Stearoyl-CoA desaturase 1 is a novel molecular therapeutic target for clear cell renal cell carcinoma

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ABSTRACT

Purpose: Identify SCD1 as a novel molecular target in clear cell renal cell carcinoma (ccRCC) and examine its role in tumor growth and viability in vitro and in vivo independently as well as in combination with FDA approved regimens.

Experimental Design: Patient normal and ccRCC tissue samples and cell lines were examined for SCD expression. Models of genetic knockdown and targeted inhibition of SCD through use of a small molecular inhibitor, A939572, were analyzed for growth, apoptosis, and alterations in gene expression using gene array analysis. A therapeutic model of synergy was evaluated by combining A939572 with an mTOR inhibitor, temsirolimus.

Results: Our studies identify increased SCD1 expression in all stages of ccRCC. Both genetic knockdown and pharmacologic inhibition of SCD decreased tumor cell proliferation and induced apoptosis in vitro and in vivo. Further analysis of A939572 treated or SCD1 lentiviral knockdown samples demonstrated induction of endoplasmic reticulum (ER) stress response signaling, providing mechanistic insight for SCD1 activity in ccRCC. Furthermore, combinatorial application of A939572 with temsirolimus synergistically inhibited tumor growth in vitro and in vivo.

Conclusions: Increased SCD1 expression supports ccRCC viability and therefore we propose it as a novel molecular target for therapy either independently or in combination with an mTOR inhibitor for patients whose disease cannot be remedied with surgical intervention, such as in cases of advanced or metastatic disease.

BACKGROUND

• Renal cell carcinoma (RCC) is the third most prevalent urological cancer, the 10th most common cancer in men and the 9th most common cancer in women.
• clear cell carcinoma (ccRCC) is the most common subtype of RCC accounting for ~48% of all renal cancers.
• Standard of care for patients presenting with localized ccRCC is partial or whole nephrectomy, however ~30% of these patients go on to develop metastatic ccRCC.
• For individuals presenting with advanced disease, treatment options are limited with no cancer drug therapy leading to long term survival with the exception of 6-7% of patients who respond to interferon-2a.
• Currently there are very few hallmark genetic features which are known to contribute to ccRCC development and proliferation which can be specifically targeted as an anti-tumor treatment strategy.
• Our group has identified that SCD1 is overexpressed in ccRCC at all stages of disease.
• SCD1 is an anti-convulsing enzyme belonging to the family of fatty acyl desaturases, whose role is to catalyze the biosynthesis of all monoenoic fatty acids (MFA), oleic and palmitoleic acid, from the saturated fatty acids (SFA) stearic and palmitic acid. It is a critical enzyme in the fatty acid metabolism pathway and is a rate limiting step in MUFA synthesis.
• MUFA’s are involved in many biological processes and are a major component of biological structures such as membranes, and can also function as or modify signaling molecules. This suggests a potential higher need for them in dynamic or rapidly dividing cells such as cancer cells.

CONCLUSIONS

• SCD1 is frequently overexpressed in ccRCC, and may serve as a biomarker to identify patients who are appropriate candidates for anti-tumor therapy.
• Inhibition of SCD1 both genetically and pharmacologically abrogates tumor cell growth, induces apoptosis, and promotes ER stress both in vitro and in vivo.
• Anti-tumor activity is mediated by the ER stress response, and therefore ER stress factors can serve as biomarkers for response to anti-SI1 therapy.
• The SCD1 inhibitor A939572 when combined with the mTOR inhibitor temsirolimus yields strong anti-tumor synergy in vitro and in vivo, providing a novel multi-targeting strategy which should be investigated for ccRCC patients presenting with advanced or metastatic disease.

FUTURE DIRECTIONS

Current Literature: SCD1 converts SFA into MUFA and therefore inhibition of SCD1 likely leads to an increase in RA content in cells. Current literature suggests that increased exposure of cells to SFAA corresponds to an accumulation of SCA content in membrane structures, altering the morphology and decreasing membrane fluidity (5). This may compromise the integrity as well as the functionality of the membranes, including those of the ER, leading to a stress response (5). Deactivation of fatty acids is thought to counter these effects, and is protective against SFA mediated stress (5, 6, 7).

Future Directions: Identify molecular mechanisms regulating SCD1 expression in ccRCC in order to assess the role of SCD1 in ccRCC initiation, development, and progression. Identify how loss of SCD1 mediates the ER stress response (cloned) in order to understand the mechanism by which SCD1 is repressed.

The preclinical data shown here strongly supports the investigation of an SCD inhibitor alone or in combination with an mTOR inhibitor in a phase I clinical trial for patients with advanced or metastatic ccRCC.

REFERENCES

