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REVIEW

Stearoyl-CoA desaturase-1: a novel key player in the mechanisms of cell proliferation, programmed cell death and transformation to cancer

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As part of a shift toward macromolecule production to support continuous cell proliferation, cancer cells coordinate the activation of lipid biosynthesis and the signaling networks that stimulate this process. A ubiquitous metabolic event in cancer is the constitutive activation of the fatty acid biosynthetic pathway, which produces saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) to sustain the increasing demand of new membrane phospholipids with appropriate acyl composition. In cancer cells, the tandem activation of the fatty acid biosynthetic enzymes adenosine triphosphate citrate lyase, acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) leads to increased synthesis of SFA and their further conversion into MUFA by stearoyl-CoA desaturase (SCD) 1. The roles of adenosine triphosphate citrate lyase, ACC and FAS in the pathogenesis of cancer have been a subject of extensive investigation. However, despite early experimental and epidemiological observations reporting elevated levels of MUFA in cancer cells and tissues, the involvement of SCD1 in the mechanisms of carcinogenesis remains surprisingly understudied. Over the past few years, a more detailed picture of the functional relevance of SCD1 in cell proliferation, survival and transformation to cancer has begun to emerge. The present review addresses the mounting evidence that argues for a key role of SCD1 in the coordination of the intertwined pathways of lipid biosynthesis, energy sensing and the transduction signals that influence mitogenesis and tumorigenesis, as well as the potential value of this enzyme as a target for novel pharmacological approaches in cancer interventions.

Introduction

The fate of the cell, whether it divides, differentiates, enters a transient (quiescence) or permanent (senescence) growth arrest or triggers a suicidal mechanism of death, demands a finely tuned sequential activation and deactivation of both biosynthetic and energy-generating metabolic pathways. In mammalian organisms, the processes of cell growth, proliferation and survival requires the formation of new membranes, which, in turn, entails the production of new lipids with an appropriate molecular composition. A basic step in the synthesis of lipids is the formation of saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs), the major fatty acid species in mammalian cell lipids. As building blocks of phospholipids, diacylglycerols, triacylglycerols and cholesteryl esters, these fatty acids are fundamental constituents of membrane structures, vital pools of metabolic energy and important mediators/signals that regulate many cellular activities (Figure 1). Since alterations in the balance of SFA and MUFA in lipids can influence this wide array of cellular functions, the content and distribution of SFA and MUFA within the cell must be tightly adjusted. One key regulator of the fatty acid composition of cellular lipids are Stearoyl-CoA desaturases (SCD), also known as fatty acyl-CoA delta-9 desaturases, the endoplasmic reticulum-resident enzymes that catalyze the introduction of the first double bond in the *cis*-delta-9 position of several saturated fatty acyl-CoAs (Figure 1), principally palmitoyl-CoA and stearoyl-CoA, to yield palmitoleoyl- and oleoyl-CoA, respectively (1). Mammalian organisms contain between two and four variants of SCD, whose expression is predominantly organ specific (2). Two isoforms of SCD, SCD1 and SCD5 (also known as ACOD4), have been described for humans (3–5). The human SCD1 gene is ubiquitously expressed, with highest levels in brain, liver, heart and lung (3). SCD1 is highly expressed in oncogene-transformed lung fibroblasts and in cancer cells (6–8). SCD5 exhibits limited expression in adult human tissues (4,5). SCD5 has also been detected in normal human fibroblasts and cancer cells (R.A.Igal, unpublished results), but its physiological function is virtually unknown.

Although there is evidence that SCD1 can be modulated by posttranscriptional mechanisms involving ubiquitin proteosome-dependent and independent pathways (9,10), the levels of mammalian SCD1 appear to be principally determined by its rate of transcription (2). The promoter region of human SCD1 contains a wide variety of transcription factor-binding sites (3), including several elements known to regulate murine SCD1 transcription-like NF-1, AP-2, sterol response element-binding protein (SREBP) and PPAR. Nevertheless, the intricate molecular mechanisms of transcriptional modulation of SCD1 are awaiting further elucidation.

