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Lipid metabolism and lung cancer

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ABSTRACT

Lung cancer is currently one of the most serious health issues in developed and developing countries. There are multiple available treatment options; however survival still remains very poor. Despite metabolism alteration being one of the hallmarks described in human cancer, lipid metabolism disorders

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are less known. They are recently becoming more important in this setting and therefore achieving a deeper knowledge might be helpful to obtain new strategies to accurate diagnosis, estimate prognosis, and develop therapeutic agents based on bioactive compounds such as cerulenin, SCD1, ACLY inhibitors, statins, polyphenolic compounds, etc. The present paper reviews the basis of lipid metabolism in lung cancer and suggests potential biomarkers. Further investigation is crucial to improve our knowledge in this area.

1. Introduction

One of the hallmarks of cancer is metabolic reprogramming. Tumoral cells alter their capability to metabolize carbohydrates, lipids and proteins in order to support cell proliferation.

Compared to non-malignant cells, cancer cells exhibit significant metabolic alterations. While normal cells modulate anabolic and catabolic pathways in response to changes in nutrient availability, cancer cells show unregulated growth even under nutrient scarcity. Although most of the knowledge regardless metabolic dysregulation in cancer focuses on carbohydrates, the importance of alterations related to lipid metabolism is starting to be recognized and the increased in *de novo* lipogenesis is considered a new hallmark in many aggressive cancers (Robey et al., 2015). Moreover, cancer cells present increased levels of *de novo* adipogenesis through increased expression of various lipogenic enzymes such as ACLY (ATP citrate lyase) and FASN (fatty acid synthase). In addition, recent studies have demonstrated that constitutive activation of growth promoting pathways results in a dependence on unsaturated fatty acids (FA) for survival under oxygen deprivation

Lung cancer is the leading cause of cancer related death in both men and women and it is often associated with a serious prognosis. There are three main types of lung cancer and this will condition the treatment options and prognosis. About 85% of lung cancers are non-small cell lung cancers which includes squamous cell carcinoma, adenocarcinoma, and large cell carcinomas. About 10%-15% of lung cancers are small cell lung cancers which tend to spread quickly. Fewer than 5% of lung cancers are lung carcinoid tumors. They are also sometimes called lung neuroendocrine tumors. Most of these tumors grow slowly and rarely spread. One of the most important risk factor for the development of lung cancer is cigarette smoking.

Lots of efforts have been carried out towards a better molecular characterization of NSCLC at the level of the genome, transcriptome and metabolome and although the lipidome remains poorly explored, there is some interesting data. Lung tumors present abnormalities in vessels structure which limits nutrient supply to the tumoral cells and produces hypoxia and this induces multiple metabolic alterations, including lipid metabolism in order to support cell growth (Santos and Schulze, 2012).

Herein, we first describe major lipid metabolism alterations described in cancer. Then we specifically focus in lung cancer regardless incidence, risk factors, treatment and prognosis. And we end up with the use of bioactive compounds for lung cancer treatment based on targeting lipid metabolism.

2. Altered lipid metabolism in cancer

Lipid metabolism is highly altered in proliferating cells. Different to normal cells that rely mostly in the uptake of exogenous fatty acids (FA), cancer cells increase *de novo* adipogenesis which is crucial for membrane biosynthesis and signaling molecules.

Fatty acid synthesis takes place in the cytoplasm. They derive from acetyl-coenzyme A (AcCoA) which is mainly provided by citrate produced by the tricarboxylic acid (TCA) cycle. That is why cancer cells also upregulate glucose and glutamine uptake as carbon and nitrogen sources and to feed TCA cycle. Conversion of citrate into acetyl-CoA is catalyzed by ATP citrate lyase (ACLY). The next step of fatty acid biosynthesis requires the activation of AcCoA to malonyl-CoA, which is catalyzed by AcCoA carboxylase (ACC). The product of this reaction is coupled to the multifunctional enzyme fatty-acid synthase (FASN). Repeated cycles of acetyl groups condensation generate the primary fatty acid palmitate that can then undergo separate elongation and/or unsaturation cycles to yield other fatty acid molecules (Fig. 1). In addition, FAs need to be activated with CoA by fatty acyl-CoA synthetases (ACSLs) which is critical for phospholipid and triglyceride synthesis, lipid modification of proteins as well as for fatty acid β-oxidation. Importantly, these enzymes have been related to carcinogenesis (Fig. 2).

2.1. *Increased of* de novo *adipogenesis in cancer*

2.1.1. *Fatty acid synthase (FAS)*

It is well known the correlation between FAS expression and tumor aggressiveness. There are numerous studies showing this correlation for example in patients with sarcomas, endometrial and colorectal cancer (Takahiro et al., 2003; Pizer et al., 1998a; Rashid et al., 1997).

