Progress in Lipid Research 52 (2013) 585–589

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

Lipogenesis and lipolysis: The pathways exploited by the cancer cells to acquire fatty acids

Nousheen Zaidi [a,*], Leslie Lupien [b,c], Nancy B. Kuemmerle [b,c,d], William B. Kinlaw [b,e], Johannes V. Swinnen [f], Karine Smans [g]

[a] Microbiology and Molecular Genetics, University of the Punjab, Lahore 54590, Pakistan
[b] The Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
[c] Program in Experimental and Molecular Medicine, The Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
[d] Department of Medicine, Section of Hematology and Oncology, White River Junction Veteran's Administration Medical Center, White River Junction, VT, USA
[e] Department of Medicine, Section of Endocrinology and Metabolism, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
[f] Laboratory of Lipid Metabolism and Cancer, Department of Oncology, Faculty of Medicine, KU Leuven, Leuven, Belgium
[g] Department of Oncology, Janssen Research and Development, A Division of Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340 Beerse, Belgium

ARTICLE INFO

Article history:
Received 15 February 2013
Received in revised form 19 August 2013
Accepted 22 August 2013
Available online 31 August 2013

Keywords:
Cancer
Fatty acid synthase
Fatty acid synthesis
Lipolysis
Lipogenesis
Lipoprotein lipase

ABSTRACT

One of the most important metabolic hallmarks of cancer cells is enhanced lipogenesis. Depending on the tumor type, tumor cells synthesize up to 95% of saturated and mono-unsaturated fatty acids (FA) *de novo* in spite of sufficient dietary lipid supply. This lipogenic conversion starts early when cells become cancerous and further expands as the tumor cells become more malignant. It is suggested that activation of FA synthesis is required for carcinogenesis and for tumor cell survival. These observations suggest that the enzymes involved in FA synthesis would be rational therapeutic targets for cancer treatment. However, several recent reports have shown that the anti-tumor effects, following inhibition of endogenous FA synthesis in cancer cell lines may be obviated by adding exogenous FAs. Additionally, high intake of dietary fat is reported to be a potential risk factor for development and poor prognosis for certain cancers. Recently it was reported that breast and liposarcoma tumors are equipped for both *de novo* fatty acid synthesis pathway as well as LPL-mediated extracellular lipolysis. These observations indicate that lipolytically acquired FAs may provide an additional source of FAs for cancer. This review focuses on our current understanding of lipogenic and lipolytic pathways in cancer cell progression.

Contents

1. Introduction

Cancer cells are characterized by their ability to divide more frequently than normal cells. Rapidly proliferating cancer cells exhibit increased demands for energy and macromolecules. To cope with these elevated requirements cancer cells undergo major metabolic modifications. Since the 1920s, it has been known that, in contrast to most normal tissues, cancer cells show avid glucose uptake and tend to convert glucose to lactate through the glycolytic pathway regardless of whether oxygen is present (aerobic glycolysis; Warburg Effect) [1]. Glucose metabolism via the glycolytic pathway provides not only energy, but also a carbon source for anabolic synthesis of critical biochemical precursors. It is now widely recognized that tumors frequently exhibit an increased ability to

* Corresponding author.
E-mail address: nzzaidi@yahoo.com (N. Zaidi).

0163-7827/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.plipres.2013.08.005

synthesize lipids [2,3], and that this lipogenesis is tightly coupled to glucose metabolism.

Several lines of evidence suggest that activation of the *de novo* fatty acid (FA) synthesis pathway is required for carcinogenesis [4–6]. The FA synthesis pathway is extensively studied in the context of cancer biology and is currently thought to be the major pathway exploited by the cancer cells for the acquisition of FAs [5]. However, recent findings suggest that certain cancer cells/tissues can utilize both lipogenic and lipolytic pathways to acquire fatty acids that, in turn, promote cancer cell proliferation and survival [7,8].

This review focuses on our current understanding of the roles of both the lipogenic and lipolytic pathways in mediating tumor growth and the therapeutic benefits that could possibly be achieved by targeting these pathways.

2. Fatty acids support various aspects of tumorigenesis

Fatty acids may contribute to cancer progression by multiple mechanisms (Fig. 1). The most widely discussed aspect of FA-biochemistry with respect to tumor biology is their role as building blocks for newly-synthesized membrane phospholipids. Large amounts of FAs are required to accommodate high rates of proliferation in cancer cells [5]. Cancer cells can acquire FAs through lipogenesis and/or lipolysis to support their growth and proliferation.

