

# Cytokines in Metabolic Functions

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## ABSTRACT

During infections, circulating cytokines are largely produced by immune cells. In healthy obese individuals, large parts of these circulating cytokines are produced in adipose tissue, for instance by macrophages that have accumulated there. The aim of this thesis was to investigate the role of cytokines, in particular interleukin-6 (IL-6), IL-1 $\beta$  and leukemia inhibitory factor (LIF), in the regulation of metabolism and body fat mass. Furthermore, we also wanted to examine the role of the IL-6 signal transducer (IL6ST)/gp130 receptor signalling.

We have previously shown that IL-6 depleted (IL-6  $-/-$ ) mice develop late-onset obesity and we have now found a similar effect on IL-1 depletion. We have used IL-1 receptor type I depleted (IL-1RI  $-/-$ ) mice to study the role of endogenous IL-1 on obesity, as measured by DEXA. The obesity in IL-1RI  $-/-$  was accompanied by decreased insulin and leptin sensitivity. Spontaneous locomotor activity and fat utilization, as measured in metabolic cages, were decreased in pre-obese IL-1RI  $-/-$  animals. At the hypothalamic level, deficiency of endogenous IL-1 activity in knockout mice was associated with enhanced expression of the obesity promoting peptides NPY and MCH, and decreased expression of the obesity suppressing peptide orexin. In IL-6  $-/-$  mice, the expression of corticotrophin releasing hormone, a known stimulator of energy expenditure and the sympathetic nerve system, was decreased, as shown by RT-PCR. Moreover, endogenous IL-6 and IL-1 $\beta$  seemed to affect each others' expression in the hypothalamus. Therefore, IL-6 and IL-1 may interact in the CNS, presumably in the hypothalamus, to suppress fat mass, possibly by increasing energy expenditure and maybe especially fat burning. LIF is a member of the IL-6 receptor family, which shares the IL6ST/gp130, and has been reported to decrease obesity. We found that systemic LIF treatment could reduce white and brown fat depots in ovariectomized mice, suggesting that LIF can reduce obesity independently of estrogen signalling.

Obesity and inflammation are key components in the development of atherosclerosis and myocardial infarction. We identified an association between an IL6ST/gp130 polymorphism in amino acid 148 (Gly/Arg) and risk of myocardial infarction in a hypertensive population. *In vitro* studies showed decreased proliferation and lower STAT-3 phosphorylation in cells transfected with gp130 148Arg compared to gp130 148Gly. Structural modelling suggested changes in the stability and functional properties of the gp130 148Arg molecule.

The present results suggest that the cytokines IL-6, IL-1 and LIF are involved in the regulation of body fat mass and energy expenditure. The effects of IL-6 and IL-1 may be exerted at the CNS level and involve altered expression of hypothalamic peptides regulating fat mass and energy expenditure. This can constitute a possible mechanism contributing to the mature-onset obesity in IL-6  $-/-$  and IL-1RI  $-/-$  mice. LIF may suppress obesity via estrogen independent effects in the periphery. In human subjects, the 148th amino acid arginine of the gp130 receptor is associated with decreased risk of myocardial infarction, possibly due to an impaired responsiveness to cytokines in the IL-6 receptor family.

Key words: IL-1, IL-6, LIF, obesity, fat mass, energy expenditure, hypothalamus, gp130 SNP, myocardial infarction

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Akademisk avhandling

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av

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Triemli hospital, Zürich, Switzerland

## **Avhandlingen baseras på följande delarbeten:**

### **I. Mature-onset obesity in interleukin-1 receptor I (IL-1RI) knockout mice**

M Garcia, I Wernstedt, A Berndtsson, M Enge, M Bell, O Hultgren, M Horn, B Ahrén, S Enerback, C Ohlsson, V Wallenius, J-O Jansson  
*Diabetes*, 55:1205-1213, 2006

### **II. Deficiency of interleukin-6 (IL-6) or IL-1 action influences hypothalamic fat regulating peptides**

A Benrick, L Strandberg, E Schele, S Pinnock, E Egecioglu, I Wernstedt, M Enge, S Dickson, J-O Jansson  
*Manuscript*

### **III. Leukemia-Inhibitory Factor reduces body fat mass in ovariectomized mice**

J-O Jansson, S Moverare-Skritic, A Berndtsson, I Wernstedt, H Carlsten, C Ohlsson  
*European Journal of Endocrinology*, 154, 349-354, 2006

### **IV. A non-conservative polymorphism in the IL-6 signal transducer (IL6ST)/gp130 is associated with myocardial infarction in a hypertensive population**

A Benrick, P Jirholt, I Wernstedt, M Gustafsson, J Scheller, AL Eriksson, J Borén, T Hedner, C Ohlsson, T Härd, S Rose-John, J-O Jansson  
*Regulatory Peptides*, 146, 189-196, 2008



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