RESEARCH ARTICLE

Implications of Agonizing and Antagonizing Stearoyl-CoA Desaturase-1

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Abstract

Stearoyl-CoA Desaurase-1 (SCD1) is an enzyme that catalyzes the biosynthesis of monounsaturated fatty acids from saturated fatty acids in various organ systems. SCD1's role and proposed properties make it of interest for possible pharmacological intervention to help mitigate various diseases such as cancer, heart disease, liver dysfunction, diabetes, etc. Prior research on SCD1's uses as a therapeutic agent has presented the potential for the development of compounds to act as either an agonist or antagonist. However, there is a discrepancy in the literature regarding SCD1 and its proposed uses, whether by inhibiting the enzyme or promoting its activity. A wide array of work has looked at different organ systems, inhibitors, disease state of interest, and methods of the study that included either mouse or human models. A notable trend was the incidence of a common adverse effect profile affecting the skin, the heart, adipose tissue, the liver, and the immune system. It may be possible to infer that the enzyme's extensively documented adverse event profiles, along with the integration of SCD in various metabolic circles, and potential use of an inhibiting therapeutic agent, holds potential for future development. This suggested that whole body depletion or increase in SCD1 may cause unforeseen side effects. Further research on specific agonists and antagonists suggests that future pharmacological interventions should be organ or organ system specific to avoid unwanted side effects.

Key Words: Stearoyl-CoA desaturase-1; SCD1; agonize; antagonize; pros; cons; cancer therapy; metabolism; liver health; inhibitor

1.0 Introduction

Stearoyl-CoA desaturase-1 (SCD1) is an endoplasmic reticulum membrane bound protein that catalyzes the synthesis of monounsaturated fatty acids (MUFA) by desaturating long chain saturated fatty acids (SFA) between carbons 9 and 10. SCD1 preferentially desaturates stearic and palmitic acid to Δ-9 MUFAs oleic and palmitoleic acid, respectively. SCD1 is a key player in the synthesis of endogenous MUFAs from dietary intake and is necessary for lipogenesis and lipid homeostasis. Human SCD1 is highly homologous to mouse SCD1 and is expressed in adult adipose tissue, liver, lung, brain, heart, pancreas, and skeletal muscle. The other known human isoform, SCD5, is a primate-specific isoform that is expressed predominantly in the brain and pancreas, as well as in the ovaries and adrenal glands.[1]

SCD1 was first discovered in 1988 when the expression of an mRNA transcript, being highly induced during adipogenic differentiation, was identified.[2] Further research about the evolutionary history of the SCD gene family showed that SCD1 and SCD5 emerged as a part of 2R genome duplications. The regulatory variance between these isoforms can be accounted for the functional differences seen in the aftermath of 2R.[3] The SCD1 gene is found on chromosome 10 in the human genome [3], and its pseudogene is located on chromosome 24 in the sub-band 32 of region 11.[2] The size of SCD1 and SCD5 genes are 17Kb and 170Kb, respectively. [3] While SCD1 is made up of 359 amino acids and SCD5 is 330 amino acids in length.[4]

This iron-containing enzyme has four transmembrane domains with both its N- and C-terminus located in the cytoplasm (**Figure 1**). The structure of the cytosolic domain provides a framework for regioselectivity and stereospecificity of the desaturase reaction.[2] Transcription factors such as Sterol Regulatory Element-Binding Protein transcription factor 1 (SREBP-1c), liver X receptor (LXR), Peroxisome Proliferator-Activated Receptor alpha (PPAR-α), and CCAAT/Enhancer-Binding Protein alpha (C/EBP-α) bind to the promoter activity region of SCD1, a *cis*-element binding site, to regulate the enzyme's gene expression.[2]

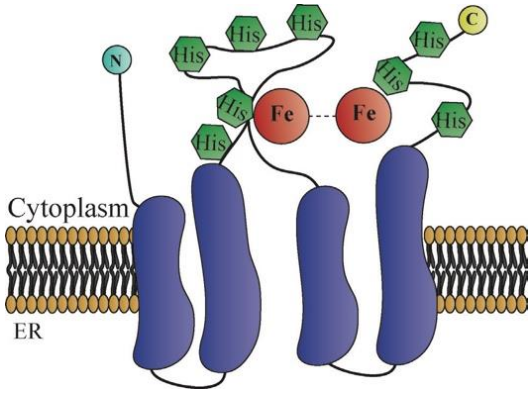

Figure 1: SCD1 is an iron-containing enzyme that has four transmembrane domains with both its N- and C-terminus located in the cytoplasm.[2]