Alterations in SCD1 expression and MUFA biosynthesis have been reported in several prevalent metabolic diseases, such as diabetes, obesity and atherosclerosis. It is interesting to note that in these metabolic diseases, as well as in cancer, a common dominant feature is the metabolic shift toward biosynthetic reactions that yield new lipid macromolecules. In the case of obesity and diabetes, targeted cells, such as adipose, liver and muscle cells, exhibit abnormally elevated lipid biosynthetic activity with a consequent overproduction of predominantly energy storage lipids, chiefly triacylglycerols and cholesteryl esters (11). In cancer cells, although they display a similar highly anabolic metabolism, most of newly synthesized lipid products are utilized for the formation of new phospholipids for membrane biogenesis (12). The observation that abnormally high levels of SCD1 appear to be critically linked to the metabolic perturbations found in diabetes and obesity, a disease that has been associated with cancer, suggests that SCD1 may be a common molecular link among these pathological disorders. A considerable effort has been devoted to the understanding of the critical involvement of SCD1 in the deregulation of lipid metabolism in relation to diabetes, obesity and other associated conditions like cardiovascular diseases. These comprehensive investigations have been extensively described in several excellent reviews (2,13–15). In recent years, studies have revealed a novel function for SCD1 in the modulation of metabolic and signaling processes related to cell proliferation, survival and malignant transformation to cancer. The present review summarizes the growing body of evidence that highlights the relevant role of SCD1 in the integration of lipid metabolism and the molecular signals that control metabolism in proliferating cells, particularly cancer cells, as well as on the potential value of this enzyme as a novel target for cancer therapeutics.

Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, adenosine monophosphate-dependent protein kinase; FAS, fatty acid synthase; MUFA, monounsaturated fatty acids; SCD, Stearoyl-CoA desaturase; SFA, saturated fatty acid; SREBP, sterol response element-binding protein.

Regulation of SCD1 in cell proliferation, senescence and programmed cell death

The control of cell proliferation, death and senescence in normal and cancer cells are critically linked to the regulation of metabolism,

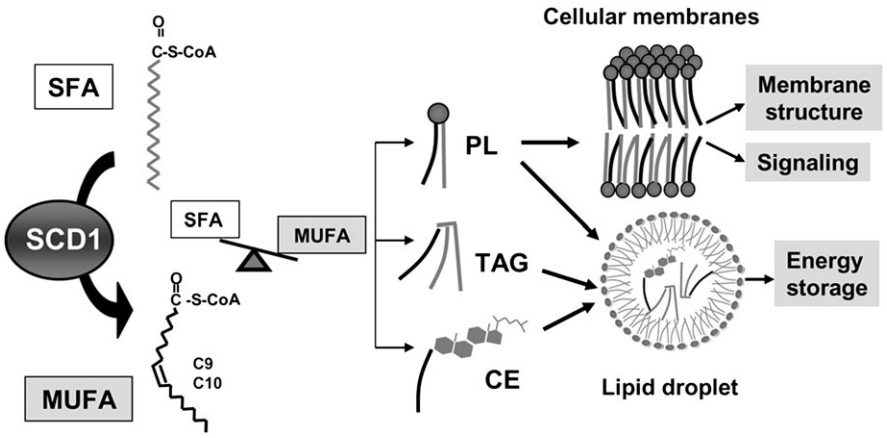

Fig. 1. Regulation of MUFA/SFA balance in mammalian cell lipids by SCD1. CE, cholesterol esters; PL, phospholipids; TAG, triacylglycerols.

particularly the synthesis and remodeling of lipid signals and structures. Before cell division, cells must double their membrane content in order to maintain the size/surface ratio in daughter cells (16,17). Thus, external factors that induce cell proliferation, such as nutrient availability and growth factors, trigger the synthesis of membrane lipid components. Specifically, the synthesis of phospholipids and cholesterol, the two major components in mammalian cell membranes, is coordinately regulated with cell cycle (17–19). Cells must then expand the amount of lipids with a distribution of fatty acid species that is appropriate for maintaining the functions of dividing cells. The control of the diversity of molecular lipid species in proliferating cells exhibits fundamental biological relevance; structural and signaling functions of phospholipids and its bioactive derivatives, such as diacylglycerols, lysophosphatidic acid and phosphatidic acid, depend on the content of their fatty acyl species, particularly the abundance of SFA and MUFA, to trigger specific responses during mitogenesis (20–22). Although it has been long established that SCD1 is a key regulator of lipid fatty acid composition in mammalian cells and tissues (2), the role of SCD1 in the molecular mechanisms involved in cell division has remained surprisingly understudied. Recent work, however, has demonstrated that, as part of the concerted mechanism of regulation of lipid synthesis during the events of cell proliferation, SCD1 is a central target of growth factors and hormones that regulate key cell cycle events. A large number of potent mitogens (platelet-derived growth factor, epidermal growth factor, insulin, fibroblast growth factor-2, fibroblast growth factor-4, keratinocyte growth factor, transforming growth factor-β and retinoic acid) have been shown to stimulate SCD1 expression in a variety of untransformed human cell types (23–26). Furthermore, other studies clearly demonstrated that the mitogen-induced up-regulation of SCD1 expression is parallel to the activation of the synthesis of phospholipids and cholesterol (27,28), suggesting the active participation of MUFA synthesis in the mechanisms of membrane biogenesis during cell replication.

