Overview over the core gene panel used by Lipocyte BioMed

Content

General

Lipocyte BioMed focusses on the four mRNAs HMGA2, PPAR-gamma, ADIPOQ and IL-6 as a core panel for diagnostics and therapeutics. This core panel can be expanded either further mRNAs or by other drivers or clinical values.

HMGA2

This gene encodes a protein that belongs to the non-histone chromosomal high mobility group (HMG) protein family. HMG proteins function as architectural factors and are essential components of the enhance some. This protein contains structural DNA-binding domains and may act as a transcriptional regulating factor. Identification of the deletion, amplification, and rearrangement of this gene that are associated with myxoid liposarcoma suggests a role in adipogenesis and mesenchymal differentiation. A gene knock-out study of the mouse counterpart demonstrated that this gene is involved in diet-induced obesity". (see NCBI: Gene ID: 8091). In adipose tissue the HMGA2 gene is only activated in mesenchymal stem cells (MSC) and preadipocytes. HMGA2-activity indicates i.a. cell proliferation, therefore a high HMGA2-activity represent the formation of new preadipocytes and MSCs. A high activity of HMGA2 and PPARɣ in adipose tissue reflects a parallel formation of preadipocytes and a coincidental differentiation towards insulin-sensitive adipocyte with weight gain, but this represents a metabolic "healthy" adipose tissue. High HMGA2 and low PPAR-ɣ activity reflects an increase of immature preadipocytes, but these preadipocytes have not the ability to store or mobilize triglycerides, respond to insulin and other hormones, and to release different hormones as well as other para- and autocrine factors like insulin-sensitive mature adipocytes. This state represents a metabolic dysfunctional adipose tissue.

PPAR-ɣ

This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes. The protein encoded by this gene is PPAR-ɣ and is a regulator of adipocyte differentiation. Additionally, PPAR-ɣ has been implicated in the pathology of numerous diseases including obesity, diabetes, atherosclerosis, and cancer." (see: NCBI: Gene ID: 5468) *PPAR-ɣ* is a major regulator of adipose tissue maturation and essential to maintain the insulin sensitive mature adipocytes state. A high activity of *PPAR-ɣ* compared to the activity of *HMGA2* reflects a metabolic "healthy" adipose tissue => a high fraction of mature adipocytes. With regard to the treatment of type 2 diabetes (T2D) via oral antidiabetics a high *PPAR-ɣ* activity indicates a metabolic "healthy" adipose tissue, therefore the source of T2D could probably be found in liver, skeletal muscle, gastrointestinal tract or ß-cells of pancreas. *PPARɣ* activates the expression of *ADIPOQ* => a high activity of *PPAR-ɣ* and a lower activity of *ADIPOQ* probably pointing to a dysfunctional signal pathway in mature adipocytes.

ADIPOQ:

This gene is expressed in adipose tissue exclusively. It encodes a protein with similarity to collagens X and VIII and complement factor C1q. The encoded protein circulates in the plasma and is involved with metabolic and hormonal processes." (see NCBI: Gene ID: 9370) *ADIPOQ* encodes for the peptide hormone adiponectin and is only active in mature adipocytes. There is a correlation between a decrease in the circulating adiponectin with a concurrent development of insulin resistance obesity, metabolic syndrome and T2D. Furthermore, adiponectin has an array of anti-atherosclerotic effects and improves insulin sensitivity through inhibition of hepatic glucose production and enhancing glucose uptake in muscle, increasing fatty acid oxidation in both liver and muscle. In an insulin-resistant mouse model administration of adiponectin has been shown to ameliorate hyperglycaemia and hyperinsulinaemia (Yamauchi et al., 2001). A high activity of *ADIPOQ* reflects presumably a healthy adipose tissue and an increased insulin-sensitivity, thus medication to increase insulin secretion might be the first choice.

Interleukin-6 (IL-6):

This gene encodes a cytokine that functions in inflammation and the maturation of B cells. In addition, the encoded protein has been shown to be an endogenous pyrogen capable of inducing fever in people with autoimmune diseases or infections. The protein is primarily produced at sites of acute and chronic inflammation, where it is secreted into the serum and induces a transcriptional inflammatory response through interleukin 6 receptor, alpha. The functioning of this gene is implicated in a wide variety of inflammation associated disease states, including susceptibility to diabetes mellitus and systemic juvenile rheumatoid arthritis." (see NCBI: Gene ID: 3569) Interleukin-6 is an inflammatory mediator, which can be produced by many cell types. In adipose tissue, where it is produced in large quantities, adipocytes and macrophages are responsible for the production of this inflammatory mediator and thus ensure a subclinical inflammatory response. This subclinical inflammatory response attracts monocytes and macrophages which eliminate immature senescent adipocytes. This in turn leads to a release of stored fatty acids and an increase in insulin resistance and lipotoxicity in the remaining tissue. Elevated IL-6 plasma levels are associated with insulin-resistance and increased risk of diabetes, independently of body weight. Furthermore IL-6 can induce hepatic insulin resistance, and loss of IL-6 selectively improves hepatic insulin action in obese mice. IL-6– induced hepatic insulin resistance is mediated, in part, by increased expression of SOCS3, a protein that binds and inhibits the insulin receptor. A high activity of *IL-6* reflects a subclinical inflammation in adipose tissue and a hepatic insulin resistance.