SCD1 has been extensively studied both *in vivo* and *in vitro* in order to understand the enzyme's role in cancer treatment, cardiac health, insulin resistance, hepatic steatosis, inflammation, and diet-induced obesity. Since lipid metabolism is essential for normal processes, SCD1 is believed to be integral in the homeostasis of every organ and organ system. The products of SCD1 have various uses in the body, from the formation of

phospholipids for cell proliferation, to the synthesis of triglycerides and cholesteryl esters.[5] MUFAs are substrates for the synthesis for energy storage, biological membrane, and signaling molecules. The ratio of saturated to unsaturated fatty acids is crucial for proper membrane fluidity and cell signaling imbalance and the expression of SCD1 can disturb this ratio, which is associated with diseases such as diabetes, cancer, etc.[3] The versatile nature of SCD1 has made the enzyme controversial in terms of inhibiting versus overexpressing. Pharmacological agents to both agonize this antagonize the enzyme have been researched for potential uses in cancer therapy, reversal of obesity, insulin resistance, etc. Unfortunately, there is little to no research on agents that specifically target SCD5 to inhibit or agonize the enzymes activity. There have been no studies to show the effects of inducing or inhibiting SCD5 in brain or pancreatic tissue. But, the question of whether the proposed use of pharmacological agents to either inhibit or stimulate SCD1 remains unanswered.

2.0 Antagonist-Cancer

Extensive research has indicated that SCD1 is overexpressed in metastatic cells. Cancer cells induce high levels of SCD1 production due to their need for MUFAs in membrane biosynthesis during cell replication. Hence, overexpressing SCD1 leads to more endogenous MUFA production. Tumor cells obtain most of their fatty acids (FA) from de novo lipogenesis. Therefore, SCD1 inhibition would result in an imbalance of FA composition in intracellular lipids which may lead to cell death through lipotoxicity and ER stress response.[6] Inhibition of SCD1 by siRNA or small molecule antagonists have shown to induce apoptosis and display growth delay in tumor cells.[7] SCD1 inhibited tumor spheroids show irregular cell growth, cellular damage, and cell apoptosis. Inhibition of SCD1 also targets cells with stem-cell-like properties making SCD1 a target for lung cancer-initiating cells.[8] ER stress, which is seen in SCD1 inhibited conditions, induces SREBP-lc and thus activates the transcription of SCD1.[9] This suggests the role of SCD1 in tumorigenesis via this protective mechanism.[9]

SCD1 transcription can be activated by LXR, SREBP-lc, dietary carbohydrates, etc.[9] Fibroblast Growth Factor Receptor 3 (FGFR3) controls cells cycle proliferation, differentiation, survival, etc. In cancer, FGFR3 regulates lipid metabolism to maintain tumor growth by activating SREBP-1c, which in turn induces the expression of SCD1.[10] SCD1 is a target for growth factors and hormones that regulate cell cycle events, emphasizing the importance of MUFAs in membrane biogenesis and cell replication.[11] Inhibition of SCD1 in cancer cells, specifically colon cancer cells, suppresses the SREBP signaling pathway which leads to the suppression of tumor growth and initiation through downregulating cellular lipid biosynthesis.[12] Inhibition of SCD1 in cancer also induces ceramide biosynthesis as a result of SFA accumulation, allowing for tumor cell apoptosis in cancers such as colorectal cancer.[13]

When cells become metastatic, they undergo epithelial to mesenchymal activation (EMT). This results in a loss of E-cadherin, a cell to cell adhesion molecule, which is known to interact with elements of adherent junctions such as β-catenin.[14] When E-cadherin is inhibited in cancer cells, β-catenin can translocate to the nucleus and activate the transcription of oncogenes, further promoting tumor growth and development. When SCD1 is inhibited in cancer cells, the β-catenin found in the nucleus decreases, E-cadherin reduction is reversed, and glycogen synthase kinase 3 (GSK3) activation is increased. This mechanism offers an explanation as to how SCD1 inhibition decreases the proliferation

rate of cancer cells.[14] In cancer, the Wnt signaling pathway is also highly activated which also leads to the translocation of β-catenin and the activation of hepatic stellate cells (HSC), which supports tumorigenesis by overexpressing SCD1 in the liver.[9]

The adjunctive treatment of cisplatin and SCD1 inhibitors in lung cancer cells has also been found to reverse the upregulation of cancer stem cell markers, inhibit spheroid formation, and induce cancer stem cell (CSC) apoptosis.[15] This points to SCD1 as being a potential target for cancer therapy. By understanding the mechanism by which SCD1 helps promote tumor growth, a pharmacological intervention to inhibit SCD1 in humans can be determined. A summary of these mechanisms can be seen in **Table 1**, as well as a schematic of the proposed pathways in **Figure 2**.

