**Diabetes: Series GSE53454**

-> Human islets exposed to cytokines IL-1β and IFN-γ

**GSM12938 \* Zahl**

* 05 bis 17: Control
  + 0, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 h
* 18 bis 28: Cytokine
  + 1, 2, 4, 12, 24, 36, 48, 60, 72, 84, 96 h

Eventuell rausnehmen:

* **GSM1293806: Control 12 h**
* **GSM1293821: Cytokine 24 h**

Human islets were isolated and exposed (or not) to IL-1β and IFN-γ. The samples were collected at various time points for profiling with Affymetrix arrays.

Process

The human pancreatic islets were isolated from the pancreas of brain-dead organ donors using collagenase digestion and Biocoll gradient centrifugation. After isolation the islets were pre-cultured free floating in Sterilin dishes for 3-5 days.

Following the initial culture period, islets were cultured for the indicated time points (1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120,132, 144 and 168 hours.) at 5.6 mM glucose RPMI-1640 containing 10% FCS and recombinant human IL-1β (25 units/ml) (PeproTech, London, U.K.) and IFN-γ (1,000 units/ml) (PeproTech) before being retrieved for RNA extraction and array analysis.

Extracted molecule: total RNA

Summary

In the context of T1 Diabetes, pro-inflammatory cytokines IL-1β and IFN-γ are known to contribute to β-cell apoptosis;  
The measurement of mRNA expression following β-cell exposure to these cytokines gives a picture of the changes in gene expression characterizing the path to β-cell dysfunction and death.

* Environment similar to the one observed in T1D induced apoptosis.

Sources: GEO database; Related papers (Marroqui et al., 2015) & (Lopes et al., 2014)

**General information: Type 1 Diabetes**

Type 1 diabetes (T1D) is an autoimmune disease caused by loss of pancreatic β cells via apoptosis while neighboring α cells are preserved.

Type 1 diabetes is caused by a person’s immune system attacking the cells in their pancreas that produce insulin. This eventually kills off so many of these cells—known as beta cells—that the pancreas is unable to make enough insulin. As a result, individuals with type 1 diabetes must inject insulin to help their bodies process sugars.

* Cause: combination of environmental and genetic factors

Related Papers

Differential cell autonomous responses determine the outcome of coxsackievirus infections in murine pancreatic α and β cells (Marroqui et al., 2015)

* Pancreatic α and β cells are neighboring endocrine cells with a common embryonic origin
* α-cells are spared from immune system: boost the expression of the genes needed to clear the virus to a greater extent than the beta cells, and so respond more efficiently to the virus.
* Infection is more likely to establish itself in the beta cells -> trigger inflammation and the immune system’s attack on the cells

Temporal profiling of cytokine-induced genes in pancreatic β-cells by meta-analysis and network inference (Lopes et al., 2014)

* Meta-analysis to identify a group of genes whose expression levels are consistently and strongly modified by cytokines on both human and rat datasets, before or after 24 h
* List of genes that are strongly regulated by cytokines
* Previously unknown genes in T1D: RIPK2 and ELF3

**Pancreas: Series GSE59761**

-> Capan-1 cells were transfected with control-siRNA or siRNA against human TBL1. RNA was isolated 24h later.

**GSM144617 \* Zahl**

* 1 bis 3: siRNA
  + 24 h
* 4 bis 6: Control-siRNA
  + 24 h

Process

Capan-1 cells were transfected with siRNA against human TBL1X using Lipofectamine 2000 (Invitrogen). RNA was isolated with the RNeasy Mini Kit.

* siRNA-mediated knockdown of TBL1X

Extracted molecule: total RNA

Summary

The transcriptional co-factor Transducin beta-like (TBL) 1 was over-expressed in both human and murine PDAC.

* Inactivation of TBL1 in human and mouse pancreatic cancer cells reduced cellular proliferation and enhanced chemosensitivity, correlating with diminished glucose uptake, glycolytic flux, and PI3kinase signaling.
* TBL1 deficiency both prevented and reversed pancreatic tumor growth in mice, triggering transcriptional PI3kinase inhibition also in vivo.
* As TBL1 mRNA levels were also found to correlate with overall and disease-free survival in a cohort of human PDAC patients and to predict therapy responsiveness in these subjects, TBL1 expression may serve both as a novel prognostic marker and molecular target in the treatment of human PDAC.

(Paper: Transcriptional co-factor Transducin beta-like (TBL) 1 acts as a checkpoint in pancreatic cancer malignancy)

Sources: GEO database, related paper (Stoy et al., 2015)

**General information: Pancreas**

Overview

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer fatalities in Western societies, characterized by high metastatic potential and resistance to chemotherapy. Critical molecular mechanisms of these phenotypical features still remain unknown, thus hampering the development of effective prognostic and therapeutic measures in PDAC (Stoy et al, 2015).

* > 200 000 death each year worldwide
* 5-year survival rate: 4 % (Stoy et al, 2015); 9 % (Hruban et al., 2019)
* At diagnosis: already metastasized in more than 80 % of the cases
* Main reason for fast progression: prominence of venous invasion in this disease, and rapid development of liver metastases (Hruban et al., 2019)

Molecular level

Main driver for tumor formation and progression: KRAS proto-oncogene

* Triggers downstream signaling pathways, including PI3 kinase
* PI3 kinase seems which seems to be responsible for the majority of KRAS-dependent pancreatic tumorigenesis

The four genes most commonly somatically mutated in pancreatic cancer are KRAS, p16/CDKN2A, TP53, and SMAD4 (Hruban et al., 2019) (Kleeff et al., 2016).

* Activating mutations: KRAS (> 90 % of tumors)
* Inactivating mutations: CDKN2A, TP53, and SMAD4 (50 – 80 %)

TBL1 transcriptional complex: an integrator of proliferative and metabolic pathways in pancreatic cancer (Stoy et al, 2015).

Diabetes

Most tumors: drastically increased uptake of glucose and/or glutamine (because of high proliferation of cell, they switch to glycolysis even in aerobic conditions to meet high demand of amino acids and nucleotides) (Stoy et al, 2015).

Diabetes mellitus: Risk factor and consequence (Kleeff et al., 2016).

* Stellate cells have been suggested to have a role in the new-onset diabetes mellitus (type 3c) of pancreatic cancer via their inhibition of β-cell function (Kleeff et al., 2016).

Treatment

Very few effective drugs have been identified (Kleeff et al., 2016):

* Gemcitabine: a nucleoside analogue (modest success)
* Erlotinib: a tyrosine kinase inhibitor of EGFR, in combination with gemcitabine (modest success)
* FOLFIRINOX: a combination of folinic acid (leucovorin), 5- fluorouracil, irinotecan and oxaliplatin (robust activity, but has toxicities)
* regimen of gemcitabine and albumin-bound paclitaxel (improved efficiency, but toxicities)
* chemoradiation for locally advanced, respectable disease