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#6989 Novel Metformin Analogues for Treatment of Pancreatic Cancer

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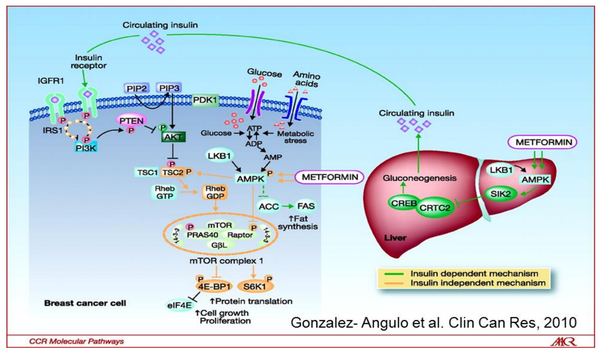
Background

- Pancreatic ductal adenocarcinoma (PDCA) is one of the leading causes of cancer death in the US.
- PDCA is generally presented in an advanced stage with poor prognosis and limited treatment options.
- Diabetes mellitus (DM) and chronic pancreatitis are well known to be associated with pancreatic cancer, and the development of PDCA.
- Metformin is widely prescribed worldwide as a first-line therapy for DM type 2.
- Recent clinical trials report on modest antiproliferative effects from the use of neoadjuvant metformin in several malignancies but no significant clinical benefit occurred when metformin was dosed at glycemic control levels in patients with advanced cancers.
- These findings suggest that development of more potent and less toxic anticancer metformin analogues with antitumor activity at lower doses *in vivo* may potentially help boost clinical benefit and patient survival.

Mechanisms of Action of Metformin



- Metformin lowers blood glucose and reduces hyperinsulinemia associated with insulin resistance.
- Epidemiologic reports show that patients with DM-type 2 treated with metformin, but not other antidiabetic drugs, have a reduced risk of PDCA and an increased survival rate among those with PDCA.
- Metformin stimulates AMP-activated protein kinase (AMPK) and inhibits mTORC1 signaling regulating cell growth.

Results 1

Metformin analogues are more effective than metformin at inhibiting cell proliferation of PDCA cells in vitro

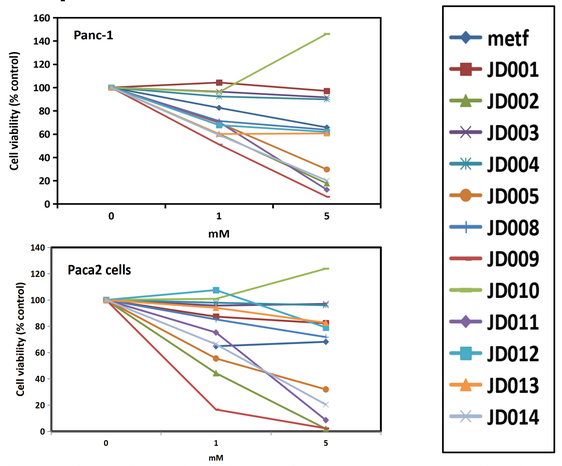


Fig.1 Selected metformin analogues are more effective at inhibiting cell proliferation of PDCA cells than metformin. Cell viability assays (Panc 1, MIA Paca-2) were treated with metformin or analogues at 1 and 5 mM concentrations. After 72 hours cell viability was assessed by manual cell counts and with an MTS cell assay. P< 0.001, n > 3.

Results 2

Selected analogues of metformin induce AMPK phosphorylation and stimulate apoptosis

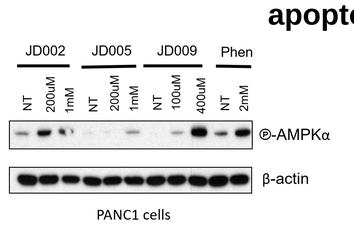


Figure 2. Selected analogues activate AMPK. PANC1 cells were treated with 0.2 and 1 mM JD002 and JD005, 0.1 and 0.4 mM JD009, and 0.2mM phenformin (Phen) as positive control. After 18 h cell lysates were probed with anti-phospho-AMPKα (Thr172). Total protein levels of AMPK were unchanged after 18 h treatment (not shown), Actin was used as loading control. Blot is representative of at least 3 experiments. Analogues JD002 and JD005 also inhibited mTOR downstream signaling (data not shown).

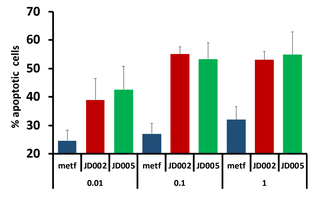


Figure 3. Metformin analogues are more effective than metformin at inducing apoptosis. PANC1 cells were treated with 0.01, 0.1 and 1 mM concentrations of metformin and analogues JD002 and JD005. After 48 h cells were harvested and stained with Annexin V and PI. Graph shows average of early and late apoptosis of at least 3 experiments P<0.05.

Results 3

Metformin analogues are more effective at reducing oxygen consumption than metformin

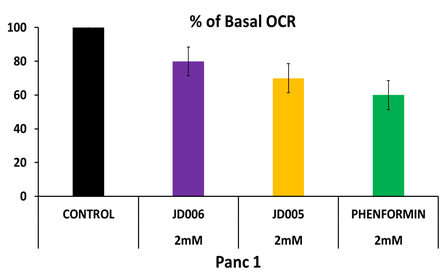


Figure 4. Metformin analogues decrease oxygen consumption rate more effectively than parental metformin. Panc1 cells were incubated in the presence of metformin control, analogues JD005, JD006 and phenformin. Oxygen consumption rate was measured using a Seahorse XF analyzer. % of basal OCR is expressed as percentage of metformin as 100%.

Metformin analogues inhibit Panc-1 xenografts *in vivo*

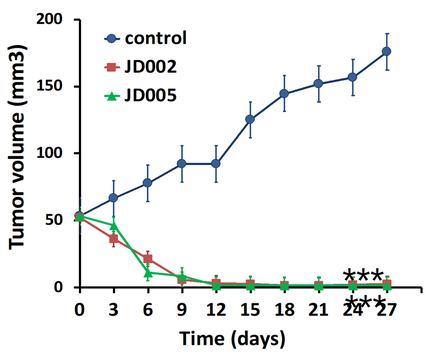


Figure 5. Metformin analogues show significant inhibition of human Panc-1 xenograft progression. Panc-1 subcutaneous xenografts were used with 5 mice/group. Metformin (250 mg/kg), analogue JD002 (50 mg/kg), analogue JD005 (50 mg/kg) or control were given Qd by oral gavage after tumors were 50-75 mm^3. Antitumor effects of analogues exceeded those of metformin or controls (***P<0.001). Of note, mouse body weights were not significantly different from controls in the analogue group, suggesting little toxicity *in vivo*.

Summary

- **Selected metformin analogues are more effective than metformin at inhibiting cell proliferation and inducing apoptosis of Panc-1 cells compared to parenteral metformin.**
- **Metformin analogues induce AMP kinase (AMPK) activation.**
- **New metformin analogues inhibit mTORC1 downstream signaling and induce cell death.**
- **Selected metformin analogues have potent anticancer activity in preclinical *in vivo* PDCA models, and may have promise as new targeted therapeutics for patients afflicted with this deadly disease.**
- **New orally-bioavailable, targeted and less toxic therapies to improve TNBC patient survival may be developed for use in the clinic.**

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