Table 1: Summary of potential tumor-producing mechanisms of SCD. Modified from.[9]

Effector/Pathway	**Potential Mechanisms**
Wnt	MUFA stabilizes LRP5/6 via HuR [36]
YAP/TAZ	Activates YAP/TAZ by inhibition of Hippo pathway through Rho activation [37]
AKT	Activates AKT via phosphatidylinositol generation, inhibits GSK3β and stabilize β-catenin [38,39]
AMPK	Inhibits AMPK and upregulates lipogenesis via ACC induction [40]
NF-κB	MUFA activates NF-κB which transcriptionally upregulates *SCD* [41]
EMT	Suppresses E-cadherin and induces vimentin [42]
Metabolic reprogramming	Links glycolysis to lipogenesis
ER stress	Provides cytoprotection against palmitic acid-induced ER stress [43]

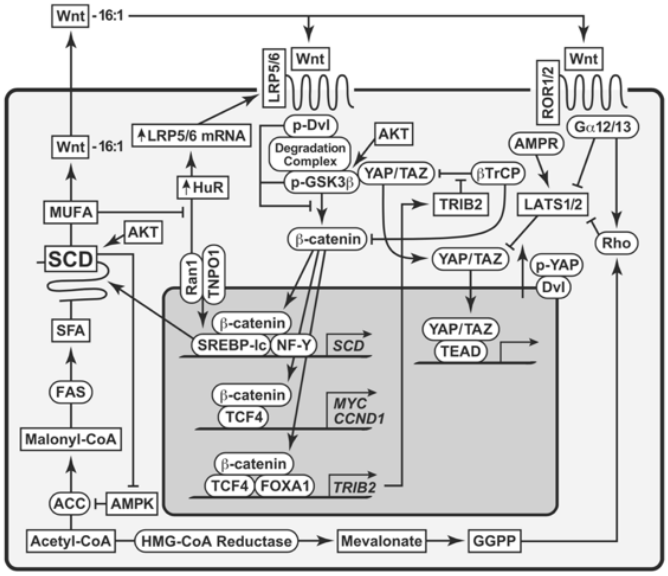

Figure 2: A visual representation how SCD establishes tumor-promoting pathways.[9]

2.1 Inhibitors of Scd1 in Cancer

Many antagonists have been synthesized to inhibit the expression of SCD1 in cancer cell models in order to test the possibility of SCD1 being a target for tumor growth suppression. Inhibitor A-939572 (aka A-37062) (**Figure 3**) was developed in 2008 by Abbott Laboratories. [16] Roongta and team tested this urea-based inhibitor which showed an IC50 value of 19nM against FaDu cells.[7] A5499 and H129 9 lung cancer cell lines were used in this experiment and A-939572 was found to be equally capable at suppressing desaturation *in vivo* and *in vitro*. This inhibitor showed moderate results in A5499 and very good results in H1299. It showed a correlation with SCD1 inhibition, induction of apoptosis, and growth inhibition in tumor cells. A-939572 was shown to cause sebaceous gland atrophy, but also was seen to be effective in inhibiting the growth of clear cell renal carcinoma.[17] Additionally, A-939572 showed an IC50 value of 30 nM towards inhibiting bladder cancer cell survival through the inhibition of MUFA production.[10] A-939572 caused side effects such as mucosal discharge from eyes, increased squinting, hair loss, and eye ptosis.[16]

