Roles of Stearoyl-CoA Desaturase-1 in Hepatocellular Carcinoma

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Metabolic deregulation is emerging as an important molecular hallmark for cancer cells, which is accompanied with increased of glycolysis and lipogenesis that fuel the tumor growth [1]. During these processes, Stearoyl-CoA desaturase 1 (SCD1), a key enzyme in the lipogenesis pathway, has been recently drawn intensive attention in cancer research. SCD1, an enzyme that is located in the endoplasmic reticulum, is the major enzyme to catalyze the conversion of saturated fatty acid (SFA) to delta-9 MUFA [2,3]. In lipogenesis pathways, SCD1 works synergistically with other major lipogenic enzyme like fatty acid synthase (FAS), acetyl Co-A carboxylase (ACC) and ATP citrate lyase (ACL). All enzymes are directly related to another important transcription factor, SREBP. SREBP is considered to be one of the most important transcription factors in the lipid metabolism [4,5]. By upregulating the expression of SCD1, it enhances the rate of de novo synthesis of MUFA for synthesis of cell membrane to support rapid growth of cancer cells [2]. The major substrates for SCD1 are palmitoyl- and stearoyl-CoA. It also requires oxygen and NADH as coenzyme to convert the substrates to palmitoleoyl- and oleoyl-CoA [6]. SCD-/- mice are resistant to gain weight and do not induce SREBP-1c or increase lipogenic gene expression even when they were fed with high carbohydrate diet. Supplement with 5% oleate by weight in normal diet also cannot induce lipogenic gene expression and increase triacylglycerols (TG) level in plasma membrane. It implies that exogenous intake of MUFA is less accessible than the endogenous synthesized MUFA [6] in vivo and SCD1 may be the central hub for providing MUFA for the proliferation of cancer cells.

SCD1 was found to be upregulated in different types of cancer and play a major role in lung cancer [7], renal carcinoma [8], and breast cancer [9]. In normal tissues, SCD1 was found to be ubiquitously expressed in brain, liver, heart and lung [10]. Another isoform, SCD5, was also found in human but only has limited expression [10]. In hepatocellular carcinoma (HCC), SCD1 was found to be overexpressed in surgical resected HCC tissues, when compared with their adjacent normal counterparts [11]. Levels of monounsaturated palmitic acid, the product of SCD activity, were increased in aggressive HCCs [12]. SCD1 overexpression conferred chemoresistance and proliferation to HCC cells, through activation of phosphatidylinositol 3 kinase/c-Jun N-terminal kinases pathway [11]. In Akt- activated mice model, complete inhibition of SCD1 activity may be required to efficiently suppress liver tumor development [13]. SCD1 was also found to be one of the HCC signature proteins for HCC diagnosis and risk assessment [14].

SCD1 is also associated with other important signaling pathways which regulate the cell death and survival. Two pathways were found. The first pathway is the Akt pathway which is well known to enhance cell survival by inducing lipid synthesis and other metabolic pathways [3,15]. Knockdown of SCD1 can decrease the phosphorylation of Akt and subsequently decrease the lipogenic enzyme expression, including SREBP. Another pathway is the AMPK pathways. AMPK has opposite effect to Akt as it decreases the expression of lipogenic genes and enhances fatty acid oxidation [3]. Overexpression of SCD1 can inhibit the phosphorylation of AMPK and decreases its activity. Ablation of SCD1 has shown to increase the cell apoptosis via different mechanisms. One of the hypothesis is that the imbalance of SFA and MUFA in cell membrane may trigger the ER stress and ultimately leads to the unfold protein response (UPR), either through the IRE1α or PERK pathways. Since both pathways can sense the imbalance of SFA to MUFA [16] in ER membrane lipid composition. Furthermore, the accumulation of SFA in the cells is known to be lipotoxic. The detailed mechanism of lipotoxicity is not fully understood yet but in nerve cells, it was found that over accumulation of SFA may increase the ROS level, mitochondrial membrane permeabilization and activation of caspase activation [17]. As a result, knockdown of SCD1 may also lead to cell death by over accumulation of SFA.

From above studies on SCD1, it is shown that this enzyme might play a critical role in maintaining cancer cell growth and survival. Interestingly, in senescent fibroblast, SCD1 is dramatically reduced [18] while in other robust growth cells like various types of cancer, SCD1 is upregulated. SCD1 seems to be a potential therapeutic target to suppress tumor growth, metastasis, and even tumor-initiating cells [7]. As HCC is frequently associated with deregulation of lipogenesis, investigation into the use of small molecule inhibitors against SCD1 or in combination with other drugs as a potential therapeutic regimen may be of great value to improve the clinical outcome of this disease.

References


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