Studies from our laboratory revealed the presence of a strong functional association of SCD1 activity with membrane lipid synthesis in neoplastic cells. In these cells, a several fold overexpression of SCD1 is the cause of the marked enrichment of phospholipids with MUFA (7,8,27,28). Importantly, SCD1 is able to efficiently convert both exogenous and endogenously synthesized SFA into MUFA (7); however, as a result of the massive *de novo* formation of SFA in cancer cells produced by constitutively overexpressed fatty acid synthase (FAS) (12,29,30,31), these endogenous SFA are the main source of substrate for the catalytical conversion into MUFA by SCD1 (7). The metabolic fate of MUFA in cancer cells is dictated by the rate of acylation reactions in the formation of different lipids. Although the overall synthesis of glycerolipids is activated in cancer, the dominant lipid biosynthetic pathway is the formation and recycling of phospholipids (12,27–29). Therefore, virtually all MUFA produced by SCD1 are channeled into the avid phospholipid biosynthetic machinery, which will supply the dividing cancer cell with new lipids for continuous membrane biogenesis (7,28).

More evidence that reveals a tight regulation of SCD1 during cell proliferation was obtained by studying the synthesis of MUFA during replicative senescence, a process in which, after several rounds of mitosis, aging cells progressively lose their ability to divide but remain metabolically active. In this study, it was observed that the expression and activity of SCD1 were dramatically reduced when the senescent state in normal fibroblasts was reached (32). Interestingly, it was also found that the observed reduction in SCD1 was parallel to a decrease in FAS, the main substrate provider for the SCD1 reaction, suggesting a coordinated repression of fatty acid synthesis and desaturation when cells slow down or stop proliferation.

Other mechanisms that limit the multiplication of cells growing in culture, such as cell stress response and apoptosis, also target SCD1. It was observed that SCD1 activity and expression in non-transformed and neoplastic cells were downregulated upon induction of programmed cell death with proapoptotic agents such as etoposide and ceramide (7) or with cell stressors like tunicamycin (D.Hess and R.A.Igal, unpublished results). In these conditions, cell proliferation is halted and the rate of membrane lipid synthesis declines (33); hence, the fact that SCD1 activity is suppressed when mitogenesis is turned off reinforces the argument that MUFA biosynthesis is differentially modulated according to the metabolic requirements of different stages of the cell life.

Role of SCD1 in the regulation of cancer cell lipogenesis, proliferation and tumorigenesis

Metabolism in cancer cells is characterized by an abnormally high rate of aerobic glycolysis and an accelerated biosynthesis of macromolecules, including DNA, proteins and lipids (34). The high rate of glycolysis in cancer cells and tumors offers the advantage of abundant production of adenosine triphosphate, the energy currency of the cell (35–38). Importantly, glycolysis also provides metabolites, such as citrate and glycerol, which are used for the *de novo* synthesis of cellular lipids (Figure 2). As mentioned above, a ubiquitous metabolic alteration in cancer cells occurs in the *de novo* synthesis of fatty acids. Although in normal cells fatty acid synthesis is inhibited by exogenous fatty acids taken up from the circulation, cancer cells display a high rate of *de novo* fatty acid synthesis, propelled by aerobic glycolysis, elevated activity of acetyl-CoA carboxylase (ACC) and constitutively overexpressed FAS (7,29,39,40). Although the main products of glucose-derived fatty acid synthesis are SFA, which are abundant in cancer cells, an increased content of MUFA is also found in transformed and cancer cells and tissues (7,41–43). This observation suggests that the parallel activation of glycolysis and fatty acid synthesis in cancer is tightly coupled to the conversion of SFA into MUFA and also implies that MUFA are major end products of glucose metabolism in cancer cells. If this hypothesis is true, a constantly