Regarding lung cancer, *Visca* et al. explored the expression of FAS and its association with clinicopathological features and prognosis. They examined FAS expression by immunohistochemistry in 106 patients with NSCLC (Visca et al., 2004). FAS staining was observed in 57% of cases with an overall low prognostic value ($p = 0$, 14) while FAS negative expression in stage I tumors showed a trend for better survival ($p = 0$, 10). Similar data were reported by *Wang* et al. (Wang et al., 2002) in which FAS expression in stage I lung cancer was associated with a poorer prognosis. They also suggest that FAS overexpression in early lung tumors may be a signal of aggressiveness.

2.1.2. *Stearoyl CoA desaturase 1 (SCD1)*

SCD is a key enzyme in lipid metabolism. It is involved in the introduction of a double bound into palmitic and stearic acids giving rise to palmitoleic and oleic acid, respectively. The ratio between saturated and monounsaturated fatty acids (SFA and MUFA, respectively) affects membrane fluidity and cell function and an increased content of MUFAs has been proposed as a predictive marker for poor prognosis in several cancers (Agustsson et al., 2007). SCD expression has been correlated with malignant transformation, proliferation and survival. Moreover, *Noto* et al. have shown that SCD1 is a key factor for lung cancer-initiating cells. These authors reported that culture cells derived from malignant plural effusions (MPE) of patients with adenocarcinoma of the lung when growing in non-adherent conditions were able to form spheroids and importantly they identified SCD1 gene significantly upregulated lung tumor spheroids *vs* adherent cultures (Mancini et al., 2011). Moreover, preclinical data have demonstrated that SCD1 is also required for lung cancer spheroids propagation both in stable cell

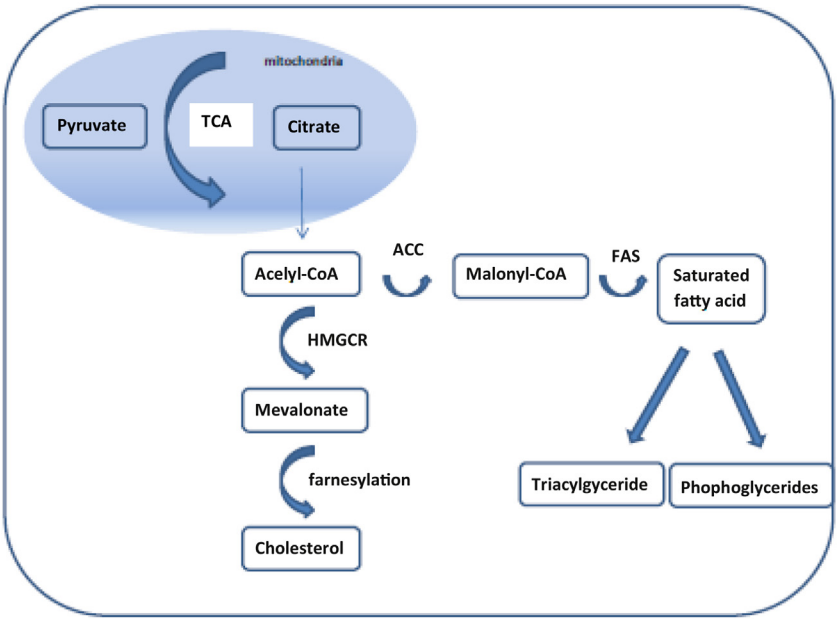

Fig. 1. Fatty acid synthesis. (TCA: tricarboxyilic acid cycle,ACC: aceltly– CoA carboxylase,FAS: fatty acid synthase,HMGCR: HMG– coA reductase).

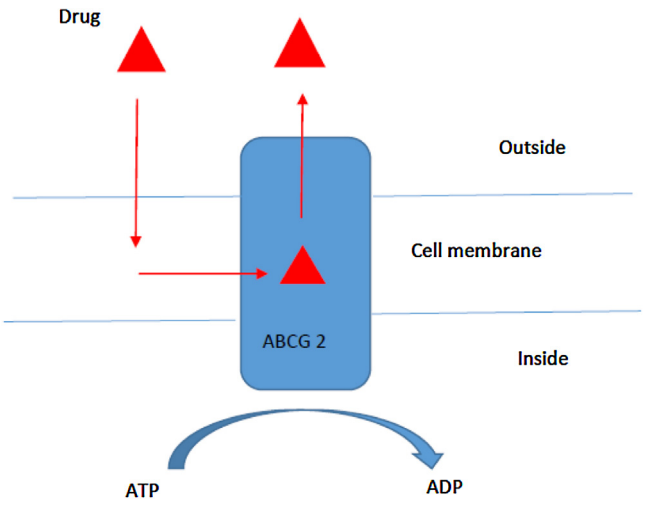

Fig. 2. ABCG 2 limits the accumulation of therapeutic agents within cells. ABCG: ATP binding casette,ATP: adenosine triphosphate. ADP: adenosine diphosphate.

lines and in MPE- derived tumor cultures (Noto et al., 2013). *Huang* et al. recently demonstrated that SCD 1 is highly expressed in lung adenocarcinomas and promotes *in vitro and in vivo* tumorigenesis, cell migration and invasion (Huang et al., 2016). According to this, SCD1 may be a promising target for lung cancer treatment (Tables 1 and 2).

