Background

- Obesity-associated inflammation and oxidative stress are regarded as key disease processes related to insulin resistance (IR) and atherosclerosis. However, it remains to be determined if stimulation of inflammatory cells precedes or follows the development of IR and oxidative stress.
- Double knock-out (DKO) mice with combined leptin and LDL-receptor deficiency have several metabolic syndrome components: obesity, hypertriglyceridemia, IR, and hypertension. Increased oxidative stress and inflammation in these mice is associated with accelerated atherogenesis and PPARs appear to play an important role in the development of the metabolic syndrome and atherosclerosis.

Objectives

- Determine the sequence of underlying molecular events in adipose and vascular tissues, and their associations with the development of the metabolic syndrome and atherosclerosis.
- Determine the importance of PPARs in this development by treatment with the PPAR-agonists fenofibrate and rosiglitazone.

Methods

- Animals: C57BL6 and LDLR-/-;ob/ob (DKO) mice (C57BL6 background)
- Experimental protocol:
  - DKO interventions: fenofibrate (50 mg/kg/day) or rosiglitazone (10 mg/kg/day)
  - Plasma was collected to measure different blood variables
  - Visceral adipose tissue and aorta were used for immunohistochemical and gene expression analysis
  - Mice were compared to age-matched control mice

Conclusions

Our observations indicate that IR and oxidative stress develop early in obese mice, rendering them susceptible to macrophage-driven inflammation and atherogenesis. Common molecular pathways were identified in adipose and vascular tissues, most of which are under transcriptional control of PPARγ. Furthermore, our data support the importance of adiponectin as signaling molecule between the adipose tissue and vascular wall.