

Emerging molecular targets to treat diabetes and prevent its complications

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Section of Internal Medicine 3

Treatment

Insulin clearance

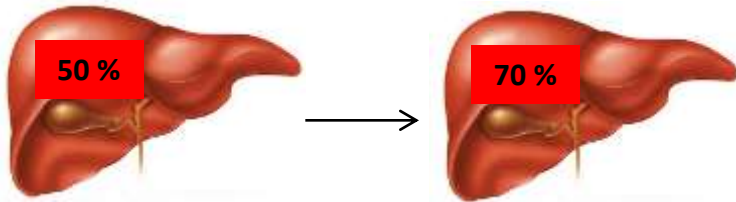
Prevention

Targeting HDL functions

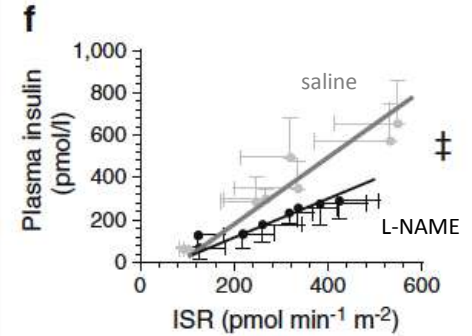
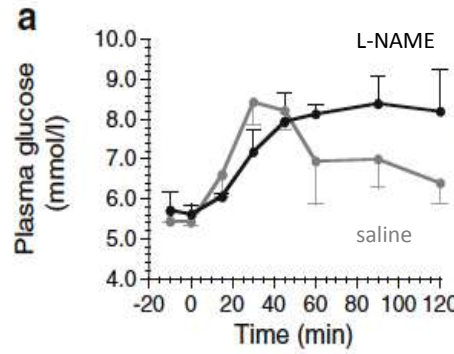
P2X₇ receptors and inflammation

Insulin clearance, nitric oxide and glucose homeostasis

NO blockade

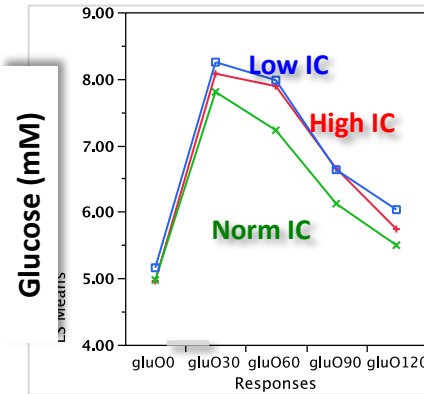
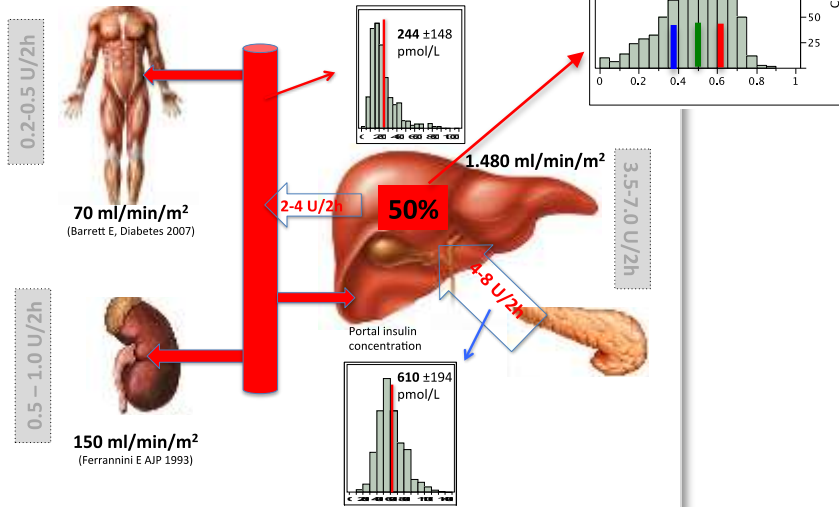