2.1.3. *Adenosine triphosphate- binding cassette family (ABC family)*

One important lipogenic cancer effector is ABCA1 protein. It is a member of the ABC family of transporters and it is implicated in the ATP-dependent transport of cholesterol through the plasma membrane. In normal cells ABCA1 contributes to maintain the cellular cholesterol homeostasis through the transfer of phospholipids and cholesterol to apolipoprotein A1 (ApoA1), leading to the formation of high density lipoprotein. In cancer cells, its role is unclear. However, as an essential component of cellular membranes it could be rate-limiting for the rapid growth and division of cells, as well as influencing cell–cell signaling (Troost et al., 2004).

Transporters of the ABC family have a major role as drug efflux transporters which may affect the pharmacological behavior of many drugs. In this sense, overexpression of ABCA proteins has been shown to decrease the intracellular drug concentration and to render multidrug resistance. *Yoh* et al. (Yoh et al., 2004) have shown a positive correlation between ABCG2 expression levels and low response to platinum based chemotherapy in patients with advanced NSCLC. This points to ABCG2 as one of the responsible for the drug resistance in patients with NSCLC. Another study has indicated that the combination of CD133 and ABCG2 markers (CD133+/ABCG2+) could be used as an independent predictor of the relapse in stage I NSCLC. Moreover, these tumors had a higher micro vessel density and higher expression levels of angiogenic factors and so this group of patients will benefit from antiangiogenic therapy (Li et al., 2011).

Galetti et al. used NSCLC cell lines with different levels of ABCG2 and studied the distribution and accumulation of EGFR inhibitor Gefitinib. They suggested that Gefitinib inhibition of ABCG2 activity will contribute to increase the intracellular Gefitinib content. (Galetti et al., 2015)

2.1.4. *ATP citrate lyase (ACLY)*

ACLY is one of the main enzymes of *de novo* FA synthesis linking glucose to lipid metabolism. It has been associated with local tumor stage and with longer overall survival in young patients with NSCLC. By contrast overexpression of ACLY appears to predict the opposite for older patients (Csanadi et al., 2015). Osugi J et al. indicated that patients with high ACLY expression exhibited poorer overall survival compared with ACLY negative tumors (Osugi et al., 2015). *In vitro* studies have demonstrated that ACLY inhibition limits tumor proliferation and induces cell differentiation. Hanai et al. used NSCLC cell lines to show that inhibition of ACLY promotes apoptosis and differentiation. In addition, they found that statins improve the anti-tumor effects of ACLY inhibition (Hanai et al., 2012).

Table 1
Treatments in lung cancer. EGFR: epidermal grown factor receptor. PD 1: programmed death 1. ALK: anaplastic lymphoma kinase.

	CHEMOTHERAPY	TARGETED THERAPY	INMUNOTHERAPY
FIRST LINE TREATMENT	Carboplatin + paclitaxel +/− bevacizumab Cisplatin+ pemetrexed Carboplatin + pemetrexed Cisplatin + gemcitabine Cisplatin + vinorelbine	EGFR mutation: erlotinib, gefitinib, afatinib ALK rearrangement: crizotinib	
SECOND LINE TREATMENT	Docetaxel Pemetrexed Gemcitabine	Chemotherapy EGFR or ALK inhibitors	PD 1 inhibitors: Nivolumab

Table 2
Agents modifying lipid metabolism with therapeutic potential in lung carcinoma. RNA: ribonucleic acid. ACLY: adenosine triphosphate citrate lyase. FAS: fatty acid synthase. HMG–CoA: 3–hydroxy–3–methylglutaryl Coenzime A.

