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Editorial

Targeting Tumor Initiating Cells through Inhibition of Stearoyl Co-A Desaturase

Mark Kin Fai Ma[1,2] , Irene Oi Lin Ng[1,2] and Terence Kin-Wah Lee[1,2,*]

[1]State Key Laboratory for Liver Research, University of Hong Kong, Hong Kong

[2]Department of Pathology, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong

***Corresponding author:** Dr. Terence KW Lee, Department of Pathology, University of Hong Kong, Room 704, 7/F, Faculty of Medicine Building, 21 Sassoon Road, Hong Kong, Tel: 852 3917-9390; Fax: 2819-5375; Email: tkwlee@hku.hk

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Editorial

Alteration of cancer metabolism is one of the major hallmarks in cancer progression. It has been extensively studied in various cancer models and demonstrated that targeting cancer metabolic pathways can effectively suppress the tumor progression [1]. However, various cancer recurrence rate is still high after the treatments according to National Cancer Institute statistics in 2015 [2]. It prompts us to think that some of the cells can still survive under the "metabolic attack" and serve as a "source" to differentiate and reconstitute back to the tumor bulk. These subpopulations of cells are believed to be Tumor Initiating Cells (T-ICs). T-ICs possess the characteristics of normal stem cells like self-renewal ability and they are able to differentiate to a specific cell lineage [3-5]. Their metabolomics pattern might be different from those differentiated lineage and hence they can survive under the cancer metabolism interference treatments. As a result, if we can identify those crucial metabolic pathways in T-ICs population, we can target the T-ICs population specifically by using small molecules inhibitors. Together with the present available treatments, the clinical outcome and the patient survival time would be greatly improved.

Stearoyl Co A Desaturase – A Potential Therapeutic Target for T-ICs

Stearoyl Co-A desaturase 1 (SCD1) is a key metabolic enzyme in the lipogenesis pathways. The major function of this enzyme is to convert Saturated Fatty Acid (SFA) to Mono-Unsaturated Fatty Acid (MUFA) [6]. MUFA formed by this ER membrane bound enzyme can be used for energy storage, cell signalings as well as the formation of cell membrane to maintain the cell integrity [7]. It works synergistically with other lipogenesis enzymes including Fatty Acid Synthase (FAS), ATP Citrate Lyase (ACL) and Acetyl Co-A Carboxylase (ACC) [7]. Interestingly, SCD1 was found to be mostly upregulated among these lipogenesis enzymes in various types of cancers including lung [8], renal [9], liver [10] and breast cancer [11]. Suppression of SCD1 can effectively inhibit cell proliferation, enhance apoptosis and sensitize cancer cells toward chemotherapeutic drug treatments [10].This may due to the alteration of lipogenesis as well as intracellular signaling such as Akt and AMPK pathways [8, 12]. More recently, SCD1was found to play crucial role in the maintenance and survival of T-ICs. Noto et al., has demonstrated that knock down of SCD1 in lung carcinoma suppressed the self-renewal ability, as evidenced by the decrease in sphere forming ability upon SCD1 inhibition [8]. In addition, SCD1 small molecule inhibitor (MF-438) can selectively kill cells with expression of ALDH1A1, a T-IC marker for lung carcinoma [8]. Consistently, spheroids formed from SCD1 depleted cells strongly attenuated the ability to form tumor *in vivo*. Lastly, they showed that T-ICs are 100 folds more sensitized to SCD1 inhibitor, when compared with their differentiated counterparts [8]. It has been hypothesized that the imbalance of SFA to MUFA on ER membrane may enhance the ER stress and subsequently activate the Unfold Protein Response (UPR) pathway [13]. CHOP and XBP are two major genes which are expressed in the UPR. Expression of CHOP may lead to cell autophagy or apoptosis [14]. Another recent study in line with this finding is that targeting SCD1 can be used as a specific and unique way to eliminate Human Pluripotent Stem Cells (HPSCS) in stem cells therapy [15].This study is crucial as it potentially reduces the risk of teratoma formation after transplantation of undifferentiated stem cells in patients. Using high throughput screening of 52,448 small molecules against HPSCS, a small molecule that appeared at the top list is SCD1 inhibitor [15]. Although HPSCS are different form T-ICs, they share many common characteristics of stem cells. Further analysis of the downstream pathways after inhibition of SCD1 also revealed that the level of CHOP and spliced XBP1 in the UPR pathway are upregulated, which is coherent with the hypothesis that ablation of SCD1 may enhance ER stress and activate the UPR in the cells [15].

In conclusion, SCD1 in lipogenesis pathway has been shown to be critical in maintaining cancer cell proliferation, survival and conferring chemoresistance [10]. Recent studies have suggested the role of SCD1 in maintaining the survival of T-ICs. Since SCD1 may be preferentially expressed in T-ICs, targeting T-ICs using SCD1 small molecule inhibitor may be an attractive therapeutic strategy against cancers. However, further characterization of SCD1 in T-ICs is needed before future clinical application in cancer patients.

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