Natali A. Diabetologia 2013

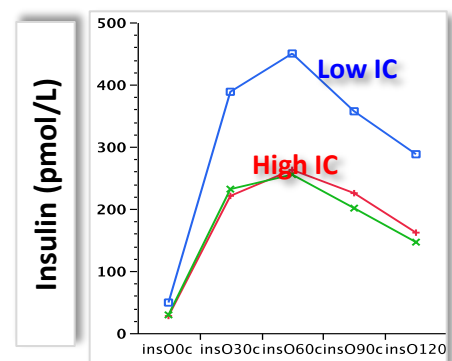
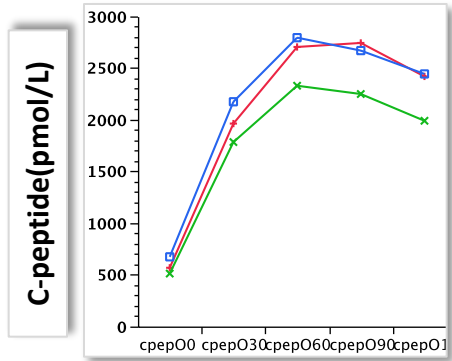


MCR-I Ogtt (1.700 ml/min/m²)

Hepatic FE
0.50+/-0.16

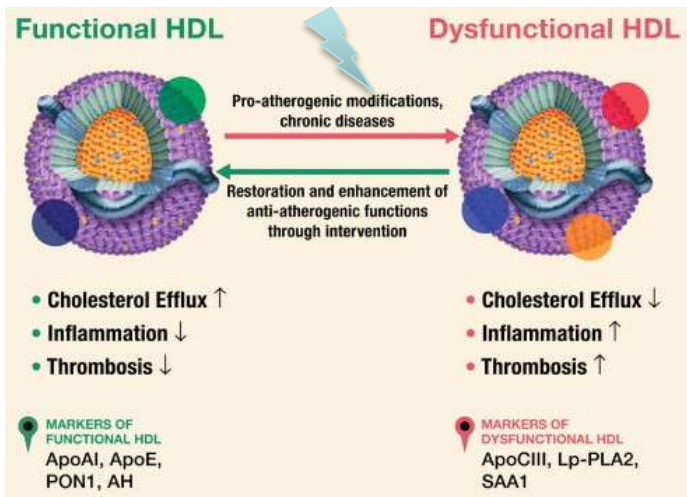


*Age, gender and centre adjusted

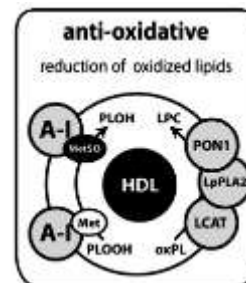
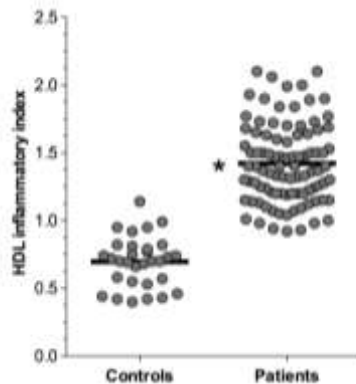


HDL Function

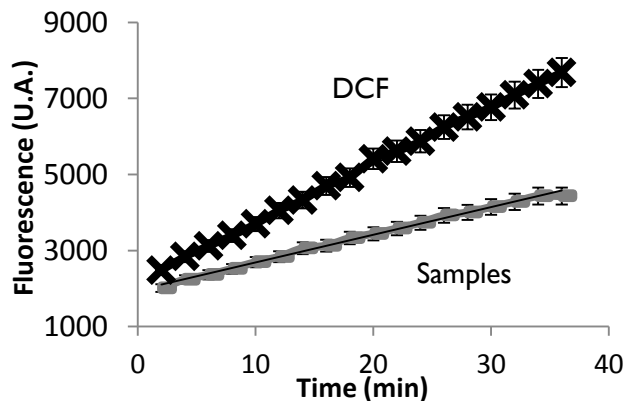
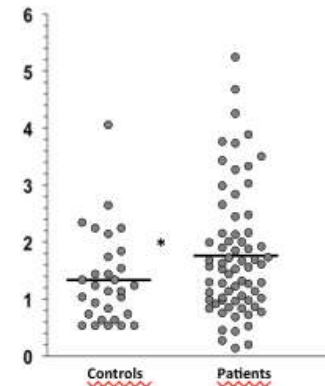
Diabetes