DRUG	ACTION	REFERENCE
C93	FAS inhibitor	Orita H et al. (Fu et al., 2015; Altenberg and Greulich, 2004)
MF 438	FAS inhibitor	Noto et al. (Noto et al., 2013)
Interference RNA ACLY	ACLY inhibitor	Migita T et al. (Su et al., 2011)
SB 204990	ACLY inhibitor	Hatzivassiliou G et al. (Shi et al., 2016)
Lovastatin	HMG- CoA reductase inhibitor	Walther U et al. (Pizer et al., 1998b)
Simvastatin	HMG- CoA reductase inhibitor	Lee HY et al. (Pizer et al., 2000)
Epigall-3-gallate	Polyphenol	Li Y et al. (Hatzivassiliou et al., 2005)

2.2. Increased FAs uptake: FABP4, CD36 and the crosstalk with surrounding adipocytes

Instead of increasing fatty acid synthesis some tumors rely on an increased uptake of lipids from their environment. Cancer associated adipocytes metabolically interact with adjacent cancer cells to support tumor proliferation and metastasis. FABP4, a cytoplasmic transport protein for FAs and other lipophilic substances, provides FAs from surrounding adipocytes to ovarian tumors (Nieman et al., 2011). *Uehara* et al. showed that exogenous overexpression of FABP4 promoted cancer cell invasion *in vitro* (Uehara et al., 2014).

CD36 is a widely expressed transmembrane receptor involved in adipocyte differentiation. *DeFilippis* et al. found that CD36 expression was decreased in multiple stromal cell types of malignant breast lessions compared to histologically normal adjacent tissues, suggesting that low levels of CD36 could be related to early steps in tumorigenesis (DeFilippis et al., 2012).

2.3. Signaling lipids and cancer

Phospholipids are a major component of cell membranes and the inter and intracellular signals as they work as second messengers in signal transduction. It remains unknown to what extent phospholipids are altered in NSCLC. Marien et al. (Marien et al., 2015) profiled 179 phospholipid species in malignant and matched non-malignant lung tissue of 167 NSCLC patients by a mass spectrometry –based approach. They identified 91 phospholipids species that were differentially expressed in cancer *versus* normal tissues. Most important changes included a decrease in sphingomyelins (SM), an increase in specific phosphatidylinositols (PI), a decrease in multiple phosphatidylserines (PS), and an increase in several phosphatidylethanolamine (PE) and phosphatidylcholine (PC) species. These findings are of particular interest regardless lung cancer as phospholipid alterations have been described in other tumor types. PI, for example, plays an important role in cancer as a source of lipid second messengers activating the Akt pathway, frequently activated in NSCLC. Specifically PI38:3, the most increased lipid species in this study has been found to be upregulated in myc-induced lymphoma (Eberlin et al., 2014). This suggests that these lipids species might be under the control of the myc gene, which is amplified in NSCLC (Mitani et al., 2001). In addition, they could also differentiate the main subtypes of NSCLC, although no correlation with the clinical outcome was found. This could be explained because of changes in phospholipid metabolism that occur early in carcinogenesis irrespective of stage and cancer subtype.

2.4. Cholesterogenesis and cancer

Another important biosynthetic process related to cancer is the mevalonate pathway, which mediates cholesterol synthesis. The first step of this pathway is the condensation of AcCoA with acetoacetyl-CoA to form 3-hydroxy-3-methylgrutaryl (HMGCoA). The reduction of HMG-CoA to mevalonate by HMG-CoA reductase (HMGCR) represents the rate-limiting reaction of the cholesterol synthesis pathway and it is highly regulated. Interestingly, HMGR is the target for a class or cholesterol-lowering drugs known as statins. Statins could have an important role in the treatment of several tumors such as ovarian and colorectal cancer and the use of statins could also improve lung cancer outcome. A recent study of the Danish population linked the use of statin in cancer patients to a reduction of cancer-related mortality (Nielsen et al., 2013). In epithelial ovarian cancer, a retrospective study showed that the use of statins was associated with an improvement of the clinical outcome. By the contrary, an elevated low-density lipoprotein cholesterol levels in serum correlated with poorer prognosis (Li et al., 2010).

Ling Y. et al. conducted a meta-analysis to assess the association between statin intake and colorectal cancer prognosis (Ling et al., 2015). Pre-diagnosis statin use was associated with a reduction in all cause and cancer-specific mortality. However, they did not note reduced mortality for post diagnosis statin use. Consistent with these data, *Cai H.* et al. found that patients with colorectal cancer and a prediagnosis statin use had prolonged specific cancer survival and no benefits for patients with a post-diagnosis statin use (Cai et al., 2015).

3. Lung cancer

3.1. Incidence, clinical outcome

Lung cancer is a major global health problem with more than 1.6 million new patients diagnosed each year with this disease. It is the second most common cancer in both men and women (excluding

skin cancer) and the leading cause of death among both men and women (Siegel et al., 2016). The most common clinical manifestations are cough, hemoptysis, dyspnea and chest pain. Due to the late onset of symptoms, most cases are diagnosed in advanced stages (stage III or IV), with a poor prognosis. Median overall survival for patients with advanced lung cancer is about 8–12 months. Treatment depends on histology, molecular characteristics, tumor stage and patientís performance status. Patients with stage I, II and III are generally treated with curative intent with surgery, chemotherapy, radiotherapy or chemoradiotherapy. Systemic therapy is indicated for almost every patient with advanced disease. Platinum based chemotherapy for patients with wild type EGFR tumors is the first line approach and EGFR inhibitors for patients with EGFR mutations. There is a wide range of therapeutic options for the second line treatment, including standard chemotherapy (platinum based therapy, taxanes, pemetrexed, gemcitabine) and targeted therapy such as anti PD 1(programmed death) agents, EGFR inhibitors and ALK inhibitors. However, in spite of the multiple treatment options the prognosis of these patients remains poor.

