Stearoyl Co-A Desaturase 1 as a ccRCC Therapeutic Target: Death by Stress

Janet Y. Leung and William Y. Kim

There is a need for the discovery of novel therapeutic strategies to effectively treat advanced clear cell renal cell carcinoma (ccRCC). Inhibition of stearoyl-coA desaturase 1 (SCD1) in ccRCC reveals antitumor activity, independently and in synergy with mTOR inhibition. SCD1 may be a potential novel therapeutic target in treating ccRCC. Clin Cancer Res; 19(12); 3111–3. ©2013 AACR.

In a recent issue of Clinical Cancer Research, von Roemeling and colleagues report that inhibition of aberrant stearoyl-coA desaturase 1 (SCD1) expression attenuates cell proliferation and induces apoptosis in clear cell renal cell carcinoma (ccRCC) cells via the induction of endoplasmic reticulum stress response signaling (1). These observations implicate SCD1 as a potential therapeutic target.

The process of lipid biosynthesis is essential for metabolic energy, regulation of cell signaling, and the formation of new membranes and organelles during cell proliferation and growth. A fundamental step in lipid synthesis is the production of saturated fatty acids (SFA), which subsequently are converted to monounsaturated fatty acids (MUFA), the major fatty acid constituents in cell lipids (2). Catalytic enzymes central to this regulation of fatty acid composition are the SCDs, also known as fatty acyl-CoA delta-9 desaturases (3). The human genome contains 2 homologs of SCD (SCD1 and SCD5), among which SCD1 is the best characterized in humans.

Many cancer cells are characterized by a high rate of aerobic glycolysis resulting in an abundance of pyruvate, which generates citrate upon entry into the tricarboxylic acid (TCA) cycle. Citrate, through its sequential activation by adenosine triphosphate citrate lyase, acetyl-CoA carboxylase, and fatty acid synthase, can serve as a building block for the de novo synthesis of cellular lipids (Fig. 1; ref. 2). Although the main products of glucose-derived fatty acid synthesis are SFAs, an abundance of MUFAs is also found in cancer cells and tissues, implicating an essential role for synthesis of cellular lipids (Fig. 1; ref. 2).

To establish the underlying mechanism responsible for the decreased proliferation and induction of cell death associated with loss of SCD1 activity, the gene expression changes induced by A939572 treatment were assessed. Pathway analysis revealed increased expression of genes associated with endoplasmic reticulum stress and unfolded protein response (UPR), a cellular response that occurs in reaction to the buildup of misfolded and unfolded proteins in the endoplasmic reticulum (4). von Roemeling and colleagues found that mRNA expression of a number of endoplasmic reticulum stress markers [BiP, CHOP, HERPUD1, GADD45, CDBP] were indeed upregulated in ccRCC cell lines treated with A939572. Moreover, ATF6, a central mediator of the UPR stress response, was also found to be activated upon inhibition of SCD1 activity (Fig. 1; ref. 4). Importantly, knockdown of ATF6 using shRNAs blocked the induction of endoplasmic reticulum stress
response genes in response to A939572 and rescued the phenotypes induced by A939572 treatment. These observations show that SCD1’s regulation of proliferation and apoptosis is dependent upon the initiation of endoplasmic reticulum stress and the UPR.

The clinical significance and potential application of the work by von Roemeling and colleagues is most evident by the reductive carboxylation of glutamine in a glutaminase and isocitrate dehydrogenase 1–dependent manner (10). Therefore, whether glutaminase inhibition when combined with SCD1 and mTOR inhibition leads to further therapeutic gains should be explored. In summary, the observations by von Roemeling and colleagues underscore the notion that cancer cells have altered metabolic demands that can be therapeutically targeted. In addition, their findings highlight the increased recognition that tumor cells, in contrast to nontransformed cells, are dependent upon de novo fatty acid synthesis (rather than exogenous fatty acids) for maintenance of cellular homeostasis (2).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: W.Y. Kim, J.Y. Leung
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