The source of FAs may determine the phospholipid composition of membranes. In this context, it is important to consider that mammalian cells have a limited ability to synthesize polyunsaturated fatty acids *de novo*, as they lack the Δ 12 desaturase. Therefore, enhanced *de novo* lipogenesis enriches the cancer cell membranes with saturated and/or mono-unsaturated fatty acids [9]. As these FAs are less prone to lipid peroxidation than polyunsaturated acyl chains, *de novo* FA synthesis was proposed to make cancer cells more resistant to oxidative stress-induced cell death [9]. Moreover, as saturated lipids pack more densely, increased lipogenesis also alters lateral and transverse membrane dynamics

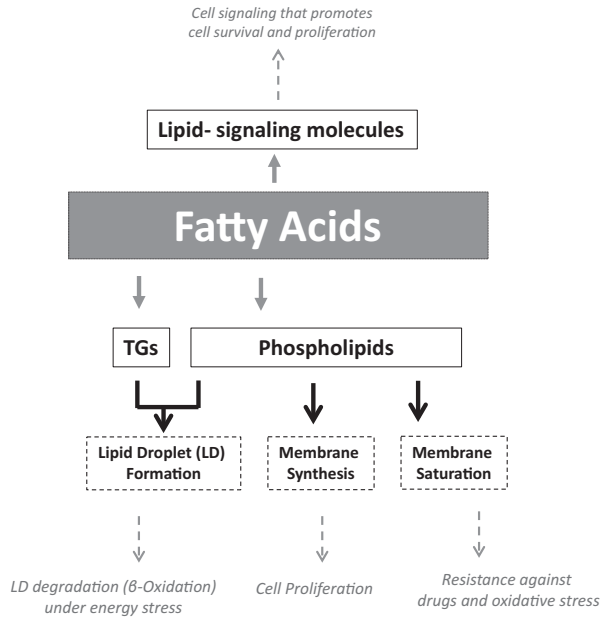

Fig. 1. Fatty acids promote various aspects of tumor cell development, progression and survival. Fatty acids provide the cancer cells with membrane building blocks, signaling molecules and energy source that supports their rapid proliferation and survival. *(See text for more details).*

that may limit the uptake of drugs, making the cancer cells more resistant to therapy [9].

Fatty acids may also be used to supply energy. Most tumors show a high rate of glucose uptake that supports their energetic as well as biosynthetic requirements [10]. However, certain types of tumors, including prostate tumors, display increased dependence on β-oxidation of fatty acids as their main source of energy. Prostate tumors exhibit low rates of glucose consumption [11,12], increased fatty acid uptake [13] and overexpression of certain enzymes involved in β-oxidation [14]. Likewise, human leukemia cells have been shown to require β-oxidation for their proliferation and survival [15].

Fatty acids can also be used for the biosynthesis of an array of protumorigenic lipid-signaling molecules. A lipid messenger considered to be particularly important in contributing to cancer is phosphatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P3], a molecule that is formed by the action of phosphatidylinositol-3-kinase and activates protein kinase B/Akt to stimulate cell proliferation and survival [16,17]. Other prominent examples of lipid messengers are lysophosphatidic acid (LPA) that signals through a family of G protein-coupled receptors to promote cancer aggressiveness [18], and prostaglandins, a class of lipid messengers that are formed by cyclooxygenases and support migration and tumor-host interactions [19,20].

3. Lipogenesis *versus* lipolysis

Various tumor types display increased endogenous FA biosynthesis irrespective of extracellular lipid availability [21], whereas most normal cells, even those with comparatively high proliferation rates, preferentially use dietary/exogenous lipids for synthesis of new structural lipids [5,21]. A few normal tissues such as adipocytes, hepatocytes, hormone-sensitive cells [22], the cycling endometrium, and fetal lung tissue [23] may have a very active FA-synthesis pathway. However, *de novo* FA synthesis is suppressed in most normal cells. The upregulated FA synthesis in tumor cells is reflected by a significant increase in expression and activity of various enzymes involved in the lipogenic pathway [21]. For example, elevated levels of fatty acid synthase (FASN), the major enzyme responsible for fatty acid biosynthesis, are correlated with poor prognosis in breast cancer patients [4,5]. Increases in both FASN expression and activity are observed early in oncogenesis and correlate with cancer progression [5], with FASN-overexpressing tumors exhibiting more aggressive phenotypes [5]. The upregulated FA-synthesis fuels membrane biogenesis in rapidly proliferating cancer cells and renders membrane fatty acids more saturated (Fig. 2) [9]. This affects fundamental cellular processes including signal transduction, gene expression, ciliogenesis [24], and therapeutic responsiveness [9].

Chemical or RNAi-mediated inhibition of key enzymes involved in FA synthesis, including FASN [5,21,25], acetyl-CoA-carboxylase (ACACA) [26] and ATP-citrate lyase (ACLY) [27–30], has been shown to attenuate cancer cell growth and to induce cell death. However, cytotoxic effects of *de novo* FA synthesis inhibition can be averted by FA supplementation [25,26,31,32]. The ability of exogenous FAs to functionally substitute for endogenously derived FAs in promoting cell viability suggests that cancer cells can incorporate and utilize exogenous lipids as an alternative source of FAs.

Generally, lipogenesis has been considered as the major means of FA acquisition in cancer cells. However, a recent study clearly showed that, in addition to lipogenesis, cancer cells can also use exogenous fatty acids to fuel their growth (Fig. 2) [7]. It was reported that the aggressive "triple-negative" breast cancer cell lines express lipoprotein lipase (LPL), the key enzyme for extracellular lipolysis, and the transmembrane channel for exogenous free FA