EGFR status is an important issue in lung cancer. Patients whose tumors harbor an EGFR mutation are treated with tyrosine kinase inhibitors and have a better overall prognosis and quality of life than those without any mutation.

Although there is limited data about specific lipid metabolism species associated to mutated *vs* wild type EGFR lung tumors, it has recently been reported by Ho YS. et al. that there is some differential lipid expression (polyunsaturated fatty acids and phospholipids) between EGFR mutated and non-mutated lung cancer cases (Ho et al., 2016).

Further research in lipid metabolic pathways in lung cancer is needed as it opens new possibilities for diagnosis and selection of patients for targeted therapy.

3.2. Risk factors

3.2.1. Cigarette smoking

It is widely established that cigarette smoking is the main risk factor for lung cancer (Alberg et al., 2013). The risk of developing lung cancer for a current smoker is related with the number of cigarettes smoked per day and the lifetime duration of smoking. Second hand smoke is also a significative risk factor for this tumor. There are some occupational or environmental carcinogens such as asbestos and radon that can also increase the risk of lung cancer (Barone-Adesi et al., 2016).

Recently, there is increased interest regarding lipid metabolism associated differences between smokers and non-smokers. Ortega-Gómez et al. studied gene expression profiles of primary lung adenocarcinoma and found that those with history of tobacco exposure had some differentially expressed genes related to lipid metabolism (Ortega-Gomez et al., 2016).

Titz et al. investigated the effects of tobacco exposition on lung lipid metabolism in mice and showed that it affected several categories of lung lipids and lipid-related proteins such as surfactant lipids and some ceramides (Titz et al., 2016).

These differences have not yet been validated in lung cancer patients, although it would be interesting because of its potential role as molecular markers for risk assessment in the future.

Even though a significant proportion of lung cancers can be attributable to tobacco exposure, there is increasing evidence of lung cancer cases in non-smoking patients (Xiao et al., 2011). Furthermore, lung cancer in never smokers is characterized by an increased incidence in females, a higher rate of adenocarcinoma and a better prognosis than tobacco- related tumors (Yano et al., 2011).

Otherwise, never-smoker patients are more likely to harbor a mutation in EGFR; therefore they potentially have more treatment options, including targeted therapy with tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib (Rosell et al., 2012).

3.2.2. Obesity, cachexia and weight loss

There is some evidence that cancer cells are able to induce the secretion of lipids by stromal cells that are subsequently imported to promote tumor growth. *Nieman* et al. suggested that adipocyte-derived lipids appear to impact cancer progression in ovarian cancer metastases to the omentum, at least partly because of adipocytes secreted cytokines that attract cancer cells. Through unknown mechanisms, malignant cells provoke adipocytes to increase lipolysis and to secrete fatty acids that are taken up by cancer cells to support cell growth. Obesity has long been known to increase the risk of some cancer types (Renehan et al., 2008; Keum et al., 2015). Up to 20% of all tumors and 50% of endometrial and esophageal cancer could be attributed to obesity (Calle and Kaaks, 2004). However, there are inconclusive and surprising data about the relationship between obesity and lung cancer. A meta-analysis that included 31 relevant studies found that excess body weight (body mass index >25 kg/m2) had an inverse relationship with lung cancer incidence (relative risk 0,79) specially for current and former smokers (Yang et al., 2013). According to this *Duan P* et al. conducted another meta-analysis that showed a negative association between the risk of lung cancer and excess weight, with a linear dose-response association. This effect was attenuated when restricting the analysis to non-smokers (Duan et al., 2015).

On the other side, cachexia is also an important metabolic disorder in cancer patients. It is a wasting syndrome associated with extreme weight loss and physical decline. This is believed to be mainly caused by an increased lipolysis in adipose tissue rather than by a reduction in lipid biogenesis (Esper, 2005; Ryden et al., 2008). and one of the mechanisms causing this is the enhanced expression of the hormone sensitive lipase (HSL) in adipocytes (Agustsson et al., 2007). There are some hypothesis, such as the metabolic changes occurred during cachexia can promote tumor growth by fueling the metabolism of cancer cells: in cachectic ovarian cancer patients increased levels of free fatty acids, monoacylglycerides and diacylglycerides have been observed (Gercel-Taylor et al., 1996). Thus, glycerol molecules released during the degradation of triacylglycerides can be used for gluconeogenesis by the liver, while free fatty acids may provide energy for the tumor or for signaling molecules (Argiles et al., 1997). Whether this increase in cancer risk can be explained through lipid availability remains to be seen, as obesity not only affects circulating lipid levels, but it is also associated with hormonal changes, cytokine release and inflammation.