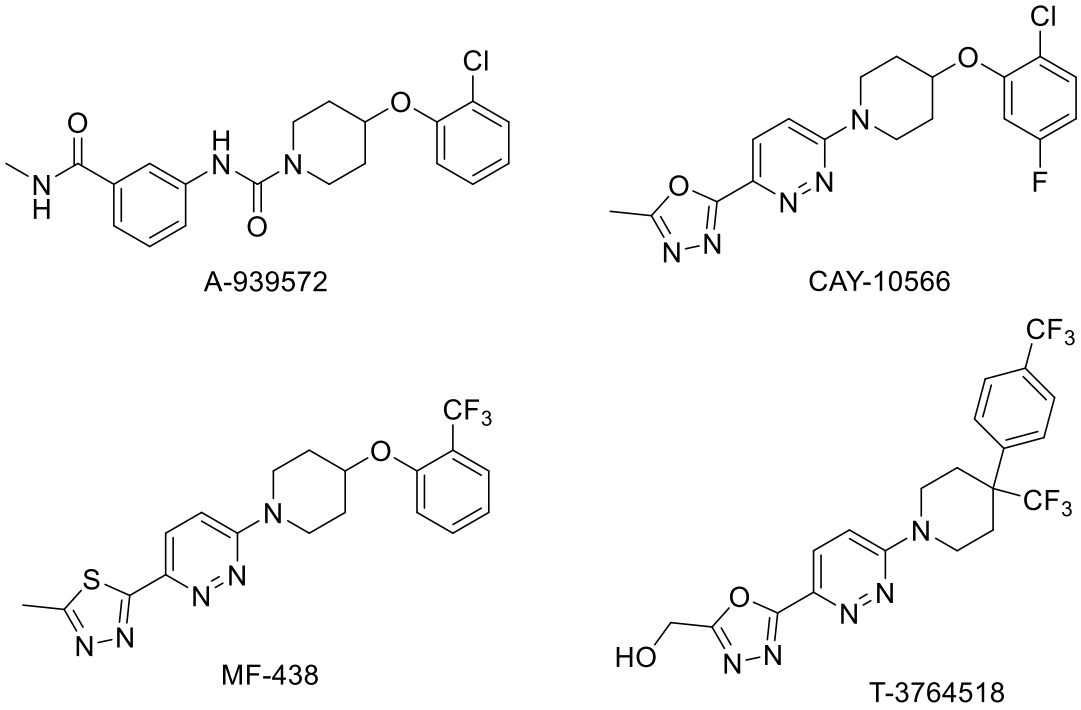

Figure 3: Structures of thiadiazole-pyridazine analog SCD1 inhibitor MF-438, oxadiazole- pyridazine based SCD1 inhibitor CAY-10566, oxadiazole-pyridazine based SCD1 antagonist T-3764518, and urea-based SCD1 inhibitor A-939572 (aka A-37062).[8, 12, 16, 17]

Noto and team showed that thiadiazole-pyridazine analog SCD1 inhibitor MF-438 (**Figure 3**) presented with an IC50 value of 2.3 nM when tested in MPEDCC and NCI-H460 lung cancer cell lines.[8] This inhibitor selectively killed cells that portrayed stem like properties, suggesting potential effectiveness for lung cancer tumor-initiating cells.[17] It was also observed that spheroids formed in the presence of MF-438 presented with reduced ALDH1A1 (aldehyde dehydrogenase 1A1) activity.[17] MF-438 caused mucosal discharge from eyes as well as an increase in squinting due to SCD1 inhibition.[16] Oxadiazole-

pyridazine based CAY-10566 (**Figure 3**) inhibited the growth of colon cancer cells in colon cancer cell lines.[12] It was also seen as effective in human hepatocellular carcinoma (HCC) by reducing cancer cell viability and also inducing apoptosis of HCC cells.[17] CAY-10566 was also found to inhibit proliferation of ovarian cancer stem cells and suppress the stemness of ovarian cancer cells.[16] Lastly, also an oxadiazole-pyridazine based antagonist, T-3764518 (**Figure 3**) showed an IC50 value of 4.7nM and caused tumor growth suppression without presenting severe toxicity when tested in HCT116 mouse xenograft models.[6] This antagonist inhibits the proliferation and causes apoptosis in colorectal and mesothelioma cancer cells while reducing toxicity in mouse models.[16] It was also seen to suppress tumor growth in a mouse xenograft of human renal adenocarcinoma.[16]

3.0 Antagonist- Liver Health, Obesity, Metabolism, Insulin Resistance, Skin Conditions

A high carbohydrate diet leads to increased SCD1 expression and triglyceride (TG) synthesis, and TG accumulation leads to increased fat storage. SCD1's nature to promote lipogenesis has been linked to cause hepatic steatosis, insulin resistance, fatty liver disease, obesity, and other metabolic diseases. Along with carbohydrates such as fructose, SCD1 expression is regulated by SREBP-lc, LXR, and PPARα (**Figure 4**), which are induced in response to dietary SFA. SFA such as stearate promotes SCD1 expression and is desaturated to oleate, and this MUFA induces lipogenesis which further increases SCD1 expression leading to obesity and increased fat storage. [5] This brings light to the fact that oleate and not stearate promotes fat accumulation.[5] In an experiment to see how the induction of SCD1 works, rats were fed high levels of fructose which increased the mRNA levels of SCD1, but when the fructose intake stopped, the induction of SCD1 did not drop leading to increased hepatic triglycerides and the promotion of hepatic steatosis and fatty liver disease.[18]

Inhibition of SCD1 has been shown to cause increased energy expenditure, reduced adiposity, increases metabolism, leanness, and insulin sensitivity. Reduced levels of triglycerides help with treating obesity, hepatic steatosis and other metabolic disorders.[19] For example, leptin is a hormone that helps to regular energy balance by suppressing hunger and decreasing the activity of SCD, and mice with increased leptin where found to be hypermetabolic and lean.[19] When SCD1 activity is inhibited, SFA accumulation increases, leading to decreased concentrations malonyl CoA. Malonyl CoA decreases fatty acid synthesis and increases fatty acid oxidation which in turn decreases overall adiposity.[19] SCD1 inhibition increases the genes of fatty acid oxidation (Cpt-1, Pgc-1α) triggered by SFA accumulation and causing decreases in SREBP-lc.[5] AMPK is promoted as white adipose tissue and glycogen levels decrease, giving protection from diet-induced obesity and other conditions.[5] SCD1 inhibition has also been recognized to be an option for alcohol fatty liver disease (AFLD) by counteracting the downward effects of ethanol consumption in mice.[20]

Increased expression of SCD1 has been known to cause insulin resistance among other issues like obesity. SCD1 controls glucose production in the liver, and when this enzyme is inhibited, SCD1 decreases the amount of glucose production. This leads to a drop in blood glucose levels. When glucose levels are decreased, insulin resistance can be resolved due to increased insulin sensitivity in the body.[21] Increased insulin sensitivity could also be due to an increase in Akt phosphorylation when SCD1 is inhibited.[21]

