

Metabolism-Protein



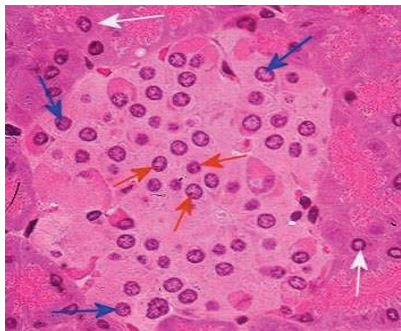
Jean-Charles Sanchez,
MER Proteomics

β -cell dysfunction

Whether insulin resistance or insulin secretion defects are primary events in the development of type 2 diabetes has been a highly debated topic and there is no consensus today. However, it is clear that overt type 2 diabetes only occurs when the insulin output from the pancreatic islets fails to match the insulin requirement as a result of the insulin resistance. The notion that hyperglycaemia itself (with or without hyperlipidaemia) can decrease insulin secretion has led to the concept of glycotoxicity. It implies the development of irreversible damages in a number of cellular component of β -cells mainly due to the over production of reactive oxygen species (ROS) and glycation. ROS are known to induce apoptosis and inhibit transcription factors in β -cells. However, the exact nature of impaired insulin secretion is still elusive. The biochemical mechanisms of glucotoxicity probably involve a number of still unknown biological pathways provoking deterioration of insulin secretion, apoptosis and finally β -cell death.

The aim of the present project is to examine the effect of long term glucose exposure to the β -cell protein content and sub-organelles (insulin granules, mitochondria, plasma membrane) using proteomics strategies. This will determine a number of potential candidates implicated in impaired insulin secretion and β -cell dysfunction. These candidates will be further validated by western blot, immunocytochemistry, electronic microscopy, in vivo over-expression and/or silencing technologies. The use of putative activators or inhibitors of the transport and exocytosis of secretory granules could potentially lead to the improvement of the pathological conditions of insulin secretion defects and associated disorders.

In conclusion, these studies should provide new molecular insights into β -cell dysfunction mechanisms associated to glucotoxicity and might define potential new drug targets to improve the defective insulin secretion in type 2 diabetes and preserve functional β -cells.



Number of publications : 150
Total Impact Factor estimated: 598
Average Impact Factor: 3.99
H Index: 43
Total time cited: 6'109
Funding: Sfr 7'500'000.-

Group's publications

- Corthals G.L., Wasinger V. C., Hochstrasser D.F., Sanchez J.-Ch.
The dynamic range of protein expression : a challenge for proteomic research.
Electrophoresis, Vol. 21, No 6, p. 1104-1115, 2000.
- Sanchez J.-Ch., Chiappe D., Converset V., Hoogland Ch., Binz P.-A., Paesano S., Appel R.D., Wang S., Sennitt M., Nolan A., Cawthorne M.A., Hochstrasser D.F.
The mouse SWISS-2DPAGE database : a tool for proteomics study of diabetes and obesity.
Proteomics, Vol. 1, No 1, p. 136-163, 2001.
- Sanchez J.C., Converset V., Nolan A., Schmid G., Wang S., Heller M., Sennitt M.V., Hochstrasser D., Cawthorne M.A.
Effect of rosiglitazone on the differential expression of diabetes-associated proteins in pancreatic islets of C57Bl/6 lep/lep mice.
Molecular cellular Proteomics, Vol. 1 (7), p. 509-516, 2002 Jul.
- Sanchez J.C., Converset V., Nolan A., Schmid G., Wang S., Heller M., Sennitt M.V., Hochstrasser D.F., Cawthorne M.A.
Effect of rosiglitazone on the differential expression of obesity and insulin resistance associated proteins in lep/lep mice.
Proteomics, 2003, 3, p. 1500-1520.
- Deshusses J., Burgess J., Scherl A., Wenger Y., Walter N., Converset V., Paesano S., Corthals G.L., Hochstrasser D.F., Sanchez J.C.
Exploitation of specific properties of trifluoroethanol of extraction and separation of membrane proteins
Proteomics, 2003, 3, p. 1418-1424.
- G. Schmid, V. Converset, N. Walter, M. Sennitt, M. Ward, D. Hochstrasser, M. Cawthorne, Sanchez J.-Ch.
Effect of high fat diet on the expression of proteins in muscle, adipose tissues and liver of C57BL/6 mice
Proteomics 2004, Aug;4(8):2270-82.
- Carrette O, Burkhard P.R, Hochstrasser D, Sanchez J.C.
State-of-the-art two-dimensional gel electrophoresis: a key tool of proteomics research
July 2006; Nature Protocols: Vol. 1 N° 2
- Vollmer M, Horth P, Rozing G, Coute Y, Grimm R, Hochstrasser D, Sanchez J.C.
Multi-dimensional HPLC/MS of the nucleolar proteome using HPLC-chip/MS.
J Sep Sci. 2006 Mar; 29(4):499-509
- Brunner Y, Couté Y, Iezzi M, Foti M, Fukuda M, Hochstrasser DF, Wollheim CB, Sanchez J.C.
Proteomics analysis of insulin secretory granules.
Mol Cell Proteomics. 2007 Jun;6(6):1007-17.
- Schmid GM, Meda P, Caille D, Wargent E, O'Dowd J, Hochstrasser DF, Cawthorne MA, Sanchez J.C.
Inhibition of insulin secretion by betagranin, an N-terminal chromogranin A fragment.
J Biol Chem. 2007 Apr 27;282(17):12717-24.