Found 4 Records

FINAL ID: RF3

TITLE: Benzofuran-Isatin Conjugate (5d) Presents Anticancer Activities in vitro Associated with Cyclin, Apoptotic Proteins, p53, EMT Alterations, and Enhances Chemosensitivity in Human Colorectal Cancer Cell Lines

ABSTRACT BODY:

Purpose/Background: Colorectal cancer (CRC) is one of the most common malignant tumors in the global health problem due to its high prevalence and mortality rate. New anticancer agents are needed to treat advanced stage CRC and prevent cancer metastasis, the primary cause of morbidity and mortality. A novel synthesized benzofuran-isatin conjugate (3-methyl-N'-(2-oxoindolin-3-ylidene) benzofuran-2-carbohydrazide) named as 5d has recently shown potent anticancer effect in vitro on human colon adenocarcinoma HT29 and metastatic CRC (mCRC) SW620 cell lines. However, the mechanism underlying the anticancer activities remain unknown.

Methods/Interventions: Cytotoxicity was evaluated using MTT assay. The real-time cell proliferation, migration and invasion were measured by xCelligence RTDP instrument. Flow cytometry was used for cell cycle analysis and apoptotic status determination. Western blotting technology was employed to assess cyclins, tumor suppressor p53, apoptosis and epithelial-mesenchymal transition (EMT) marker protein expression levels.

Results/Outcomes: The anticancer activities of the compound 5d were revealed by the inhibition of HT29 and SW620 cell proliferation, migration, invasion, and colony formation in a dose-dependent manner, compared with the untreated control cells. Both cell line exposure to the compound 5d resulted in a cell cycle arrest at the subG1 phase, indicator of apoptotic status, and a downregulation of cyclin A1, B1 and D1 expression was monitored in the compound 5d-treated cells. Furthermore, compound 5d-induced apoptosis was associated with the downregulation of the anti-apoptotic Bcl-xl marker, upregulation of pro-apoptotic Bax, p53 and cytochrome c markers, and increased mitochondrial outer membrane permeability, suggesting the involvement of mitochondria-dependent apoptosis pathway. The compound 5d also inhibited the colony formation ability of HT29 and SW620 cells and reversed EMT markers E-cadherin and N-cadherin expression. In addition, the combination studies of the compound 5d with the main conventional chemotherapeutic drugs 5-fluorouracil, irinotecan, and oxaliplatin showed a more potent cytotoxic effect in both CRC cells compared to a single treatment. Of note, the compound 5d exhibited stronger anticancer effects on mCRC SW620 cells than on colon adenocarcinoma HT29 cells.

Conclusions/Discussion: Our findings described the interesting in vitro anticancer properties of the compound 5d, shown to have possible antitumor, antimetastatic, and pro-apoptotic activities, with the enhancement of the cytotoxic efficiency of conventional chemotherapeutic drugs. In vivo studies are requested to confirm the promising anticancer potential of the compound 5d for CRC therapy.

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FINAL ID: RF4

TITLE: LYRM1 Predicts Non-responders to Radiation in Rectal Cancer Patients

ABSTRACT BODY:

Purpose/Background: Neoadjuvant chemoradiation therapy (nCRT) is recommended for locally advanced rectal cancer. Patients with poor response have worse outcomes and potentially do not benefit from current treatment paradigms. Accurately identifying poor responders before treatment could avoid ineffective nCRT and favor proceeding directly to surgery or other treatment options. We sought to find such markers and identified the gene LYRM1 as a predictive biomarker for radiation non-responders in rectal cancer.

Methods/Interventions: We previously conducted mRNA microarrays for pretreatment rectal cancer biopsies from patients who underwent long course nCRT and then surgery. LYRM1 gene expression was identified as a potential target from that analysis. We then validated LYRM1 gene expression by RT-qPCR from these samples and analyzed them against the treatment response according to AJCC pathology regression scores. LYRM1 gene expression was measured in different colorectal cancer cell lines and quantified through RT-qPCR and correlated with radiobiological indexes IC50 (dose in Gray to kill 50% of cells), D10 (dose in Gray to obtain 10% cell survival), and SF2 (surviving cell fraction after 2 Gy of irradiation), obtained using a clonogenic survival assay.