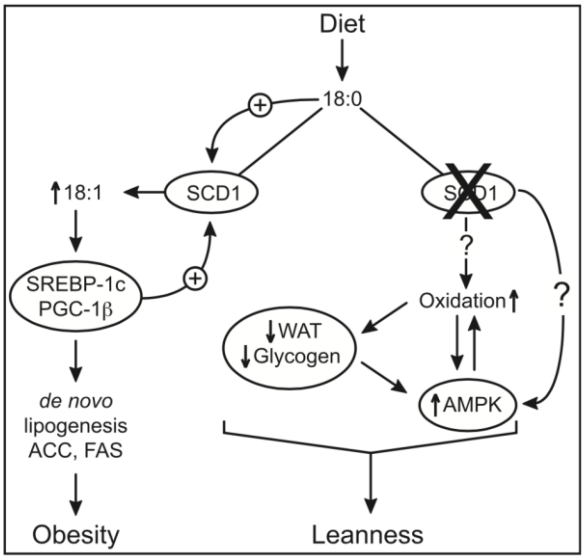

Figure 4: The role of SREBP-lc, LXR, and PPARα in the expression of SCD1.[5]

Although SCD1 inhibition reduced lipid accumulation by preventing overproduction of MUFAs and increased adiposity, SCD1 results in increased SFA accumulation which also has negative effects (**Figure 5**). SFA overproduction can cause hepatic inflammation, oxidative stress, and lipotoxicity which is usually taken care of by desaturating SFA into MUFA (**Figure 6**).[2] In some studies, increased SCD1 expression has related to an increase in inflammation and CRP (C-reactive protein).[22] When SCD1 is inhibited white adipocyte inflammation is shown to be prevented [23], but SFA concentrations are directly related to cellular inflammation and stress.[24] This emphasizes the idea that manipulating the expression of SCD1 must be tightly controlled because a change in the enzyme's expression has negative effects.[24] Inhibition of SCD1 can also cause sebaceous gland issues in the skin such as sebaceous gland atrophy, squinting of the eye, ulcerative dermatitis and more since SCD1 is expressed in the sebaceous gland and is critical for sebocyte development.[1]

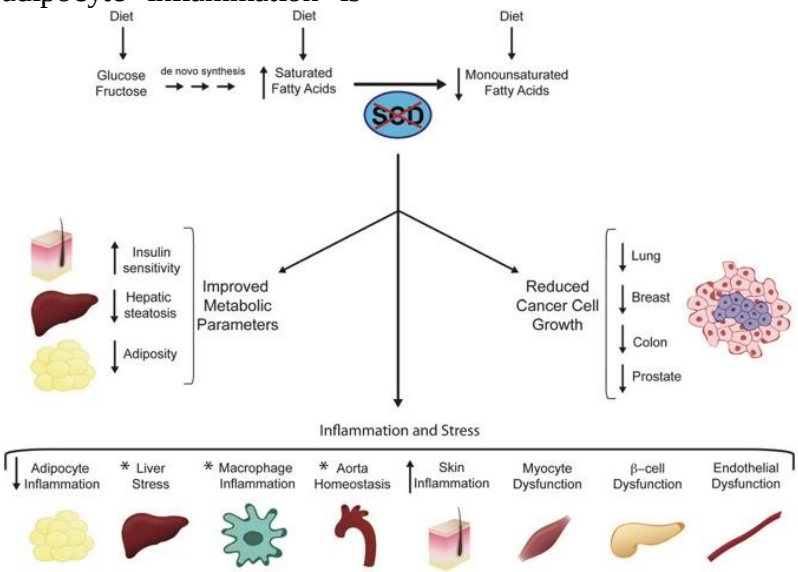

Figure 5: Outcomes of SCD1 inhibition, from a decrease in SFA production and accumulation.[24]

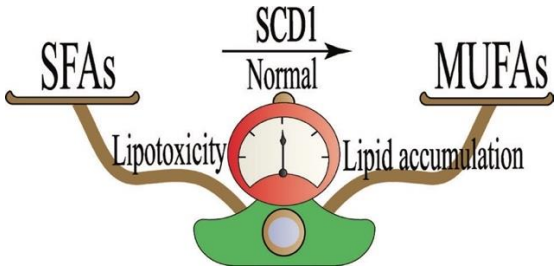

Figure 6: The role SCD1 plays in the balance of lipid accumulation from the prevention of liptoxicity.[2]