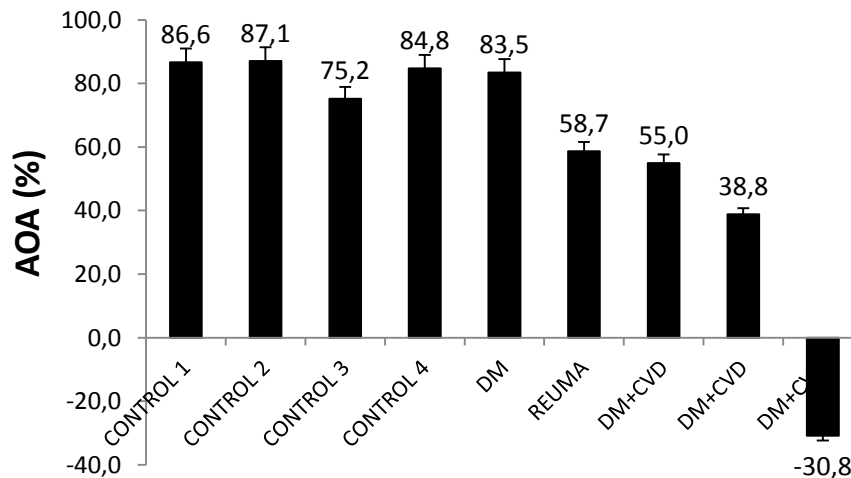
Cell-based assay



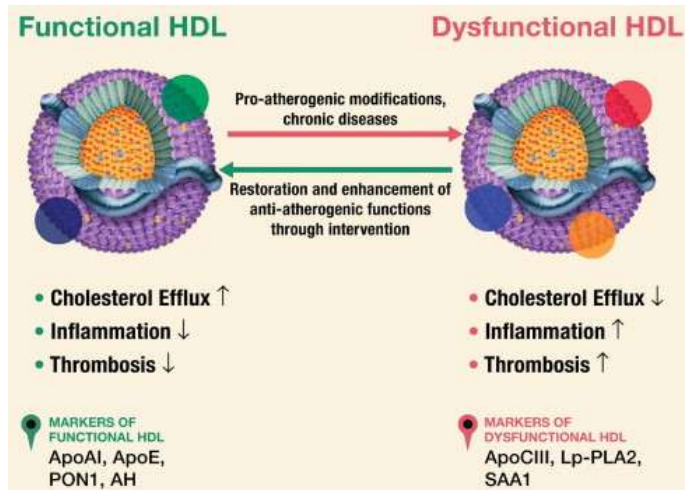
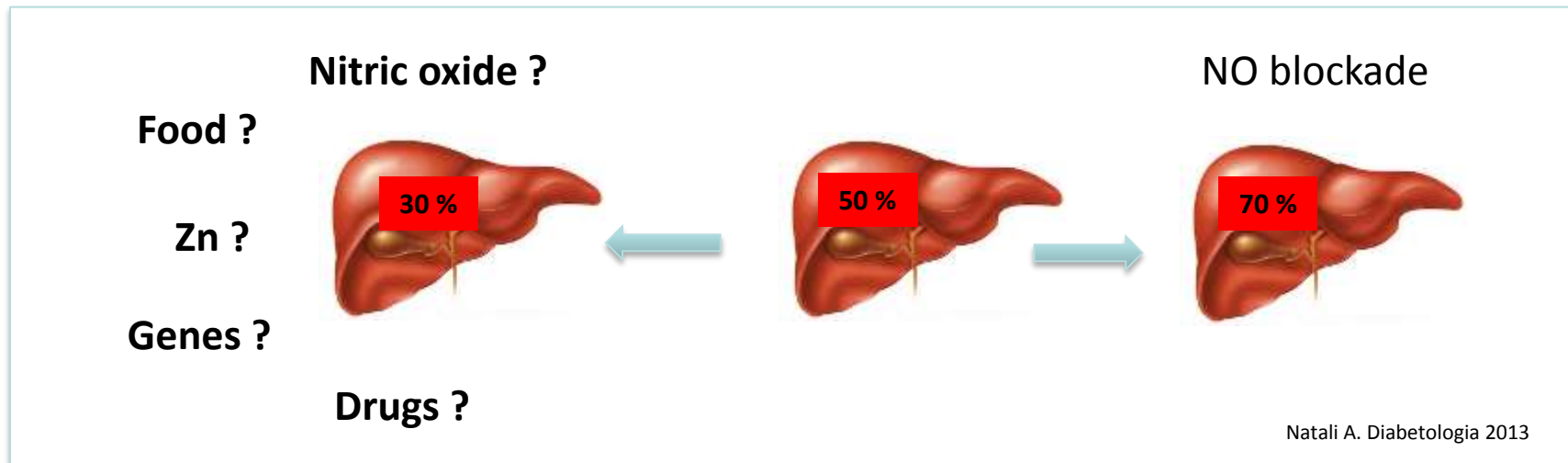
Cell-free assay



