# Interleukin (IL-)6 trans-signalling does not influence hyperglycemia and insulin sensitivity after diet-induced obesity and physical exercise

**Anna Rita Minafra[1]*, Alexandra Chadt[2], Hadi Al-Hasani[2]** and **Jvrgen Scheller[1]**

[1]Heinrich-Heine-University, Germany

[2]German Diabetes Center, Germany

In the last two decades, obesity has been described not only as increase of fat cells caused by excess of nutrients and inactivity but as an inflammatory disease: the transition from healthy lean to obese adipose tissue is accompanied by a chronic low-grade inflammation and immune system dysregulation, as well as the release of pro-inflammatory cytokines, which can consequently interfere with peripheral insulin signalling and glucose metabolism. Among others, IL-6 has been frequently associated to the impaired immune control in obese adipose tissue.

However, there is a growing consensus that IL-6 has also regenerative, anti-inflammatory and antidiabetogenic functions, mainly when secreted as myokine by skeletal muscles during physical exercise.

Furthermore, it is not yet clear which mechanism and which signalling of IL-6 is mainly responsible of these multiple metabolic aspects. Mechanistically, two main signalling pathways can be activated by IL-6. In the classic signalling, IL-6 binds to its membrane-bound receptor (IL-6R), followed by dimerization of glycoprotein 130 (gp130), leading to JAK/STAT, MAPK, and PI3K/AKT activation. In the trans-signalling IL-6 can bind soluble IL-6 receptor (sIL-6R), generated by ectodomain shedding by metalloproteases (ADAM10 and ADAM-17) or through alternative splicing of IL-6R mRNA.

Of note, classic signalling activation is limited since IL-6R is only expressed on specific cell types, such as immune cells and hepatocytes. Some studies suggest that IL-6R might be expressed also on adipocytes and myocytes, making unclear whether Il-6 metabolic functions mainly rely on classic or trans-signalling.

Accordingly, here, we metabolically characterized the previously generated transgenic soluble IL-6 receptor (sIL-6R+/+) mice with a strategy that mimics ADAM10/17 hyper-activation, reflecting a situation in which only trans-signalling is active, whereas classic signalling is abrogated. In this study, we metabolically phenotyped IL-6 rceptor deficient mice (IL-6R-KO), sIL-6R+/+ mice and wild-type littermates fed a Standard Chow (SC) and High-Fat Diet (HFD) in combination with treadmill exercise protocol. All mice have been subjected to analysis of body weight and body composition, determination of blood glucose and insulin level under fasting conditions, as well as determination of substrate preference by Indirect Calorimetry. Based on our data, IL-6 classic and trans-signalling do not influence the outcome of diet-induced obesity, hyperglycaemia and obesity-related insulin resistance. Furthermore, deficiency of IL-6 receptor and specific abrogation of classic signalling are not impairing the beneficial effect of physical exercise.

## Biography

Anna Rita Minafra graduated in 2018 in Molecular Medicine Biotechnology in the University of Bari (Italy), with the maximal score cum laude, after accomplishing the work for her Master thesis in Switzerland at the École Polytechnique Fédérale de Lausanne (EPFL), in the laboratory Prof. Joerg Huelsken, supported by a scholarship “Global Thesis”, which was attributed on a competitive basis. She is currently a PhD student at Heinrich-Heine University, Düsseldorf (Germany), in the Institute of Biochemistry and Molecular Biology of Prof. Dr. Jürgen Scheller. She is part of the Research Training Group RTG 2576 "vivid-In vivo investigations towards the early development of type 2 diabetes" since September 2020.

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