3.1 Inhibitors of Scd1- Liver

Inhibitors such as A-939572 have been used to antagonize SCD1 for liver disorders as well, but such inhibitors depleted the whole body of SCD1 resulting in various negative side effects such as skin disorders. As a result, liver specific SCD1 inhibitors have been developed to target hepatocytes and ameliorate diseases such as fatty liver disease. One such pyridazine-based inhibitor is MK-8245 (**Figure 7**) with an IC50 of 1nM developed by Merck Frosst.[17] This liver-specific SCD1 antagonist has shown to have antidiabetic and antidyslipidemic properties and is a potential agent to target diabetes, dyslipidemia, and HCV.[2] This inhibitor works to only interact with hepatocytes due to its transporting elements. MK-8245 is currently in phase II clinical trials.[2] Another inhibitor that works via a similar mechanism is a 4-hydroxy pyridine developed by Xenon and Novartis, referred to as Compound 6 (**Figure 7**).[17] This liver-specific inhibitor shows higher levels of exposure in the liver than other organs and does not display adverse effects of SCD1 inhibition.[17] This inhibitor is also a potential therapeutic agent for dyslipidemia and showed a good palmitoleic to palmitic acid ratio when administered in *in vivo* experiments.[2] A thiazole-4-acetic acid derivative known as compound 48 (**Figure 7**) was found to attenuate hepatic triglyceride accumulation by inhibiting SCD1.[2] This inhibitor led to improved glucose tolerance as well as decreased body weight while presenting without adverse skin effects.[2] This compound suggested to be beneficial to treat diabetes, hepatic steatosis, and obesity by targeting SCD1 activity in the liver when tested *in vivo*.[2]

A piperazine-based SCD1 inhibitor, N-(2-hydroxy-2- phenylethyl)-6-[4-(2 methylbenzoyl) piperidin-1-yl] pyridazine-3-carboxamide, developed by Daiichi Sankyo, known as Compound 7 (**Figure 7**), has shown to be effective in treating NASH (Non-alcoholic steatohepatitis).[2] This compound decreased triglyceride accumulation in the liver of NASH rats by 80% while reducing the increase of AST and ALT.[17] This inhibitor, with an IC50 of 15nM in humans [25], decreased hepatic steatosis, hepatocellular degeneration, and inflammatory cell infiltration when tested *in vivo*.[2] Lastly, inhibitor MF-152 (**Figure 7**) has displayed as an effective treatment for HCV (hepatitis C virus).[2] Inhibition of SCD1 reduces lipogenesis and changed membrane functions needed for HCV replication which are unfavorable for virus proliferation and therefore a potential treatment for HCV.[2] This enzymatic activity will prevent the formation of HCV complexes and halt the replication of HCV.[2] *In vitro* studies have shown success in decreasing HCV viral loads.[17]