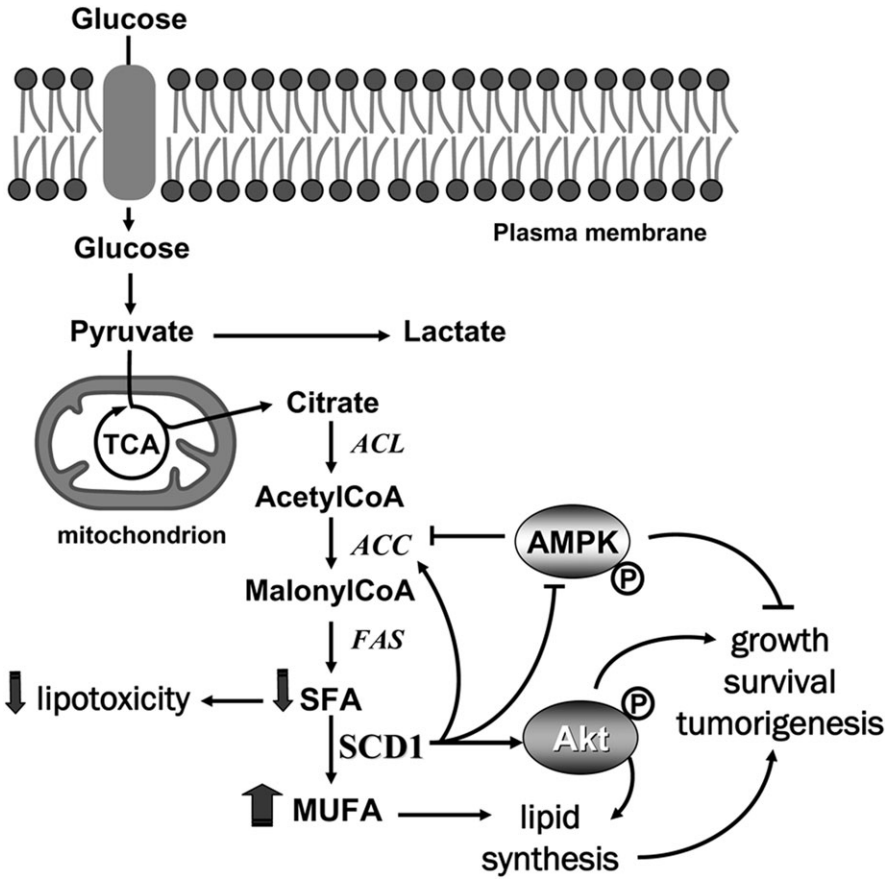

Fig. 2. Metabolic and signaling regulations by SCD1 in cancer cells. ACL, adenosine triphosphate-citrate lyase; AMPK, AMP-activated protein kinase; TCA, tricarboxylic acid cycle.

active SCD1 must be necessarily present in cancer cells in order to maintain an uninterrupted flux of glycolytic metabolites into the biosynthesis of MUFA and, hence, into the formation of major cell lipids. Adding to this notion, it has been shown that the levels of SCD1 expression and activity in transformed cells, as well as in lung and breast cancer cells, are found either highly or moderately increased when compared with normal cells (7,8). Although there is still limited information on whether there is a positive relationship between SCD1 activity and cancer progression, elevated SCD1 expression and activity have been detected in several types of cancers. Increased expression of SCD1 was found in colonic and esophageal carcinoma and in hepatocellular adenoma (44), in hepatocarcinoma (45), as well as in chemically induced tumors (46,47). However, in immunohistological studies, lower content of SCD1 protein was detected in cancerous prostate epithelium with respect to normal epithelium (48). Since in this study SCD1 activity and MUFA content were not determined, a more complete evaluation of SCD1 status in prostate cancer tissues may reveal a distinct role of the desaturase in this form of cancer. Finally, an analysis of gene expression profiles employing Oncomine (www.oncomine.org), a database that contains ∼40 000 studies worldwide, reveals the presence of high SCD1 expression in several cancer cells and tissues, including breast, lung, renal, prostate, bladder, colon and leukemia.

