cryoablation of residual tumor was 19.5 month, without – 14.1 month ($p < 0.05$), after bypass surgery – 8.6 month ($p < 0.05$). Mortality and morbidity respectively were 9.1 and 36.4%, 11.1% and 41.7%, and 2.6 and 15.8% ($p < 0.05$). Although the bypass-group recovered quicker, reaching pre-operative QoL levels after 3 months, a patients who underwent palliative PD had better QoL than patients who underwent bypass-surgery after 6 and 12 month after operation.

Conclusions: These results show the beneficial effect of palliative PD on survival and QoL, and the efficacy of cryoablation of residual tumors for survival and QoL was proved, despite of morbidity and mortality rates in the PD groups were elevated. Therefore, palliative PD for patients with advanced pancreatic cancer should be attempted especially with using cryotechnology.

JAK-2 Downregulation Sensitizes Pancreatic Cancer Cells to TRAIL Induced Cell Death

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Introduction: TRAIL is emerging as a novel therapy against multiple cancers. Unfortunately, pancreatic cancer is resistant to TRAIL. Elucidating strategies to overcome this resistance would lead to development of novel therapies against this difficult to treat disease. JAK-2/STAT-3 is a pro-survival pathway which is up-regulated in a variety of cancers. In the current study we have evaluated the role of JAK-2/STAT-3 pathway in the resistance to TRAIL mediated apoptosis.

Methods: Highly aggressive pancreatic cancer cell lines (S2013, S2VP10) were treated with JAK-2 inhibitors FLLL-31, TRAIL or a combination of JAK-2 inhibition and TRAIL. The effect on viability (MTT) and parameters of apoptosis (annexin V, caspase 3, 8 and 9 activation) was measured. We also evaluated the effect of the combination of JAK-2 and TRAIL on levels of multiple anti-apoptotic proteins including Bcl-2 family of anti-apoptotic proteins. Furthermore, the effect of the combination treatment on formation of Death Inducing Signaling Complex (DISC), which is the key event in TRAIL induced cell death, was measured and compared with that without JAK-2 downregulation.

Results: Even though TRAIL in itself was ineffective in inducing cell death in pancreatic cancer cells, combination of TRAIL and JAK2 inhibitor FLLL-31 induced marked decreased in viability. Combination of TRAIL and FLLL-31 also markedly increased annexin positivity as well as caspase 3, 9, and 8 activation when compared to TRAIL or FLLL-31 alone. JAK-2 inhibition alone or in combination with TRAIL did not decrease levels of anti-apoptotic proteins but did increase formation of DISC complex.

Conclusion: Inhibition of JAK-2 pathway sensitizes pancreatic cancer cells to TRAIL induced apoptosis and cell death through increased formation of DISC complex. Combination of JAK-2 inhibition and TRAIL could emerge as novel therapeutic strategy against pancreatic cancer.

Lipolysis of Unsaturated Triglycerides Worsens Acute Pancreatitis (AP) Outcomes in a Model Mimicking Human Disease

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Background and Aims: We recently showed intrapancreatic fat worsens outcomes of AP via unsaturated fatty acid (UFA) mediated lipotoxicity (*Sci Transl Med.* 2011 Nov 2;3(107):107ra110). The current studies were designed to test whether lipolysis of unsaturated triglyceride affects outcomes in AP. **Methods:** the triglyceride glyceryl tri linoleate (GTL) alone or with the lipase inhibitor orlistat (GTLO) were injected into the pancreatic ducts of Wistar rats. The saturated fatty acid palmitic acid (PA) or the UFA linoleate were injected separately at fatty acid concentrations found in human necrosectomy samples. Caerulein pancreatitis was induced with a single (20mcg/kg) intraperitoneal injection. Serum amylase, lipase, BUN, pancreatic necrosis, lung and renal injury, apoptosis were measured histologically. Mortality was compared between the groups. A p value < 0.05 was taken as significant.