Cachexia affects about 60% of lung cancer patients and it could also be a relevant prognostic factor. In this scenario Jafry SH. et al. described an index for cachexia (CXI) in 112 patients with advanced NSCLC and found that this index was able to predict a poor outcome in both men and women (Jafri et al., 2015).

Sanders et al. studied the impact of early weight loss on overall survival in lung cancer patients who received chemoradiotherapy. They found that weight loss was associated with worse prognosis (HR 1.9), highlighting the importance of this issue in the design of future clinical trials (Sanders et al., 2016).

3.2.3. Cholesterol

The vast majority of lung cancer cases can be attributed to smoking, however the increase in the incidence rates of lung cancer among never smokers suggest a need for the identification of other modifiable risk factors. There is a great amount of literature on cholesterol and lung cancer risk and outcomes.

Kucharska et al. examined the association of baseline plasma HDL cholesterol levels with the incidence of lung cancer in a cohort of more than 15000 men and women (Kucharska-Newton et al.,

2008). They found that low HDL cholesterol levels were associated with a higher incidence of lung cancer in the total sample and among smokers (HR 1,77 IC 95% 1,05- 2,97). The number of cases among never smokers in the study was too small to get significant conclusions. However, the clinical significance of this weak association should be further explored.

Another study evaluated preoperative total serum cholesterol as a prognostic factor for survival in 198 patients with resectable NSCLC. Total serum cholesterol below the cut-off (5,3 mmol/L) was found to be a significant prognostic factor in both univariate and multivariate analysis (Sok et al., 2009). Although retrospective, this might suggest the importance of cholesterol levels as a valuable tool for detection of high risk cases. Recently, a Chinese group has assessed the relevance of total serum cholesterol levels in NSCLC patients. Decreased total serum cholesterol level was an independent prognostic factor for worse outcome (progression free survival and overall survival), suggesting that pretreatment total serum cholesterol level is a novel prognostic biomarker in resectable lung cancer (Li et al., 2015a).

Moreover, cholesterol levels have been shown to be involved in the regulation of various membrane proteins such as ABCG2, and membrane cholesterol was also found to modulate ABCG2 activity. However, the effect of cholesterol on chemosensitivity has not been addressed yet. Wu Y et al. examined the cholesterol levels of patients with lung adenocarcinoma with quick chemo resistance (QCR) and delayed chemo resistance (DCR). They showed that QCR patients displayed an elevated level of total serum cholesterol and those tumors showed upregulated ABCG2 expression. Therefore they propose that chemo resistance may be attributed to cholesterol-induced ABCG2 expression and blocking ABCG2 may increase the efficacy of platinum agents (Wu et al., 2015).

4. Molecular biomarkers in lung cancer

So far, there are not validated tumor markers sufficiently accurate to be useful for diagnosis or follow up of lung cancer. Identifying new biomarkers could potentially improve our strategies for lung cancer diagnosis, prognosis and therapy.

4.1. Biomarkers for diagnosis and prevention

4.1.1. Glycerophospho-N-arachidonoyl ethanolamine (GpAEA)

Chen et al. investigated some potential lung cancer biomarkers and found that glycerophospho-N-arachidonoyl ethanolamine and sphingosine could be potential sensitive and specific tools for the diagnosis and prognosis in lung cancer (Chen et al., 2015). They even suggested that both were as good or more appropriate for detecting lung cancer than traditional CEA and CYFRA 21-1 biomarkers. Yu et al. found that lung cancer patients had decreased levels of sphingosine compared with healthy volunteers (Yu et al., 2013). In this sense, Claudino et al. (Claudino et al., 2007) previously have reported that sphingosine levels were diminished in preoperative lung cancer patients compared with healthy volunteers and postoperative patients. GpAEA can be hydrolyzed to produce the endocannabinoid amandamide (AEA), a long chain lipid (Sagar et al., 2009). It has been suggested that an increase of GpAEA levels lead to decrease AEA production and subsequently, to a decreased ceramide and sphingosine levels. Therefore, GpAEA and sphingosine may be involved in sphingolipid metabolism and could be developed as biomarkers of lung cancer although further studies involving larger populations are required.