HDL separation (Beads) **PEG** (Heparin Mg, Liposep)
 Fluorescent probe (DCF) **DHR**
 HDL concentration (5.0) **2.5** (1.25 - 5.0 - 10.0)
 Buffer (HEPESt) **Hepes**
 Pro oxidant (none) **AAPH** (Cu++)



Questions currently under investigation

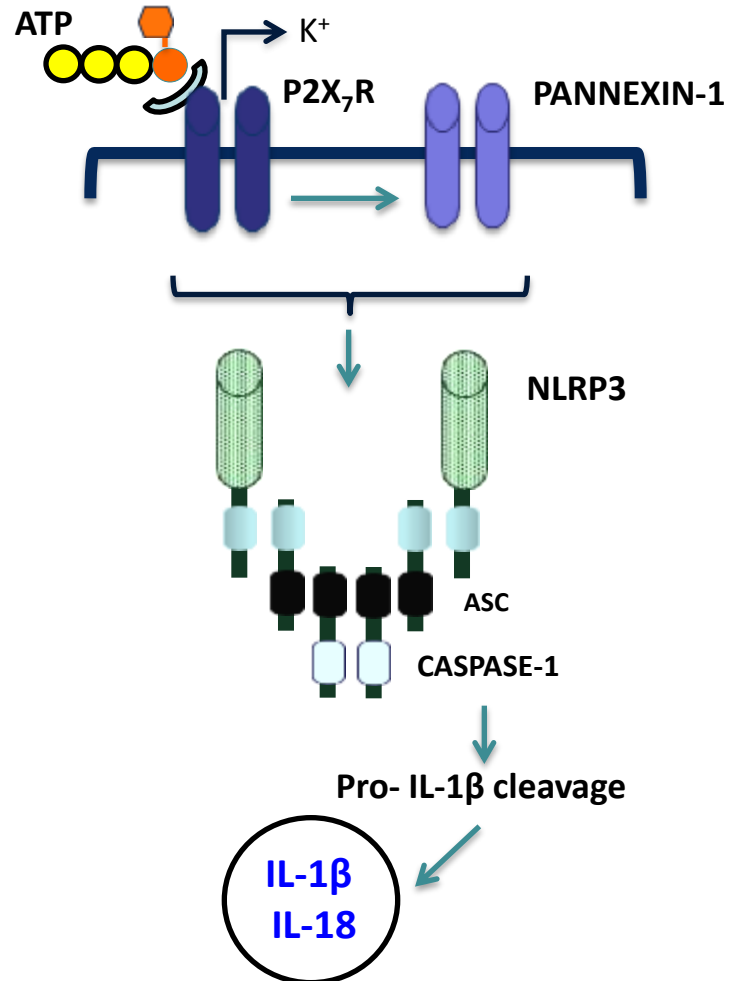


AOA vs RCT (*Parma*) vs AIA (*Monocytes*)
 AOA and HDL size (*Ultracentrifuge*)
 AOA and ApoCIII (*Harvard*)
 AOA and IMT (*RISC study*)
 AOA and Insulin secretion (*INS1E*)