Although there is still no direct epidemiological information on an aberrant tissue expression or activity of SCD1 in cancer patients, in several retrospective and prospective epidemiological studies alterations in SFA and MUFA levels were linked to cancer incidence and death. As reported by Chajes *et al.* (49), serum levels of fatty acids may have certain predictive value for breast cancer in premenopausal women. These investigators found that when fatty acid composition was determined in sera of women who developed breast cancer and age-matched controls, unbalanced levels of stearic acid (low) and oleic acid (high) appeared positively correlated to cancer but not to metastasis. Similarly, an Italian prospective study reported a positive association between unbalanced levels of SFA and MUFA in erythrocyte membranes and breast cancer risk (50). Also, a recent prospective study conducted in a French cohort reported a significant link between unbalanced levels of SFA and MUFA in prediagnostic sera and breast cancer risk (51). In addition, a prospective cohort study by Zureik *et al.* (52) shows that high MUFA levels in cholesterol esters were correlated with a greater cancer death rate in patients. A significant association between elevated oleic acid in adipose tissue and lymph node metastasis was observed in women diagnosed with breast cancer (53). Importantly, Bougnoux *et al.* (42) identified a link between low levels of stearic acid in phosphatidylcholine of breast tumors, subsequent metastasis and poor prognosis. In another study in which fatty acid composition of breast adipose tissue was determined in patients with either benign breast disease or breast cancer, no difference in MUFA content was detected between these two groups of patients (54). However, the same study found a positive correlation between MUFA content in phospholipids and degree of malignization in patients with breast cancer. Moreover, data from the EURAMIC study, in which the incidence of breast cancer in patients from different European countries was analyzed in relation to their MUFA levels in adipose tissue, provides an evidence of a positive association of the MUFA palmitoleic and *cis*-vaccenic acids with breast cancer (55). In this study, with the exception of patients from Spain in which MUFA-rich olive oil is a primary source of oleic acid, a neutral to positive relationship between oleic acid and breast cancer was observed. Overall, although changing levels of fatty acid dietary intake may affect the fatty acid profile of tumor and normal tissues in the studied subjects, the reported alterations in SFA and MUFA levels in patients appear to

reflect changes in fatty acid metabolism promoted by malignant disease. If the aforementioned findings of increased expression of SCD1 in cancer cells are taken into consideration, it is conceivable that the cause of the dysbalance in fatty acid species in cancer patients could be attributed to abnormal SCD1 activity. However, the finding of more direct evidence on the correlation between prediagnostic serum levels of MUFA/SFA and tumor membrane levels of these fatty acids among subjects who further developed cancer will determine the significance of an altered level of MUFA/SFA level in prediagnostic sera in nested case–controls studies.

Lipogenesis. Although the evidence points out to a linkage between SCD1 and abnormal lipid metabolism in cancer cells, the question of whether this relationship was either casual or causal remained unanswered until recent loss-of-function studies revealed that SCD1 is not just a passive player in the activation of lipid synthesis in cancer but a central regulator of this process. In oncogene-transformed cells and lung cancer cells in which SCD1 expression was reduced by stable gene knockdown, it was observed that the biosynthesis of fatty acid, triacylglycerol, cholesteryl esters and phospholipid synthesis is markedly impaired (27,28). Similar results were obtained in cancer cells in which SCD1 activity was acutely blocked with a specific small molecule inhibitor of the desaturase, adding more definitive proof to the concept that SCD1 controls the overall process of lipogenesis in cancer cells (8).

Although the regulation of lipogenesis by SCD1 at a molecular level in cancer cells is still not fully understood, it appears to involve at least three major mechanisms (Figure 2): the control of the fatty acid biosynthetic rate, the provision of MUFA for lipid macromolecule formation and the modulation of signaling networks that control the expression and activity of key enzymes of lipid metabolism. As described earlier, cancer cells continuously synthesize SFA and MUFA by a tandem of reactions involving adenosine triphosphate-citrate lyase, ACC, FAS and SCD1. Recent findings suggest that SCD1 activity may facilitate the high fatty acid biosynthetic rate by modulating ACC, the key regulatory enzyme in the pathway, through an allosteric mechanism and also, as described below, through adenosine monophosphate-dependent protein kinase (AMPK)-mediated phosphorylation of ACC (8). The potential allosteric control of ACC by SCD1 may involve the removal of SFA, which are major inhibitors of ACC activity (8), through conversion into MUFA. It has been long established that acyl-CoAs, the metabolically active form of fatty acids, are strong allosteric inhibitors of ACC by promoting its depolymerization (56–58). Since the most potent inhibitors of ACC are saturated fatty acyl-CoAs with 16–20 carbons, it is therefore possible that the presence of active SCD1 in cancer cell could prevent an elevation in the intracellular levels of SFA that promotes the inhibitory depolymerization of ACC and, consequently, the downregulation of lipid synthesis. In fact, in cells in which SCD1 expression was reduced, a marked increase in both free and esterified SFA, chiefly palmitic and stearic acids, was correlated with a profound decrease in fatty acid synthesis (27). Thus, in order to maintain a continuous flow of substrates to keep up with a high lipogenic rate, cancer cells may not need to express large amounts of SCD1 but just enough active enzyme to avoid the accumulation of SFA and, thereby, prevent the inhibition of ACC.