4.1.2. N-12- diacetyl spermine (DAS)

As recently publish by Wkoff WR *et al.,* N-12- diacetyl spermine (DAS), is a novel serum metabolite with significant prediagnostic value in SNCLC (Wikoff et al., 2015). DAS levels were analyzed in serum samples from more than 300 patients and controls from the CARET trial and it was found to be elevated by 1.9- fold in those patients who subsequently developed NSCLC (Wikoff et al., 2015).

4.1.3. Apolipoproteins

Shi J et al. analyzed serum proteins of SCLC patients by using proteomics. Compared to healthy controls, the expression levels of Apolipoproteins A-IV and Apolipoprotein Ewere upregulated, thus these proteins may be potential serum biomarkers for early detection of SCLC (Shi et al., 2014).

4.1.4. Oxidative stress

Several evidences have shown that oxidative stress and the resulting lipid peroxidation are involved in numerous pathological states including cancer. Glutathione S transferases (GST) are key enzymes in the detoxification of numerous carcinogens and endogenous compounds such as peroxidised lipids. Theoretically, individuals lacking a specific GST enzyme may be at a higher risk of developing cancer if exposed to certain genotoxicants (Gallegos-Arreola et al., 2003; Salagovic et al., 1998). Among the potential mutations the most widely known are the deletion of the GST01 (GSTT1) or GSTm1 (GSTM1) genes (null variants), which result in no enzymatic functional activity. Deficiency in GSTT1 isoenzyme activity may predispose to the effects of some carcinogens although there are various studies with contradictory results.

The frequency of the GST1 null phenotype is higher in Asia compared to other populations. *Zhao Y* et al. (Zhao et al., 2015) conducted a meta-analysis to estimate the association between GSTT1 gen polymorphisms and lung cancer susceptibility in the East Asia population. They included 7415 lung cancer cases and 6084 controls and found a statistically significant association between GSTT1 null genotype and lung cancer (OR 1. 17, p 0.003). Furthermore, a sub-analysis revealed that lung cancer risk in smokers carrying the GSTT1 null gen was significantly increased compared with non-smokers.

4.1.5. Carotenoids

Some studies have identified beta-carotene as being associated with an increased risk of lung cancer, especially among active smokers (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn et al., 1996). A Cochrane Database meta- analysis containing data from 3 large trials has suggested a marginally increased risk of lung cancer associated with beta-carotene supplementation among current smokers or former smokers (Caraballoso et al., 2003). *Tanvetyanon and Bepler* published a meta-analysis of 4 large studies with more than 100,000 subjects and evaluated the effect of beta carotene intake on the incidence of lung cancer among smokers or former smokers (Tanvetyanon and Bepler, 2008). They found that high dose supplementation appears to increase the risk among current smokers with no significant increased risk noted among former smokers. However, no chemoprevention trials can provide enough evidence to recommend the use of any agent to prevent lung cancer and nowadays the best advice is to stop smoking.

4.2. Prognosis biomarkers

There are no validated prognostic biomarkers for lung cancer related to lipid metabolism. However, there are some studies with encouraging results.

Recently a group of Italian investigators (Petrelli et al., 2015) have assessed the prognostic value of LDH in solid tumors. They systematically reviewed 77 studies compressing more than 22,000 patients, mainly with advanced disease, and found that higher LDH levels were associated with a HR for OS of 1.7. Importantly, this prognostic effect was found to be highest in lung cancer among

others tumors. Thus, it was suggested that it could be a useful and inexpensive prognostic biomarker in metastatic carcinomas. *Fu et al.* Fu et al. (2015) studied NSCLC cell lines and observed that the expression of LDHA in alpha enolase (ENO1) overexpressed cells was markedly increased, as was the production of lactate. Overexpression of ENO1 has been previously demonstrated in several types of tumors including NSCLC (Altenberg and Greulich, 2004) with conflicting results regarding clinical outcomes. Su WP. et al. examined the role of Apolipoprotein E in a malignant pleural effusion associated lung adenocarcinoma cell line and showed that overexpression correlated with poor survival in patients with MPE at the time of diagnosis (Su et al., 2011).

Regarding SCLC, Shi J. et al. analyzed the expression of some apolipoproteins (ApoA1 and ApoC III) in tumor samples and found that it was inversely correlated with recurrence rate (Shi et al., 2016).

4.3. Bioactive compounds for cancer treatment

There are lots of bioactive compounds capable of modulate lipid metabolism in lung carcinomas but its clinical significance is controversial, as no one has been validated.

4.3.1. Cerulenin

Cerulenin is a specific noncompetitive inhibitor of FAS with selective cytotoxicity to cancer cells due to their increased fatty acid synthesis but not to normal cells. As Cerulenin is chemically unstable, there have been developed synthetic small molecules to inhibit FAS, such as C75 compound developed by Pizer et al. (Pizer et al., 1998b). C75 has been shown to inhibit tumor growth in a xenograft breast cancer model (Pizer et al., 2000). C93 compound is a new synthetic FASN inhibitor, developed to overcome C75 compounds lack potency and side effects. Similar to C75, C93 has demonstrated a significant delay in tumor growth in NSCLC xenograft models (Orita et al., 2008), as well as to have chemopreventive effects in induced lung tumors (Orita et al., 2007).

