



**Karolinska  
Institutet**

**Department of Medicine, Solna**

# Role of Immune Mediators in Metabolic Syndrome and Atherosclerosis

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorexamen vid Karolinska Institutet offentligen försvaras i Welandersalen, Hudkliniken, B2:00, Karolinska Universitetssjukhuset Solna

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av

**Daniela Strodt Hoff**

*Huvudhandledare:*

Professor Göran K. Hansson  
Karolinska Institutet  
Institutionen för Medicin, Solna  
Enheten för Experimentell Kardiovaskulär  
Forskning

*Bihandledare:*

Professor Peter Arner  
Karolinska Institutet  
Institutionen för Medicin, Huddinge  
Enheten för endokrinologi och diabetes

PhD, Norbert Gerdes  
Ludwig-Maximilians University Munich  
Institute for Cardiovascular Prevention

PhD, Anna Lundberg  
Karolinska Institutet  
Institutionen för Medicin, Solna  
Enheten för Experimentell  
Kardiovaskulär Forskning

*Fakultetsopponent:*

Professor, Nikolaus Marx  
University Hospital Aachen  
Department of Internal Medicine I

*Betygsnämnd:*

Associate Professor, Lillemor MattssonHultén  
University of Gothenburg  
The Wallenberg Laboratory for  
Cardiovascular and Metabolic Research

Professor, Rachel Fisher  
Karolinska Institutet  
Institutionen för Medicin, Solna  
Enheten för aterosklerosforskning

Professor, Kerstin Brismar  
Karolinska Institutet  
Institutionen för molekylär medicin och  
kirurgi  
Enheten för tillväxt och metabolism

**Stockholm 20 14**

## **Abstract**

**Obesity is increasingly becoming a problem worldwide. Both location and metabolic activity of visceral and subcutaneous white adipose tissue (WAT) differ. Visceral fat is highly vascularized resulting in increased blood supply and increased infiltration of inflammatory immune cells such as macrophages, T cells and even B cells. Together with adipocytes these cells secrete adipokines/cytokines that propagate an inflammatory milieu locally as well as systemically.**

**Obesity is strongly associated with the risk of cardiovascular disease (CVD) – diseases affecting the heart and the blood vessels. The underlying pathology of most CVDs is termed atherosclerosis, a chronic inflammatory condition of the arterial wall. The fatty streak formation is the first step in atherogenesis and is an accumulation of lipid-containing cells under the endothelial cell layer, which might progress to atheroma formation. Atherosclerotic lesions develop silently without symptoms over many years. This can change dramatically when a plaque ruptures. Occlusion of the artery obstructing the blood flow may cause stroke, myocardial infarction or other life-threatening events.**

**We demonstrate that inflammation of WAT can occur even in the absence of obesity. T cell-driven WAT inflammation and obesity-associated inflammation is characterized by increased T cell infiltration and expression of pro-inflammatory cytokines. Interestingly, IL-6 expression differs in the 2 forms of WAT (paper I).**

**We further show the impact of liver-residing inflammatory iNKT cells on lipid metabolism, controlling metabolic processes distally in WAT (paper III). We also demonstrated the impact of the innate receptor TLR-3 on insulin secretion and lipid metabolism (paper IV).**

**Changes in lipid metabolism and inflammation contribute to lesion development. Different strategies, including immune-modulation and even vaccination, are conceivable to prevent, stop or slow down lesion development. The project in my thesis that demonstrate the impact of FoxP3<sup>+</sup> Tregs on lipid metabolism and atherosclerosis (paper II) encourages such work.**

**Altogether, the findings in my thesis are based on in vitro and in vivo models of obesity and atherosclerosis, diseases that can promote each other's development. We broke down the complex processes to study the involvement of single cell types (iNKT, FoxP3<sup>+</sup> Tregs), receptors (TLR-3), and cytokines (IL-6). Together these approaches contribute to the understanding of the molecular mechanisms driving these diseases and will hopefully contribute to new therapeutic approaches.**

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