In addition, by modulating the availability of MUFA substrate for acylation reactions, SCD1 may provide a second level of lipogenic regulation in cancer cells. It has been established that MUFA are more preferred substrates than SFA for lipid biosynthesis (11,59). In cancer cells, the chronically upregulated SCD1 produces MUFA to supply the overactive lipid biosynthetic machinery of these fast replicating cells with an abundant provision of ideal fatty acid substrates.

Cell proliferation and apoptosis. Probably due to its impact on cancer cell metabolism, SCD1 activity has far-reaching consequences for several phenotypical features of cancer, such as continuous cell replication, enhanced survival and increased invasiveness. The essential role of SCD1 in cancer cell mitogenesis was unambiguously demonstrated by recent work in which suppression of SCD1 by genetic and pharmacological means led to a slower rate of cell proliferation and decreased survival (8,27,28,60). In these studies, it was observed that the magnitude of growth inhibition in SCD1-deficient cells was strongly correlated to the degree of SCD1 inactivation (8), firmly establishing a positive relationship between the rate of MUFA synthesis and cell replication. Furthermore, the impact of SCD1 inhibition on cancer cell proliferation appears to be not cancer cell-type specific since the antigrowth effect of SCD1 depletion was observed in a variety of neoplastic cells, including SV40-transformed cells and lung, breast and colon cancer cell lines (8,27,28,60). Interestingly, ablation of SCD1 abolishes cell growth independently of the degree of SCD1 expression in cancer cells since we observed that MDA-MB-231 and MCF-7 breast cancer cells, which have different SCD1 activity levels (N.Scaglia and R.A.Igal, unpublished results), were similarly sensitive to the antiproliferative effect of SCD1 blockade (8). Remarkably, normal human skin fibroblasts, which display lower SCD1 activity compared with neoplastic cells (7), appear to be resistant to the cytotoxic effect of SCD1 inhibition (8), suggesting that SCD1 activity may be essential only in highly mitogenic cells.

Active biosynthesis of lipids, especially lipid precursors like SFA and MUFA, is not only a critical need for the unremitting proliferation of cancer cells but also for avoiding their entry in the program of apoptosis (33). Alterations in fatty acid metabolism, in particular fatty acid synthesis and Δ9-desaturation, are known to induce the execution of the cell death program. For instance, the inhibition of FAS induces apoptosis in cancer cells, which can only be prevented by addition of supraphysiological concentrations of exogenous palmitic (30). Studies performed in oncogene-transformed and cancer cells reported that ablation of SCD1 notably increases the rate of apoptosis (8,27), implying that neoplastic cells also require an appropriate level of SCD1 activity to evade programmed cell death. Furthermore, in a recent study designed to identify new cancer targets, a siRNA library against 3700 genes was screened in several cancer cells in search for suitable targets for inducing cytotoxicity and cell death (60). Remarkably, SCD1 was one of the three main targets identified in the screening, confirming the observations that SCD1 is a crucial factor for cancer cell survival.

Although the molecular mechanisms by which SCD1 modulates the evasion of cell death in cancer cells remains little understood, this critical feature of SCD1 may partly lie on its function as a potential barrier against SFA-mediated cytotoxicity. Excess content of long-chain fatty acids, especially SFA, triggers programmed cell death in a process known as lipid-mediated toxicity or lipoapoptosis (61). The protective action of SCD1 against SFA-mediated apoptosis was observed in non-transformed mammalian cells in which overexpression of SCD1 blocked the induction of programmed cell death by palmitic acid (62). Moreover, it was reported that abrogation of SCD1 expression markedly sensitizes cancer cells to the proapoptotic effects of exogenous palmitic acid (27,28). This prosurvival activity of SCD1 may be even more critical in cancer cells that in normal cells. As mentioned earlier, a metabolic hallmark in most cancer cells is the exacerbated *de novo* synthesis of SFA, particularly palmitic acid (30,63,64). In cancer cells, by lowering the content of SFA through conversion into MUFA, the overly active SCD1 may prevent the detrimental effects of excess SFA that result from constitutive fatty acid synthesis typically found in these cells. In support of this postulate, it was observed that enhancing fatty acid synthesis with exogenously added citrate produced a greater increase in the formation of SFA in SCD1-deficient cancer cells in parallel to a more profound decrease in the typically low cell proliferation rate observed in these cells (8).