4.3.2. SCD1 inhibitors

As we previously mentioned, SCD has been described to be upregulated in several types of human tumors and its expression has been correlated with a malignant transformation, proliferation and survival. Noto A. *et al.* studied the response to SCD inhibition with MF-438 compound on tumor spheroids. They found an increased rate of apoptosis and all MF-438 treated cells had a decreased tumorigenic potential (Noto et al., 2013).

4.3.3. ACLY inhibitors

ACLY is a key enzyme of *the novo* FA synthesis and a promising therapeutic target as shown in some experiments. Indeed, several studies targeting ACLY by RNA interfering have demonstrate its relevance inhibiting *de novo* lipogenesis and inducing growth arrest in lung adenocarcinoma cell lines (Migita et al., 2008). *Jun-Ichi Hanai* et al. created ACL knockdown A549 cells by using RNA interference and showed an impaired proliferation and higher rates of apoptosis. They additionally found that ACL inhibition leaded to differentiation and mesenchymal-epitelial transition (Hanai et al., 2012). Hatzivassiliu et al. also demonstrated that ACLY inhibition by RNA interference and SB204990 chemical compound resulted in an impaired of cell proliferation of A549 lung cancer cell line. They also validated the anti-tumor effect of ACLY inhibition on mice models and found that injected ACLY knockdown clones into mice induced significantly smaller tumors (Hatzivassiliou et al., 2005).

4.3.4. Statins

Statins inhibit 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase and are widely used to reduce circulatory cholesterol levels. Because statins are similar in structure to HMG-CoA on a molecular level, they will fit into the enzyme active site and compete with the native substrate (HMG-CoA). This competition reduces the rate by which HMG-CoA reductase is able to produce mevalonate, the next molecule in the cholesterol cascade.

Regarding *in vitro* studies, lovastatin has been shown to induce apoptotic cell death in A549 lung carcinoma cells (Walther et al., 2016) and in the same way simvastatin leads to apoptosis of NSCLC cells harboring an EGFR resistant mutation (Lee et al., 2016).

Cardwell et al. retrospectively investigated whether statin users had a reduced risk of cancer specific mortality in a cohort of lung cancer patients. There was some evidence that statin use, mainly Simvastatin, after the diagnosis was associated with reduced lung cancer specific mortality (adjusted HR, 0.89; 95% CI, 0.78-1.02; p 0.09) and the association was more evident after 12 prescriptions. Furthermore, statin use before diagnosis was associated with reduced lung cancer-specific mortality (Cardwell et al., 2015).

Recently, Lohinai et al. (Z. L P. and D Z. S., 2015) presented their retrospective analysis of 876 patients with SCLC treated with aspirin, statin, SSRIs, doxazosin or prazosin. Only statins showed a statistically significant survival benefit (median OS 8.4 months vs 6.1 months) when compared with those patients not receiving them.

4.3.5. Polyphenolic compounds

Epigall-3-gallate (EGCG) is a polyphenolic compound found in green tea extract that has shown anti-cancer effect in many *in vitro* studies and animal models (Yang et al., 2009). There are some data regarding EGCG and lung carcinoma, suggesting it could be used as a prevention agent or even as an adjuvant drug. EGCG decreases topoisomerase II alpha expression in both human NSCLC and SNCLC xenograft mice model (Li et al., 2015b) and enhances the efficacy of cisplatin in A549 cells. Thus, the combination of EGCG with cisplatin might be a potential therapeutic strategy (Zhou et al., 2014). Deng PB. et al. also suggested that EGCG could improve chemotherapy efficacy modifying microvasculature and microenvironment (Deng et al., 2013). Results from Zhou DHís experiment suggests that EGCG in combination with curcumin could repress tumor growth in NSCLC cells by stopping DNA replication and causing cell cycle arrest. Clinical application is far from being defined but it could be an interesting approach for future clinical trials.

5. Conclusion

Lipid metabolism and lung cancer is an interesting scenario with potential biomarkers involved in lung carcinogenesis, prognosis, prevention and treatment. Acquiring a deeper knowledge about the biological basis of lung cancer could contribute to develop new biomarkers and effective therapeutic strategies in this setting. This is the first review reported in the literature focusing on the implications of lipid metabolism in lung cancer biology. Hopefully, the absence of studies on this topic will stimulate more intensive research in order to obtain new molecular targets and effective bioactive compounds. All this effort could contribute to improve the current lung cancer treatment and possibly increase patients outcome.

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