Results/Outcomes: Using an initial cohort of 33 patients on microarray analysis, LYRM1 gene expression was consistently elevated in patients with no response to nCRT (AJCC 3) compared to patients with a complete or partial response (AJCC 0-1-2); ($p=0.0064$). Receiver operating characteristic (ROC) analysis revealed that LYRM1 expression level had an AUC of 0.8132 ($p=0.0121$), indicating a strong predictive power for identifying non-responders. LYMR1 expression in individual patients was validated in a cohort of 21 patients, demonstrating significant overexpression in patients with a AJCC 3 response compared to all others (AJCC 0-1-2); ($p<0.0001$); [Figure 1A]. The validation cohort ROC revealed LYRM1 expression had an AUC of 1.000 ($p=0.0067$), confirming LYRM1 as a strong predictor of non-responders. LYRM1 expression varied across 9 colorectal cancer cell lines and levels directly correlated with radiosensitivity indexes D10 ($p=0.0004$), SF2 ($p=0.0011$) and IC50 ($p<0.0001$) [Figure 1B].

Conclusions/Discussion: LYRM1 expression is a predictive biomarker for rectal cancer patients who are non-responders to neoadjuvant radiation. Further work is needed to validate this in larger populations, to determine the biological mechanisms through which it works, and to assess its potential as a druggable target.

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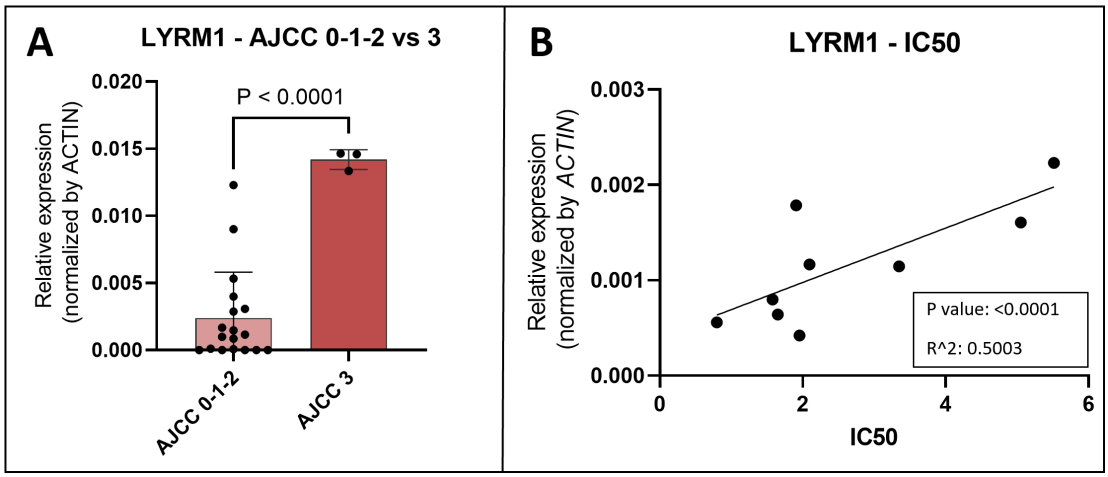

Figure 1: LYRM1 relative gene expression in (A) rectal cancer patients according to AJCC response score, and (B) in colorectal cancer cell lines with associated radiation sensitivity measured by IC50.

IMAGE CAPTION: Figure 1: LYRM1 relative gene expression in (A) rectal cancer patients according to AJCC response score, and (B) in colorectal cancer cell lines with associated radiation sensitivity measured by IC50.