Tumorigenesis. The striking effect of SCD1 ablation on cell proliferation and death mechanisms suggested that SCD1 may be an important factor in the mechanisms of tumor formation and growth. Initial evidence of the relationship between SCD1 and malignant phenotype was found in *in vitro* colony formation studies, in which the ablation of

SCD1 expression in neoplastic cells was shown to reduce anchorage-independent growth, a hallmark of malignant transformation (25,28). A direct proof that SCD1 was critically involved in the tumorigenic process was obtained in xenograft tumor models in mice. In these studies, it was observed that lung cancer cells with stably reduced levels of SCD1 exhibit a severely impaired capacity for tumor formation, as well as for the progression of tumor growth (28). Moreover, a remarkable increase in latency in tumors originating from lung cancer cells was achieved through ablation of SCD1 expression, suggesting that a certain level of endogenously produced MUFA is required in early stages of tumor formation. The relevance of SCD1 in the tumor formation process is further supported by the observation that, in mice, the background level of SCD1 expression correlates with predisposition to liver carcinogenesis (65). In this study, rodents with higher levels of SCD1 were found to be more susceptible to induction of cancer. Additionally, the finding that sterculic acid, a cyclopropene fatty acid with inhibitory effects on Δ9, Δ6 and Δ5 desaturase activities (66), displays antitumoral effects *in vitro* and in a tumor model in rats (67), adds another piece of evidence in favor of the anticancer effect of SCD1 inhibition.

More than a molecular brick mason: a novel role for SCD1 in the coordinated regulation of lipid metabolism and signaling in cancer cells

During proliferation, cancer cells activate multiple lipid biosynthetic reactions while suppressing catabolic pathways such as β-oxidation (34,64). This metabolic transformation is achieved through numerous effects of mutated tumor suppressors and oncogenes, such as p53, myc, fos and the phosphatidylinositol-3′ kinase/Akt/mTOR pathway, as well as deregulated energy sensing pathways like the AMPK pathway (34,68,69). Akt and AMPK are considered to be major, albeit with functionally opposing functions, integrators of signals that control lipid metabolism, cell proliferation, survival and oncogenic transformation (68,69). In later years, the view of a unidirectional control of macromolecule biosynthesis and energetic reactions by oncogenic signaling pathways has been challenged and a new paradigm in which a continuous regulatory cross talk between biosynthetic and catabolic metabolism and the oncogenic transduction signals is receiving more attention. In this new view, the degree of activation of these major oncogenic pathways is governed by the rate of metabolic activity, for instance, the activity levels of lipogenic enzymes (34,64). Supporting this novel postulate, recent studies in our laboratory have demonstrated that both Akt and AMPK pathways are targets for SCD1. Regarding the Akt pathway, it was observed that ablation of SCD1 expression decreases Akt phosphorylation and activity in cancer cells (28). By controlling Akt activation, SCD1 may indirectly modulate the main routes for the biosynthesis of lipids in cancer cells. Akt is a powerful inducer of glucose-mediated lipogenesis in cancer cells, mainly through the transcriptional and catalytical regulation of multiple enzymes of glycolysis and fatty acid synthesis (64,68). For instance, by activating the SREBP family, a group of transcriptional factors that are central regulators of lipogenesis (70), Akt is able to induce lipid synthesis, particularly the formation of major membrane phospholipids like phosphatidylcholine and phosphatidylethanolamine (71). Although it has been reported that expression and activation of SREBP-1 in mice are positively affected by the levels of SCD1 (2,9), whether this transcriptional factor is the molecular liaison between SCD1 and the Akt-controlled mechanism of lipid production in cancer cells is a question that remains unanswered.

In addition to the Akt-mediated transcriptional modulation of lipogenic enzymes, SCD1 may control cancer cell proliferation through the modulation of other downstream targets of Akt, such as glycogen synthase kinase-3 beta (72). Our laboratory showed that phosphorylation of glycogen synthase kinase-3 beta, which inhibits its catalytical activity, was significantly decreased in SCD1-deficient cancer cells (27). Crucial regulators of cell cycle progression like cyclin D1 and its transcriptional activator, β-catenin, are phosphorylated by glycogen synthase kinase-3 beta and, consequently, marked for ubiquitinylation and degradation (73,74); hence, the antigrowth effect of SCD1 inhibition in cancer cells could be produced, at least partly, by affecting cell cycle regulatory proteins through an Akt-dependent mechanism.