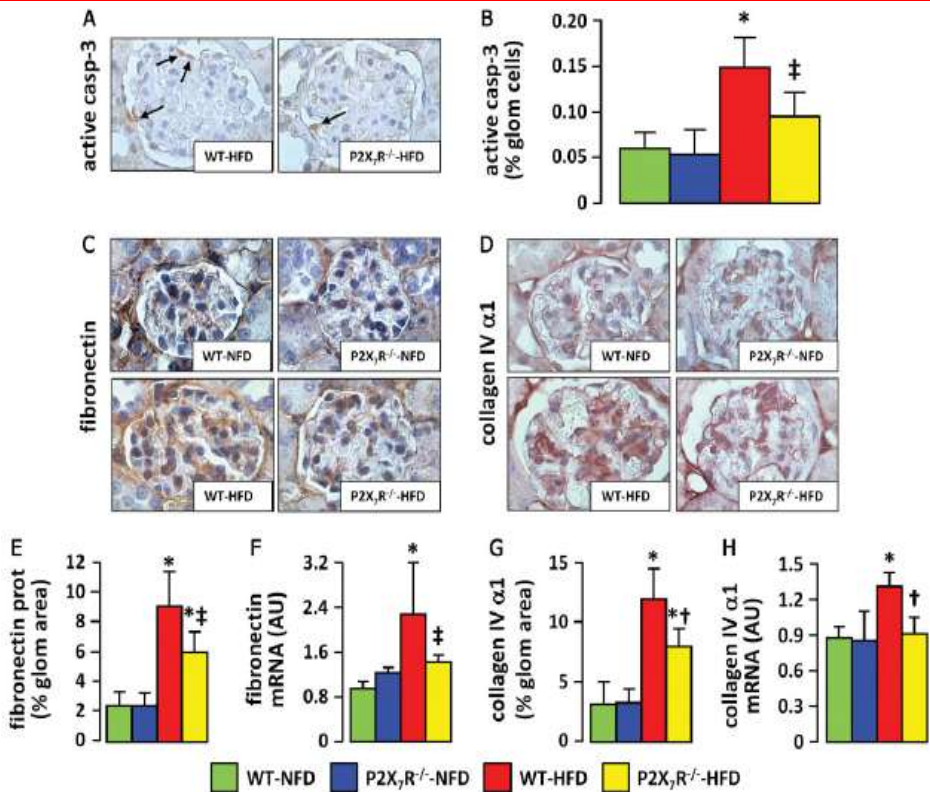
P2X₇R and inflammasome

The P2 receptors

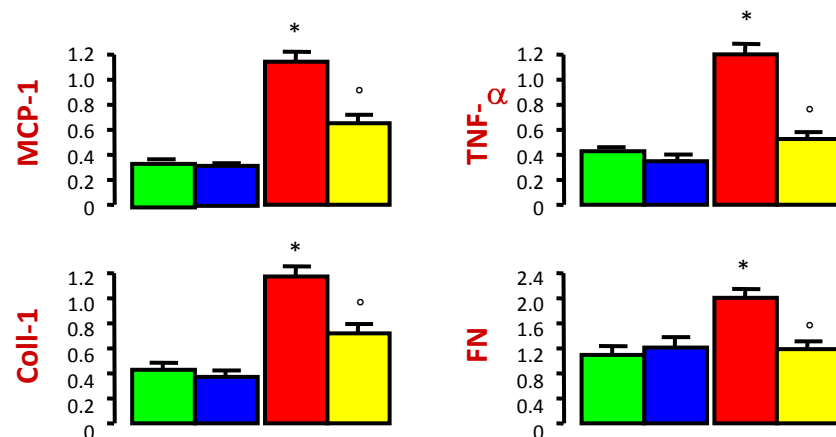
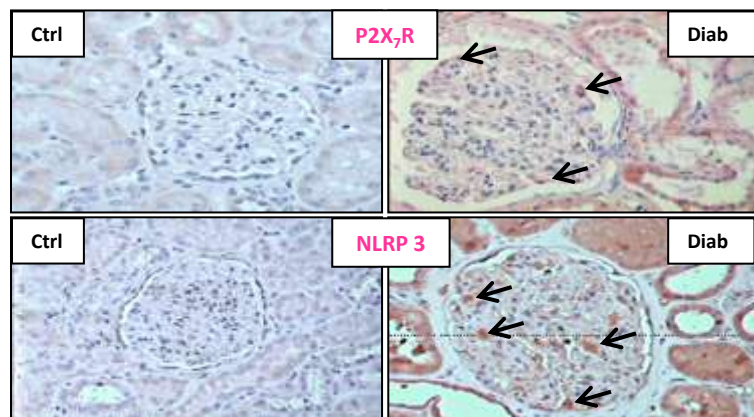
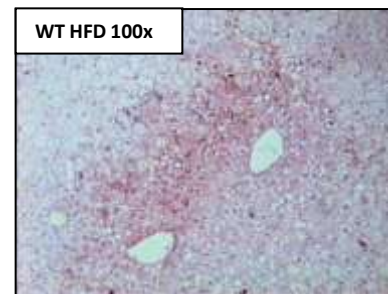
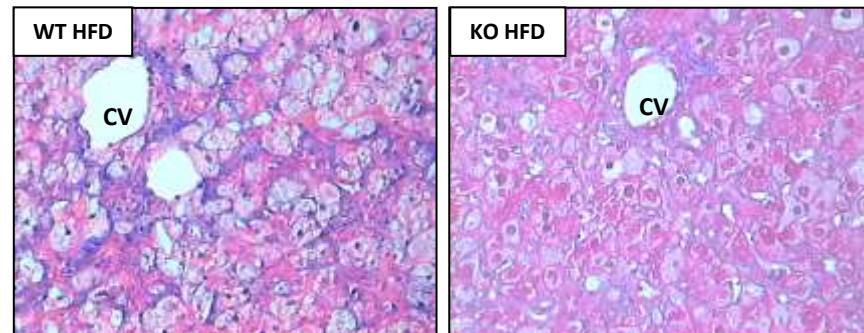
- Widely expressed ionotropic P2X and metabotropic P2Y receptors, sensitive to extracellular nucleotides (eATP)
- They can be activated in an autocrine or paracrine manner, and mediate several function, mainly calcium mobilization, actin polymerization, chemotaxis, release of mediators, cell maturation, cytotoxicity, and cell death
- Involved in neurotransmission, pain signals, regulation of vascular tone, modulation of inflammatory responses, cancer development and diffusion



