Metabolic and Immune Reprogramming via SCD1 Inhibition Enhances Chemo-Immunotherapy Response in TNBC

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BACKGROUND

Deregulated cellular energetics is a known hallmark of cancer. Stearoyl-CoA desaturase-1 (*SCD1*), is a key enzyme in fatty acid (FA) synthesis, converting saturated to monounsaturated FA. It is upregulated in TNBC, and its expression correlates with poor survival. Hence, targeting *SCD1* is a novel strategy for cancer therapy. We have developed an *SCD1* inhibitor, MTI-301 and shown anti-tumor activity in murine TNBC cell lines with MTI-301 alone and in combination with paclitaxel. Here, we study the efficacy of MTI-301 in TNBC mouse model and, molecular and immunological association of *SCD1* in TNBC.

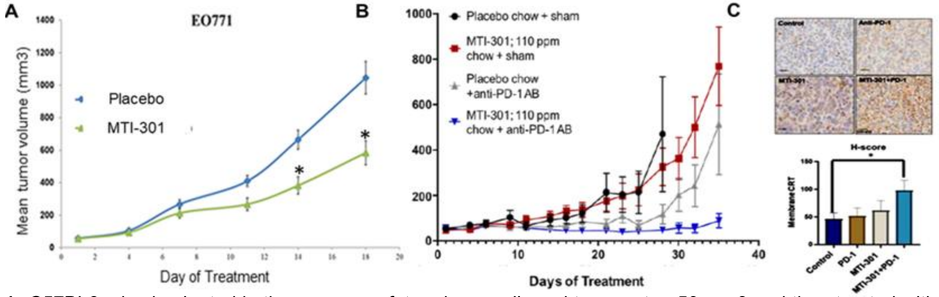
METHODS

- MTI-301 activity (10 mg/kg oral gavage daily) was evaluated in E0771 immunocompetent TNBC mouse models alone and with immune checkpoint inhibitors (ICI) Ab 200ug/mouse).
- Molecular and immune characterization was performed in 1,581 invasive ductal (ID) TNBC patient (*SCD1*-high(H) (n=791) and *SCD1*-low(L) (n=790) samples tested by NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ).
- *SCD1*-H and *SCD1*-L RNA expression were classified as above or below the 50 percentiles, respectively.
- Immune markers such as CD4+ T cell and CD8+ T cell in mice tumor tissue were assessed by immunohistochemistry (IHC) or deconvolution of WTS: quanTIseq.
- Statistical significance was determined using chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons (q < 0.05).

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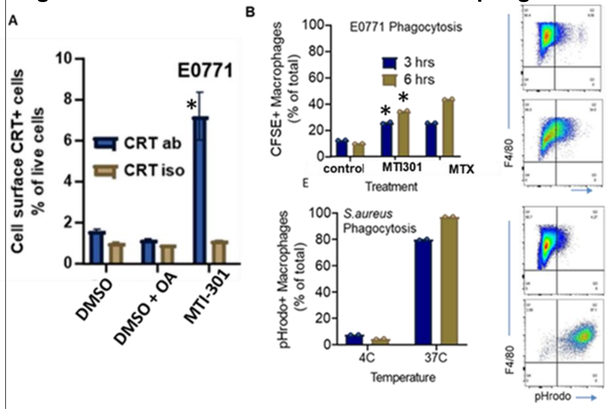
RESULTS

Figure 1. In vivo anti-tumor activity of MTI-301



A. C57BL6 mice implanted in the mammary fat pad were allowed to grow to ~50 mm3 and then treated with 1) vehicle control (MTI-301 diluent) and 2) MTI-301 (10mg/kg daily; oral) to demonstrate single agent antitumor activity. Tumor volume (length x width x height/0.523 = mm3. is measured with calipers twice weekly. B. C57BL6 mice implanted in the mammary fat pad were treated with 1) vehicle control (MTI-301 diluent +Isotype control mAb close 2A3 2) MTI-301 (10mg/kg daily 3) Anti-PD-1 Ab (100 ug; clone RMP1-14; 2x weekly) or MTI-301 +Anti-PD-1 Ab. Antitumor synergy of MTI-301 +Anti-PD-1 Ab was observed with durable response. C. E0771 tumors (75-100mm3 were treated with MTI-301 +Anti-PD1 Ab demonstrated significant upregulation of membrane CRT (by IHC). * p ≤ 0.05