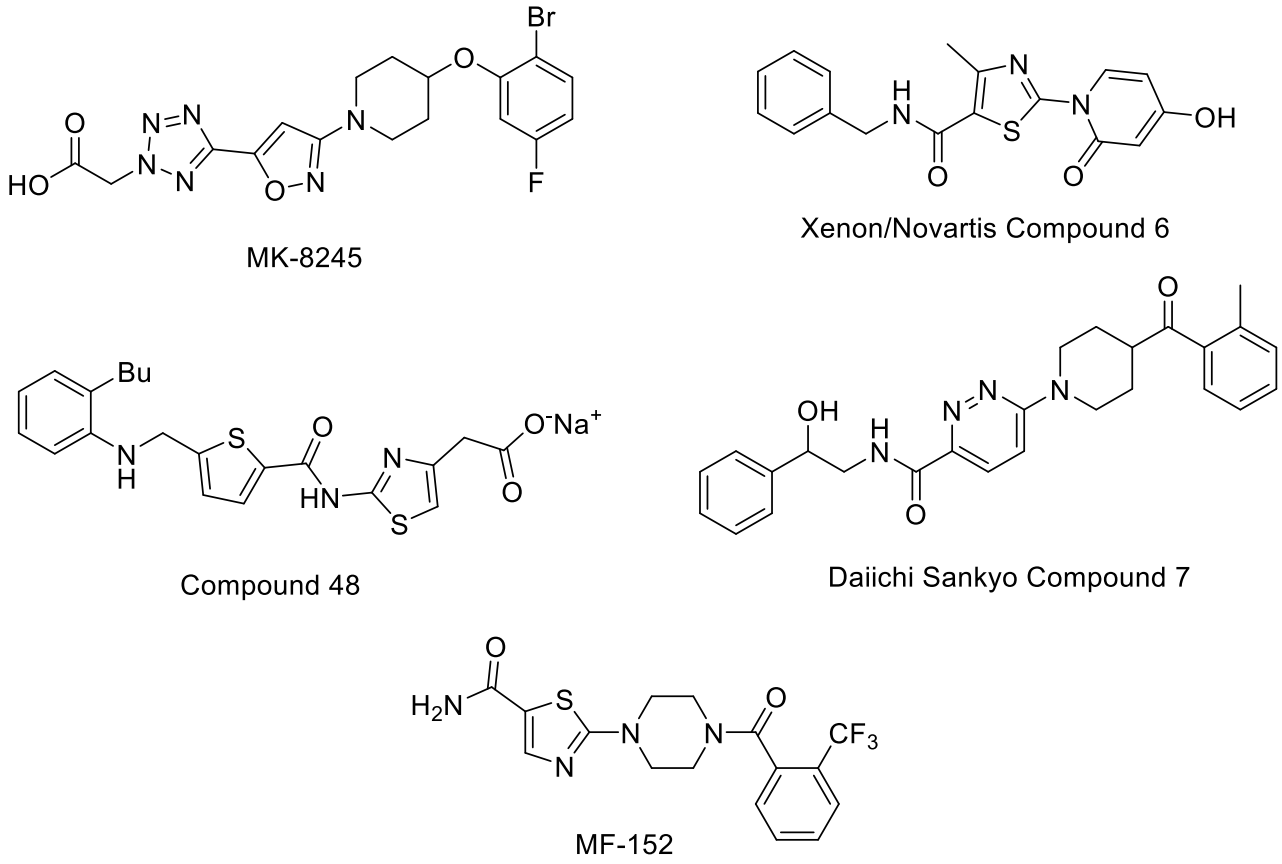

Figure 7: Structures of phenoxy piperidine isoxazole derivative MK-8245, 4-hydroxy pyridine derivative Compound 6, thiazole-4-acetic acid derivative Compound 48, piperazine-based derivative Compound 7, and thiadiazole derivative MF-152.[2, 17]

4.0 Agonist- Cardiac Health And Atherosclerosis

Similar to its effects in the liver, inhibition of SCD1 in the heart has shown affects such as decreased lipid content, reduced lipogenic proteins, decreased intracellular diacylglycerol (DAG), TG, and free fatty acid (FFA) levels in the myocardium.[26] Using small molecule antagonists, A-939572, and siRNA to inhibit SCD1 has also shown to decrease heart steatosis, FA transport, lipogenesis, ceramide synthesis, increase lipolysis, and improve left ventricle function as well as systolic/diastolic dysfunction.[27] Decreasing rates of ceramide synthesis has also been proven to decrease rates of apoptosis.[27] Lastly, SCD1 inhibition has shown to cause a shift in substrate utilization in the heart from FA uptake and oxidation to glucose oxidation which is useful to lipotoxic cardiomyopathy seen in diabetes and obesity.[28] Furthermore, SCD1 deficiency has repeatedly shown to have a negative effect on cardiac health due to increased inflammation and aortic atherosclerosis (**Figure 8**).[29]

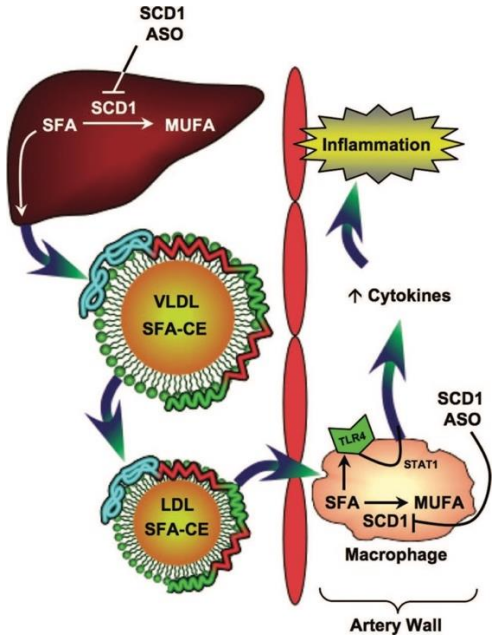

Figure 8: The role of SCD1 in the development of atherosclerosis and inflammation within vessel walls.[29]

SFA are proinflammatory molecules, and SCD1 leads to SFA accumulation. Dietary SFA's have shown to promote inflammation through the toll-like receptor-4 (TLR-4) immunological pathway, and when SCD1 in inhibited, TLR-4 have presented to be hypersensitive when agonized.[29] Increased SFA increases the expression of inflammatory genes and leads to atherosclerosis.[30] As a result, agonizing SCD1 has been researched to identify potential uses for treating atherosclerosis and inflammation. Nayaka and team tested the effects of overexpressing SCD1 in macrophages on reverse cholesterol transport (RCT) and found that this caused the production of normal and large sized HDL.[31] HDL therefore transforms into a better acceptor of cholesterol to efflux which increases the potential of cholesterol efflux, the first step of RCT.[31] This promotes RCT, giving off an overall anti-atherogenic affect through the overexpression of SCD1 by LXR agonists.[31] Another experiment found that inducing SCD1 inhibited atherosclerosis by preventing the formation of foam cells.[32] Foam cells and lipid accumulation are the first steps in the formation of atherosclerotic plaque, and SCD1 overexpression reduces vascular smooth muscle cells (VSMCs), the cells that foam cells are derived from.[33] Promoting RCT and macrophage conversion (M1 to M2), decreasing inflammation, increasing plasma HDL levels, promoting ABCA1 expression and transcription factor EB (TFEB) signaling are ways that SCD1 works to decrease development of atherosclerosis.[32, 33] Although SCD1 causes lipid accumulation, overexpression of SCD1 in cardiac myocytes prevents SFA-induced lipotoxic cardiomyopathy, SFA-induced FA oxidation, and SFA-induced apoptosis in cardiac myocytes.[30]