Opposing Akt-induced anabolic signals, the activation of AMPK by phosphorylation promotes the downregulation of several lipogenic pathways and stimulates energy-supplying reactions, such as fatty acid oxidation (75). Importantly, dysfunctional AMPK signaling has been detected in lung cancers expressing a mutated form of LKB1, a kinase that activates AMPK (76). Recently published work indicates that SCD1 activity contributes to the regulation of lipid biosynthesis in cancer cells by modulating AMPK activation. It was observed that abrogation of SCD1 activity leads to the phosphorylation and catalytical activation of AMPK in lung cancer cells and the downregulation of ACC activity (8), a major metabolic target of activated AMPK (77). A similar finding was reported in SCD1 knockout mice, in which increased AMPK activity was found in liver and muscle (9). The AMPK-dependent antilipogenic effect of SCD1 ablation might also be produced by targeting FAS activity since it has been reported that FAS is downregulated by AMPK activators in 3T3-L1 cells (78). Furthermore, the activation of AMPK could mediate for other antilipogenic effects of SCD1 ablation in neoplastic human cells, such as the decreased synthesis of cholesterol (27). In this regard, it has been reported that AMPK phosphorylates and inactivates hydroxymethylglutaryl-coenzyme A reductase, a critical enzyme in cholesterol synthesis (79) and also inhibits SREBP-1 transcription (80).

Summary and concluding remarks

The findings described in the present review strongly argue in favor of a novel role for SCD1 in the regulation of metabolism and growth signaling pathways in cancer. This concept postulates that, as part of the program of oncogenic transformation, SCD1 contributes to maintain a shift in lipid metabolism (increase in lipogenesis and inhibition of fatty acid oxidation) and intracellular signaling (activation of Akt signals and deactivation of AMPK pathway), therefore favoring an accelerated rate of cell proliferation, increased invasiveness, enhanced survival and, ultimately, a greater tumorigenic capacity. Thus, constitutively active SCD1 promotes a metabolic balance in cancer cells that favors cell proliferation and survival by at least three potential mechanisms (Figure 2): (i) stimulation of ACC activity by (a) suppression of allosteric feedback inhibition by SFA and (b) inactivation of AMPK phosphorylation; (ii) activation of Akt pathway, with potential positive effects on the transcription of lipogenic enzymes and downstream mitogenic signaling proteins and (iii) stimulation of the lipid biosynthetic machinery by continuous supply with its preferred substrates, the MUFA. Furthermore, the overexpression of SCD1 in cancer cells ensures that harmful accumulation of SFA does not occur, hence preventing the cytotoxic effects of these fatty acids. These observations, made in *in vitro* cancer cell models and xenograft tumors, may help explain the findings in experimental cancer studies and in epidemiological reports in which an alteration in the content of MUFA in plasma and tissues was observed. Nevertheless, a clear-cut molecular level picture of the biochemical and biological functions of SCD1 in cancer cells is still lacking. The recent improvements in lipid profiling techniques, particularly mass spectrometry analysis, will undoubtedly contribute to a more profound understanding of the implication of SCD1 in the control of the cellular levels of hundreds of structural, energetic and signaling lipid molecular species that are critically involved in the life and survival of the cancer cell.

Also importantly, the studies reviewed here also suggest a value for SCD1 as a target for novel pharmacological approaches in cancer interventions. Potent and specific small molecule inhibitors of SCD1 activity have been recently discovered (81–86) and, in light of their positive anticancer effects in *in vitro* and *in vivo* models of experimental cancer, the utility of these SCD1 inhibitors as potential agents for chemotherapy deserves further consideration. Furthermore, if, as observed in *in vitro* studies, the antigrowth effect of SCD1 blockade proves to be selective for cancer cells, this may offer the

possibility of interventional window for SCD1 inhibitors in cancer treatment. In any case, in order to assess their future exploitation as therapeutic agents, the novel SCD1 inhibitors will require a comprehensive preclinical examination of their anticancer properties in different cancer cell types.

Finally, a new view in which lipogenic and signaling pathways mutually sense their status and, as a result, coordinate their activities in cancer cells is receiving increasing attention. The studies discussed in this review shed new light on the fundamental role of SCD1 as a key metabolic hub in the intertwined metabolic and transduction signal networks that supports cell growth, survival and oncogenic transformation. Deciphering the molecular components and spaciotemporal regulation of these interactions that are under the control of SCD1, as well as their biological consequences for the cell, represents an important challenge for future research in cancer.

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