids and their position in the glycerol backbone of the triacylglycerides carry biological information. Consequently, we think that lipid profiling related to diseases with dysregulated lipogenesis requires the identification of the esterified fatty acids. In addition, to provide the position of the fatty acids in the glycerol backbone, the characterization by enantiomeric or regioisomeric analyses is recommendable [14].

In conclusion, we propose that the upregulation in the liver and plasma of triacylglycerides with palmitic, palmitoleic, stearic, and oleic acids –the *common fatty markers*– is a fingerprint of the LXR-mediated lipogenesis in the liver. Due to enzyme selectivity, we propose that the regioisomeric or enantiomeric analysis of TG(sn-16:0/16:0/18:1) is of special interest. The increase of these triacylglycerides talks to us about the same biological process: the dysregulated lipogenesis in the liver. This relationship has deep implications in their use as diagnostic tools in clinical practice: lipidomics studies cannot consider them as selective markers of a specific disease, but markers of dysregulated lipogenesis in the liver. To achieve selectivity in the statistical prediction of disease risk and status, we suggest the use of studies with multiple diseases. In these studies, the quantitative analysis of these triacylglycerides together with the use of other markers (metabolic or clinical) might yield selective tools of prediction of disease risk and status. As a general lesson, to improve and delimit the use of metabolic markers in clinical practice, the field should not only focus on finding statistically significant changes between two groups. It should also focus on the metabolic and medical signification of these changes.

Figure caption

Figure 1. Summarized relationship between the *common fatty markers* and diseases with dysregulated lipogenesis. Diet and exercise habits, hormonal state, and genetic factors integrate into dysregulation of lipogenesis in the liver via regulation of liver X receptors (LXRs), sterol regulatory element-binding transcription factor 1c (SREBP-1c), and carbohydrate-responsive element-binding protein (ChREBP). Among other enzymes, this dysregulation upregulates fatty acid synthase (FAS), stearoyl-CoA desaturase 1 (SCD-1), and glycerol-3-phosphate acyltransferase 1 (GPAT-1). This upregulation leads to an increase of triacylglycerides (TGs) with palmitic (P), palmitoleic (Pe), stearic (S), and oleic (O) fatty acids. Consequently, the upregulation of these triacylglycerides in the liver is statistically associated with the risk and status of diseases with dysregulated lipogenesis. This statistical association can be found in the liver tissue and the plasma lipidome by the contribution very-low-density lipoproteins (VLDL). Because of enzyme selectivity, we suggest TG(sn-16:0/16:0/18:1) as marker of special interest among the *common fatty markers*. The liver image was adapted from an image in the DataBase Center for Life Science (Creative Commons Attribution 4.0 International license)

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