Results: While serum amylase increased similarly on day 1 (3–13 fold above normal) in all groups with AP, linoleate induced significantly more necrosis than PA (12.9±4.7% vs. 2.3±0.6%, $p=0.035$) or caerulein. The GTLO group had significantly reduced serum lipase (90% reduction vs. GTL) suggesting

lipase inhibition by orlistat. GTL resulted in severe hemorrhagic pancreatitis (80–100% necrosis), with multisystem organ failure (renal, lung injury) and 100% mortality in one day. 100% of animals with GTLO survived till 5 days with normalization of amylase, BUN and significant prevention of local and systemic injury. Caerulein caused no systemic injury.

Conclusions: Lipolytic generation of UFAs from triglycerides induces pancreatic necrosis, multisystem organ failure and mortality. Unlike caerulein, the UFA induced organ failure, early serum amylase increase unrelated to AP severity mimic human disease. Prevention of UFA induced adverse outcomes may be a therapeutic option to consider in acute pancreatitis.

Molecular Basis for the Interplay of Apoptosis and Proliferation Mediated by Bcl-xL:Bim Interactions

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Introduction: A major mechanism through which cancer cells avoid apoptosis is by promoting the association of anti-apoptotic members of the pro-survival Bcl-2 proteins with BH₃ domain-only proteins.

Methods: We applied structural analysis and computational modeling of the inter-residue interactions at the Bcl-xL:Bim protein-protein interface to predict and experimentally verify the effect of various Bcl-xL single-point mutants (position A142) on binding to Bim and the effect on apoptosis and proliferation in pancreatic cancer cells. To mimic the effect of the mutants we screened a library of phytochemicals and applied the compounds that computer modeling designated to prevent Bcl-xL-Bim binding. We also measured changes in metabolic pathways.

Results: We could increase proliferation of MIAPaCa-2 cells without an effect on apoptosis by either overexpression of wild-type (wt) Bcl-xL or with a mutant A142S that increased its binding to Bim. In addition, we could prevent the effect on proliferation by introducing Bim siRNA. The mutants A142N, A142Q, and A142Y decreased binding of Bim to Bcl-xL. This effect was associated with an increase in apoptosis and a corresponding decrease in proliferation (compared to Bcl-xL wt). Computational modeling revealed that rottlerin will mimic mutants' effect. Rottlerin prevented Bim binding to Bcl-xL and induced apoptosis and proliferation inhibition at sub-micromolar concentrations. Rottlerin and mutants regulated fatty acid and deoxyribose synthesis.

Conclusion: These results show a novel role played by the Bcl-xL:Bim interaction in regulating proliferation of pancreatic cancer cells. This study presents a physiologically relevant model of the Bcl-xL:Bim interface that can be used for rational therapeutic design for the inhibition of proliferation and resistance to apoptosis in cancer cells.

Pancreatic Cancer Cells in Hypoxia Enhance the Motility of Pancreatic Stellate Cells via Increased Secretion of Vascular Endothelial Growth Factor

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Introduction: Pancreatic cancer, a hypovascular tumor, thrives under hypoxic conditions. Pancreatic stellate cells (PSCs) promote pancreatic cancer cells progression by secreting soluble factors, but the effects of pancreatic cancer cells in hypoxia on PSCs are poorly understood. This study aimed to clarify the effects of pancreatic cancer cells under hypoxic conditions on PSCs.

Method: We prepared the supernatants of pancreatic cancer cells, SUIT-2, AsPC-1, CF-PAC1 and KP-2, both in hypoxia and normoxia. We investigated the migration, invasion and proliferation of PSCs using the supernatants in both conditions. To investigate the differences in expression profiles between hypoxic and normoxic pancreatic cancer cells, we performed real time qRT-PCR and western blotting.

Result: The supernatants of pancreatic cancer cells in hypoxia significantly increased the migration and invasion of PSCs, but showed no significant differences in proliferation of PSCs. All pancreatic cancer cells in hypoxia