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FINAL ID: RF2

TITLE: Angiogenin-1 Regulates Intestinal Carcinogenesis Induced by Targeted Deletion of Apc in Lgr5+ Stem Cells

ABSTRACT BODY:

Purpose/Background: Angiogenin-1 (Ang1) is a 14-kDa ribonuclease that was the first tumor-derived angiogenesis protein. The role of Ang1 on the development of Apc-mediated colorectal cancer has not been well studied.

Methods/Interventions: Experiments utilized Apc conditional knock-out mice ((Apc$^{fl/fl}$;Lgr5 $^{eGFP\text{-}CreER/+}$), an inducible intestinal cancer mouse model using tamoxifen-dependent Cre recombinase to block the expression of Apc in Lgr5^{+}-expressing intestinal stem cells. Apc$^{fl/fl}$;Lgr5 $^{eGFP\text{-}CreER/+}$ mice were crossed with Ang1 knock-out mice, a whole-body homozygous knockout strain, to create Apc$^{fl/fl}$;Lgr5 $^{eGFP\text{-}CreER/+}$ mice that do not express Ang1. Apc $^{fl/fl}$;Lgr5 $^{eGFP\text{-}CreER/+}$ mice on both a wild-type (WT, n=8) and Ang1-KO (n=9) background were then injected with tamoxifen (75mg/kg, I.P.) to activate Cre recombinase. Three weeks after injection of tamoxifen, a mouse colonoscopy was performed using a Karl Storz Coloview miniendoscopic system. Small bowel (SB) and colon tissue was evaluated macroscopically and by immunohistochemistry.

Results/Outcomes: On macroscopic evaluation, WT mice developed significantly more tumors in the distal SB (367 tumors in 8 mice) compared to Ang1-KO mice (10 tumors in 9 mice), mean=45.88 (WT) vs 1.25 (Ang1-KO), P<0.05. Similarly, in the colon WT mice developed significantly more tumors (25 tumors in 8 mice) compared to Ang1-KO mice (14 tumors in 9 mice), mean=3.13 (WT) vs 1.56 (Ang1-KO), p<0.05. This difference in Apc-mediated tumor number was confirmed histologically in both SB [mean=32.25 (WT) vs 8.50 (KO), p<0.05] and colon [mean= 7.00 (WT) vs 0.6 (KO), p<0.05]. WT mice also developed significantly larger tumors in the distal SB [microscopic tumors <0.5mm: mean 15.5 (WT) vs 7 (KO), p<0.05; 0.5-1mm tumors: 8.4 tumors (WT) vs 1.5 (Ang1-KO), p<0.05; tumors >1mm: mean 8.2 tumors (WT) vs 0 (KO), p<0.05] and colon [large (3+ crypts): 3 tumors (WT) vs. 0 (Ang1-KO), p<0.05).

Conclusions/Discussion: In a mouse model of intestinal carcinogenesis induced by targeted deletion of Apc in Lgr5^{+} stem cells, Ang1-KO mice developed significantly fewer and smaller tumors compared to WT mice in both the small intestine and the colon. Ang1 appears to regulate both Apc-mediated tumor initiation and progression and may play an important role in intestinal carcinogenesis.

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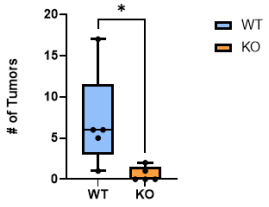
Colon Tumors (IHC)



Small Bowel Tumors (IHC)

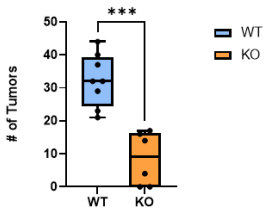


IMAGE CAPTION:

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FINAL ID: RF1

TITLE: FDXR is a Predictive Biomarker of Radiation Resistance in Rectal Cancer

ABSTRACT BODY:

Purpose/Background: Neoadjuvant chemoradiation therapy (nCRT) is recommended for locally advanced rectal cancer. Response to radiation is highly variable and correlates with oncologic outcomes. There are currently limited biomarkers or molecular targets to predict or improve radiation response, which could help develop personalized treatment and ideally targeted therapies. We identified the gene FDXR coding the adrenodoxin reductase, a protein involved in electron transport of mitochondrial P450 system, as a potential biomarker of radioresistance.