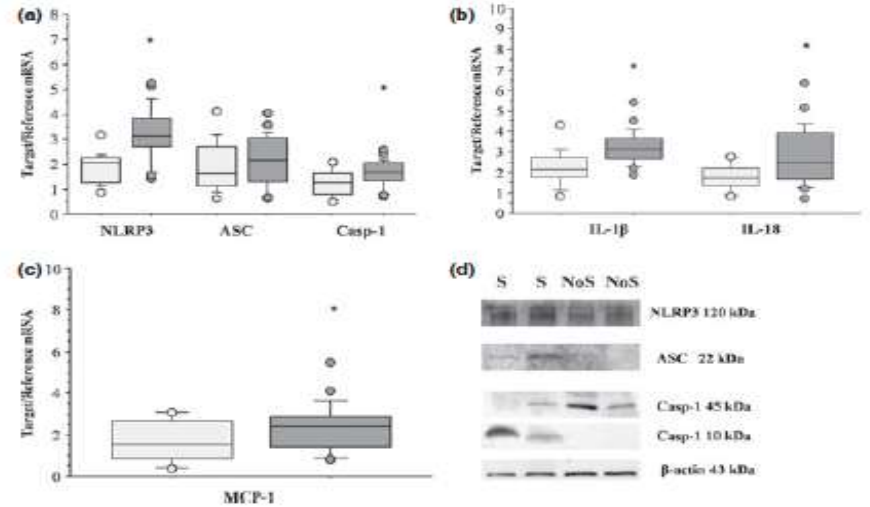
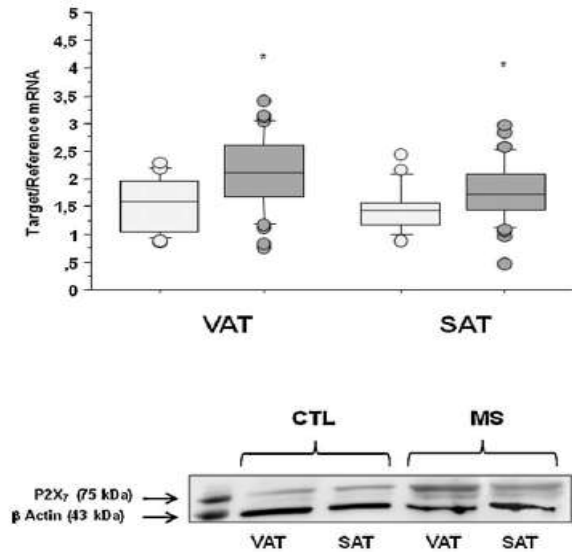
P2X₇R and inflammasome in kidney inflammation and NAFLD



Masson's trichrome stain, original magnification 250X



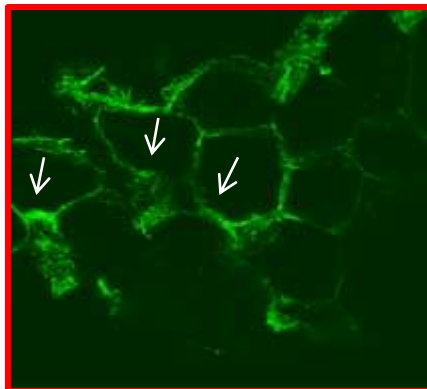
Adipocyte P2X₇R and CV risk factors



Rossi C, Eur J Clin Invest. 2014

Developing ideas:

- P2X₇R and mitochondrial function in T2DM
- Effect of *in vivo* modulation of P2X₇R on diabetic nephropathy, NAFLD and atherosclerosis



60 μm