Figure 2. MTI-301 is associated with Macrophage induced phagocytosis



A. MTI-301 (100nM) was incubated with E0771 cells with 0.5 mg/ml oleic acid. MTI-301 induced calreticulin translocation (CRT) to the cell membrane as measured by flow cytometry (CRT antibody; control CRT isoantibody). Oleic acid, the MUFA end product of *SCD1* blocks CRT translocation in the MTI-301 presence, indicative of the role of *SCD1* in CRT translocation B. E0771 cells treated with MTI-301 and co-incubated with macrophages induced phagocytosis using flow cytometry and F4/80 for mouse macrophages. The positive *S. Aureus* control is shown validating the assay. * p≤ 0.05

Figure 3. Immune cell infiltration in *SCD1-H* and *SCD1-L* TNBC

	SCD1-L	*SCD1*-H
B cell	4.03	3.78 *
DC	3.1	3.11
MΦ M1	3	3.52 *
MΦ M2	2.58	2.95 *
Neutrophil	4.1	4.5 *
NK cell	2.87	2.93
T cell CD8+	0.63	0.5
Tregs	1.83	1.9

Low Median% **High Median%**

SCD1-H had higher immune cell infiltration of M1 MΦ M2 MΦ and neutrophils, but lower B cell compared to *SCD1*-L Median% of monocytes and T cells CD4+ were 0.0 in both the groups ***q<0.05.**

Figure 4. Differential gene expression

Metabolic regulator

	SCD1-L	*SCD1*-H
PTPN22	6.37	9.82
DUSP6	26.03	45.00
PRKAA2	0.71	1.26
HIF1A	124.82	214.14
IL10	0.90	1.38
IL10RA	14.40	19.65
SOCS3	5.15	7.24

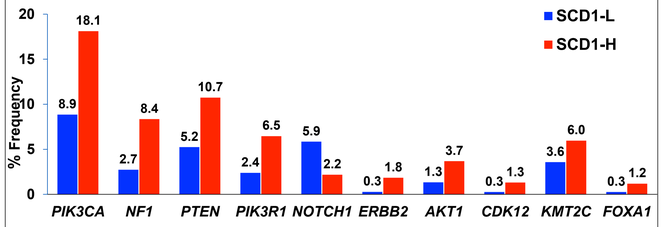
Exhausted T cells

	SCD1-L	*SCD1*-H
CXCL13	2.81	4.76
ENTPD1	11.59	17.15
CD101	1.06	1.47
CD38	2.56	3.53
CD69	2.47	3.28
ITGAE	7.19	11.13
KLRG1	1.39	1.72
GZMB	3.52	5.48
PRF1	1.06	1.54

Low Median **High Median**

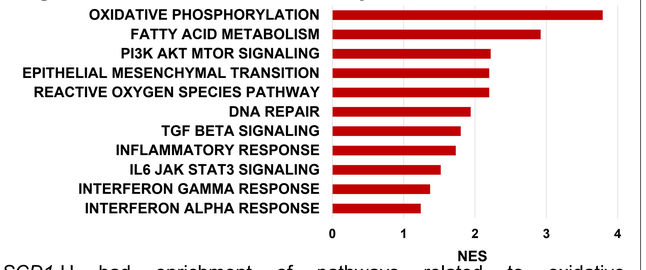
SCD1-H had higher levels of metabolic regulator (*IL10, IL10RA, SOCS3, HIF1A, DUSP6*, FC: 1.4-1.8) and markers of exhausted T cells (*CXCL13, CD38, CD101, ENTPD1, CD69, CD103, KLRG1, PRF1, GZMB*, FC: 1.2-1.7) genes, **all q<0.05.**

Figure 5. Mutation analysis of *SCD1* high vs low TNBC



SCD1-H had higher frequency of *PIK3CA, NF1, PTEN, PIK3R1, ERBB2, AKT1, CDK12, KMT2C and FOXA1* mutation compared to *SCD1*-L, **all q<0.05**

Figure . Gene set enrichment analysis



SCD1-H had enrichment of pathways related to oxidative phosphorylation, FA metabolism, *PI3K/AKT/MTOR*, EMT, DNA repair, *TGF* beta, P53 and inflammatory response (NES: 1.7-3.8, **all FDR<0.25).**

CONCLUSIONS

SCD1 high TNBC tumors are associated with immune suppressive TME, FA metabolism, and dysregulated PI3K pathway, positioning *SCD1* as a metabolic driver of therapy resistance and immune evasion and support its targeting to enhance chemo-ICI efficacy. *SCD1* inhibitor, MTI-301 significantly reduced tumor growth and enhanced effector immune cell infiltration in TNBC murine models with combinatorial activity with ICI, indicating that pharmacologic modulation of *SCD1* is a promising strategy for cancer therapy.