Methods/Interventions: FDXR gene expression was evaluated in a publicly available database (GSE87211) comparing levels in healthy and rectal cancer patients. mRNA was obtained from pretreatment rectal cancer biopsies from patients who then underwent long course nCRT and surgery. FDXR gene expression was measured from these samples and analyzed against the treatment response according to AJCC pathology tumor regression scores (TRS). FDXR gene expression was measured in a panel of colorectal cancer cell lines by RT-qPCR and correlated with radiobiological indexes IC50 (dose in Gray to kill 50% of cells), D10 (dose in Gray to obtain 10% cell survival), and SF2 (surviving cell fraction after 2 Gy of irradiation), obtained using a clonogenic survival assay.

Results/Outcomes: FDXR gene was significantly overexpressed in rectal tumors compared to healthy tissues in Gaedcke cohort of 243 patients (GSE87211; $p<0.0001$) [Figure 1A]. In our rectal cancer patient cohort, FDXR gene expression was consistently elevated in TRS 2-3 (poor responders) compared to TRS 0-1 (good responders) ($p=0.0003$) [Figure 1B]. Receiver operating characteristic analysis revealed that FDXR expression level had an AUC of 0.8577 ($p=0.0006$), indicating a strong predictive power for identifying responders from poor responders. FDXR expression was found to vary across 9 colorectal cancer cell lines. Importantly, FDXR expression positively correlated to multiple radiosensitivity indexes IC50 ($p<0.0001$), SF2 ($p=0.0001$) and D10 ($p<0.0001$) [Figure 1C].

Conclusions/Discussion: FDXR gene expression is a predictive biomarker for rectal cancer radiation sensitivity. Further work is needed to validate this in larger populations, and to determine the biological mechanisms through which it works and assess its potential as a druggable target.

(no table selected)

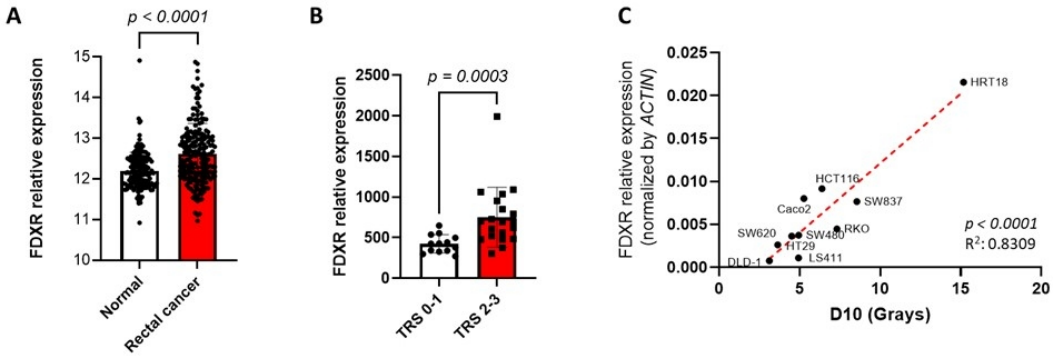
A
p < 0.0001
FDXR relative expression
15
14
13
12
11
10
Normal
Rectal cancer
B
p = 0.0003
FDXR relative expression
2500
2000
1500
1000
500
0
TRS 0-1
TRS 2-3
C
FDXR relative expression (normalized by ACTIN)
0.025
0.020
0.015
0.010
0.005
0.000
HRT18
HCT116
SW837
Caco2
SW620
SW480
RKO
HT29
LS411
DLD-1
p < 0.0001
R2: 0.8309
0
5
10
15
20
D10 (Grays)

IMAGE CAPTION:

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