4.1 LXR Agonists

In order to overexpress SCD1, LXR agonists must be used. Activators of LXR induce SCD1 expression and activity. Sulfonamide based molecule T0901317 (**Figure 9**), with an EC50 value of ~50nM, is an LXR agonist that induces both SREBP-lc and SCD1 (T0901317: ≥99%(HPLC): Selleck: Liver X Receptor agonist, 65). This

agonist has also been shown to induce hepatic lipogenesis and secretion of very low-density lipoprotein receptor (VLDL). It has also been presented that the induction of SCD1 byT0901317 is mediated by LXRα, but not LXRβ.[34] The reduction of ER stress and atherosclerosis is seen when this molecule is used. T0-901317 also reduced the number of M1 macrophages, which are induced by high cholesterol by converting them to M2 macrophages in vivo and in vitro.[32] Lastly, LXR agonists reduce the number of foam cells by inducing RCT and macrophage conversion in atherosclerotic plaque.[32] Similarly, the synthetic tertiary amine-based LXR agonist GW3965 (**Figure 9**) also increases serum TG levels by inducing SCD1 activity. This molecule demonstrated that LXRs promote lipogenesis in vivo and in vitro.[34] GW3695 has demonstrated milder effects in terms of lipogenesis and TG accumulation when compared to T0-901317, but also induces LXR genes such as SREBP-lc.[35] This agonist has an EC50 value of 190 and 20 nM for LXRα and LXRβ in cell-free assays, respectively (GW3965 HCl: ≥99%(HPLC): Selleck: Liver X Receptor agonist).

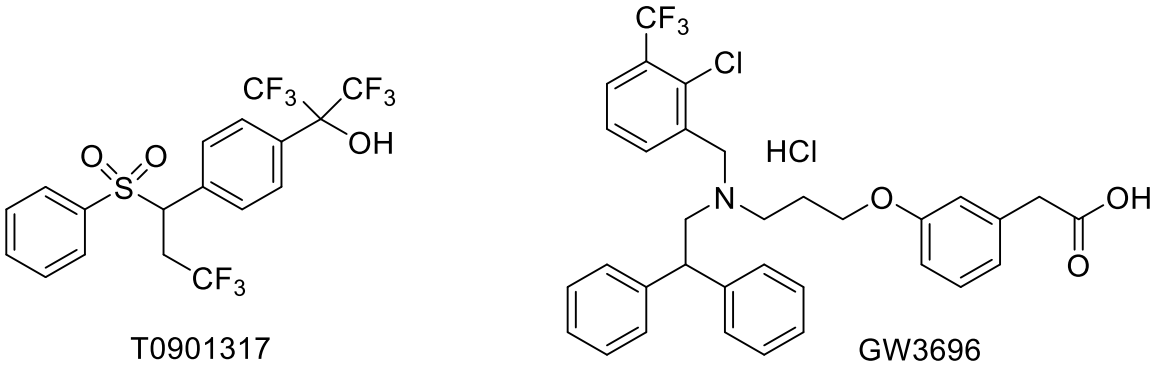

Figure 9: Structures LXR agonists, sulfonamide-based molecule T0901317, and synthetic tertiary amine-based GW3965.[32,34]

5.0 Conclusion

The versatile and ubiquitous nature of the enzyme SCD1 results in an intricate pro and con list for both agonizing and antagonizing its expression and activity. Intense research has indicated that SCD1 inhibition has shown promising results in terms of cancer and hepatic health. The development of multiple inhibitors has shown progression and hope for a future pharmacological therapeutic agent. But research has also pointed out the importance of overexpressing SCD1 to treat inflammation and atherosclerosis, as well as certain unfavorable effects of inhibiting SCD1 such as sebaceous gland atrophy and other skin disorders. This research points to the fact that it is critical to keep the whole picture in mind when agonizing and/or antagonizing SCD1. Further research and development of inhibitors and activators of SCD1 for the administration in specific organs, such as the inhibitors discussed that are liver-specific, have the potential to bring promising results to treat a variety of different disorders.

The research conducted on SCD1 has portrayed that pharmacological intervention on the enzyme has many implications, but not enough research on SCD5 has been done to make similar claims. More research on the isoform SCD5 is necessary to make further analyses and progressions towards treatments for various disorders. The similarities between SCD1 and SCD5 suggests that if proper and further research is done on SCD5, possible treatments for other or similar diseases is

plausible. With the first SCD1 inhibitor synthesized by Xenon Pharmaceuticals [44], and developed with the end goal of treating NASH, its most promising venture as of late seems to be in the area of cancer. The most profound trend was that of the adverse effects relating to the skin, as the variability from dry skin to atrophy can be quite unfavorable when attempting to implement it for a therapeutic use.

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Declaration of Competing Interest: The authors declare no conflict of interest.

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