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Metallothionein and pancreatic inflammatory disease/proposed experiments

The underpinning hypothesis and basic observations:

Extracellular metallothionein (MT) that is made as a stress response protein by cells under stress can in some circumstances be released to the extracellular environment. Extracellular MT can act as an immune modulator, both by activating chemotactic responses, by inducing lymphoproliferation, and by modifying the cellular response to other immune modulators.

We have shown that a monoclonal anti-MT antibody can diminish the severity of several mouse models of diseases with an inflammatory component (e.g. IBD, T1D and APAP-induced liver injury, AILI)

1. Some relevant observations that connect MT with T1D
    a. MT is expressed in pancreatitis. Immunohistochemical localization of metallothionein in chronic pancreatitis Pancreas. 2004 Jul;29(1):28-32
    b. MT mRNA expression levels correlate with disease severity in both NOD mice and T1D humans. Gene expression profiles for the human pancreas and purified islets in type 1 diabetes: new findings at clinical onset and in long-standing diabetes. Planas R, Carrillo J, Sanchez A, de Villa MC, Nuñez F, Verdaguer J, James RF, Pujol-Borrell R, Vives-Pi M. , Europe PMC 19912253 and Regnault B, Osorio Y Fortea J, Miao D, Eisenbarth G et al. Early over expression of messenger RNA for multiple genes, including insulin, in the Pancreatic Lymph Nodes of NOD mice is associated with Islet Autoimmunity. BMC Med Genomics 2009 Oct 2;2:63. PMID: 19799787
    c. MT is found in pancreatic acini (but not islet) cells by immunohistochemistry and in pancreatic juice DOI: 10.1152/ajpcell.1996.271.4.C1103
    d. Anti-metallothionein antibody can block the progression of T1D and the associated inflammatory cell infiltration in the pancreas (unpublished)
    e. Note: there is also a secondary literature where MT is overexpressed or under-expressed in diabetes models, but this intervention alters both intracellular and extracellular MT levels and likely alters the housekeeping functions of intracellular MT. (ex: Cai L. Metallothionein as an adaptive protein prevents diabetes and its toxicity. Nonlinearity Biol Toxicol Med. 2004;2(2):89-103. doi:10.1080/15401420490464367 and https://doi.org/10.1152/ajpheart.00123.2019
2. Experimental questions that I would like to address
    a. Does the level of MT change in human pancreatic acini or in pancreatic juice as a function of disease onset or severity? Note that a 2 week interval of antibody treatment in NOD mice from 5-7 weeks of age (where inflammation is established but glucose dysregulation has not yet begun) was sufficient to eliminate glucose dysregulation for up to 30 weeks of age.
        i. Sample needs: pancreatic juice and histology sections from T1D and heathy controls to test by MT ELISA and MT immunohistochemistry.

   b. Are there differences in MT production levels (and hence, upstream regulatory regions) that differentiate T1D patients from normal controls
      i. Sample needs: T1D and healthy patient leukocytes for in vitro stimulation of the cells to Cadmium, LPS, IL-1 (or TNF-a) and hydrogen peroxide (individual dose response curves; harvesting supernatant and cells for MT ELISA quantitation).
   c. Are there differences in the SNPS associated with the MT gene cluster that differentiate T1D patients from normal controls (in humans, the MT gene cluster is on chromosome 16 NC_000016.10 (56608584..56609497))
      i. No sample needs; but I would need someone to teach me how to do this bioinformatic analysis

3. Other connections that I have initiated/hope to make
   a. NTNU connections
      i. arne.sandvik@ntnu.no I have had contact with him and he has invited me to let him know when I might be available to visit Trondheim
      ii. pal.romundstad@ntnu.no (dean that may have recently retired) who suggested NTNU faculty to contact
      iii. kristian.hveem@ntnu.no responded to my email inquiry and suggested that since he has a close collaboration with Pal, that it might be time to set up a workshop between groups. (Kristian Hveem is at the Jebsen center of Genetic Epidemiology, engaged in the Hunt study and the Hunt biobank),
      iv. Terje Espevik was suggested by Dean Romundstad, but no contact yet.
      v. trude.flo@ntnu.no Trude Helen Flo is co-director of a center of excellence - (Centre of Molecular Inflammation Research). She will visit UCONN to give a talk in late April.
      vi. I would like to visit NTNU, and the HUNT facility
   b. I'd like any contact suggestions you might have for the University of Oslo.
   c. I am giving a talk in the UiB department of immunology, and will explore connections with the department of Biological Sciences
   d. Any other suggestions for contacts to make while I am here are welcome!