Exploring the metabolic changes occurring in *in vitro* and *in vivo* models of diabetic retinopathy

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**INTRODUCTION**

Diabetic retinopathy (DR) remains as a leading cause of blindness in developed countries. This complex pathology involves neurodegeneration and vasculature of the inner retina.

**DR stages:**
- **Early diabetic retinopathy (non-PDR)**
  - Developing of micro-vascular anomalies.
- **Proliferative diabetic retinopathy (PDR)**
  - Neovascularization process leading to occlusion of retinal vessels (hypoxia) and the loss of integrity of the inner blood-retinal barrier.

Current treatments for DR are applicable only at advanced stages of the disease, when the blood vessels proliferate PDR and they associate with significant adverse effects.

**GOAL**

Identify deregulated metabolic pathways leading to DR based on the study of *in vitro* hyperglycemic pseudohypoxic conditions and *in vivo* early stages of diabetic retinopathy.

**METHODS**

1. **Samples**

   *In vitro model*: human retinal pigment epithelium cell line (ARPE-19).

   *In vivo animal model*: high fat diet (HFD) and Irs2-/- mutant.

2. **Untargeted metabolomics**

   - Mass profiling (13C)
   - Isotope tracking (13C) using geoRge

3. **Data integration and network visualization**

   MetScape (plugin from CytoScape)
   - Input data: metabolites statistically significant (pval<0.05 and abs(FC)>1.5)
   - 600 MHz Bruker Avance III + cryoprobe + SampleJet
   - Agilent 6550 LC-qTOF MS
   - Agilent 7200 GC-qTOF MS

**RESULTS**

Network integration of the cell and animal models:

The metabolic network represents all the connections between the altered metabolites detected in the ARPE cell model and in the animal models (HFD and Irs2-/-).

**DISCUSSION**

Adenosine and inosine are considered as a potential immunomodulatory and neuroprotective agent. Adenosine is rapidly metabolized to inosine, and inosine mimics the protective effect of adenosine. This fact is in line with the results obtained from the neurodegenerative Irs2-/- model. Low levels of adenosine and inosine would not protect the retina from neurodegeneration. Contrary, the HFD mouse presents high levels of inosine. The upregulation of inosine could be explained as a response to insulin resistance with the aim of protecting the neuroglial cells. The detection of this changes in human patients could contribute to apply new therapeutic targets to avoid advanced stages of diabetic retinopathy (ref 1).

**REFERENCES**

1. Navarro et al. submitted.
2. Capellades et submitted.