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# The control of lipid-induced inflammation by macrophages

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Type 2 diabetes (T2M) arises when insulin resistance and beta cell dysfunction develop in the context of over nutrition and weight gain [1]. Several mechanisms have been proposed to explain the evolution towards diabetes, including oxidative stress, endoplasmic reticulum (ER) stress, lipotoxicity, and glucotoxicity [2]. Although individual studies pinpoint the importance of each of these factors in the pathogenesis of diabetes in rodents, progression towards T2M in humans is polyfactorial. Inflammation in the hypothalamus, liver, adipose tissue and the pancreas arises now as a potential link between these conditions. Two recent studies shed important information on how macrophages control lipid-induced inflammation.

Macrophages have been the first immune cells identified in mouse [3] and human [4] adipose tissue. An increase in the number of macrophages has also been demonstrated in pancreatic islets of T2M patients, as well as in diet induced animal models of obesity [5]. Macrophages infiltrating visceral adipose tissue belong to the M1 pro-inflammatory myeloid subtype, whereas those infiltrating subcutaneous adipose tissue are predominantly of the anti-inflammatory M2 subtype [6]. This observation might in part explain the reason why some obese individuals remain metabolically healthy while others develop diabetes and cardiovascular disease. What dictates the differentiation of macrophages into the M1 or M2 subtypes was poorly understood.

A study published by the laboratory of Shizuo Akira has now characterized Trib1, an adaptor protein of the pseudokinase tribble family involved in protein degradation, as a critical factor for macrophage differentiation into the M2 subtype [7]. Trib1 deficient mice showed a defect in M2-like macrophage generation (as well as eosinophil differentiation). These mice had a diminished adipose tissue mass but augmented lipolysis, and this was accompanied by decreased glucose tolerance. Reconstitution of the Trib1 deficient mice with $Trib1^{+/+}$ M2 macrophages abrogated these defects. This indicates that lipodystrophy and glucose intolerance in the Trib1 KO mice were a consequence of a lack in M2 macrophages. Possibly, production of IL-10 by M2 macrophages is important in this context as this cytokine is known to protect against insulin resistance [8]. This study may have important implications for humans as genome wide association studies have implicated Trib1 in metabolic disorders [9].

In contrast to M2 macrophages, M1 macrophages promote inflammation. Work from the laboratory of Roger Davis now shows that the JNK MAPK pathway in those macrophages is responsible for the induction of inflammation and insulin resistance triggered by obesity [10]. Macrophage-specific JNK deficiency led to improved glucose tolerance and reduced inflammation in mice fed a high-fat diet. This prevented the accumulation of M1 macrophages in adipose tissues but, interestingly, did not affect the infiltration of M2 macrophages in these tissues. It thus appears that peripheral insulin resistance or beta cells dysfunction can be caused by FFAs and JNK-induced polarization of macrophages towards the M1 subtype in fat tissues. This is an example of inter-organ cross-talk participating in the development of metabolic diseases.

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4. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr.: **Obesity is associated with macrophage accumulation in adipose tissue**. *J.Clin.Invest.* 2003, **112:**1796-1808.

[*]5. Donath MY, Dalmas E, Sauter NS, Boni-Schnetzler M: **Inflammation in obesity and diabetes: islet dysfunction and therapeutic opportunity**. *Cell Metab.* 2013, **17:**860-872.

Good overview on the effector molecules involved in pro-inflammatory responses in the context of obesity-induced diabetes and on past and present clinical studies targeting these pathways.

[*]6. Osborn O, Olefsky JM: **The cellular and signaling networks linking the immune system and metabolism in disease**. *Nat.Med.* 2012, **18:**363-374.

This nicely illustrated review focuses on the way macrophage activation impacts on obesity-induced insulin resistance. Why macrophages infiltrating the visceral adipose tissue are of the pro-inflammatory M1 subtype, whereas those infiltrating the subcutaneous adipose tissue are predominantly of the anti-inflammatory M2 subtype is currently an outstanding question.

[**] 7. Satoh T, Kidoya H, Naito H, Yamamoto M, Takemura N, Nakagawa K, Yoshioka Y, Morii E, Takakura N, Takeuchi O, Akira S: **Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages**. *Nature* 2013, **495:**524-528.

This work identifies Trib1 as a critical factor for the differentiation of the M2 subtype of macrophages. Furthermore, this study highlights the importance of this macrophage subtype in counteracting the pro-inflammatory effects of macrophages of the M1 subtype. Obesity, by altering the equilibrium between these two cell populations in favor of the latter subtype, induces sustained inflammation and decreased glucose tolerance. Drugs capable of increasing the number or the activity of M2-like macrophages have therefore a clear anti-diabetic potential.

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9. Varbo A, Benn M, Tybjaerg-Hansen A, Grande P, Nordestgaard BG: **TRIB1 and GCKR polymorphisms, lipid levels, and risk of ischemic heart disease in the general population**. *Arterioscler.Thromb.Vasc.Biol.* 2011, **31:**451-457.

[**]10. Han MS, Jung DY, Morel C, Lakhani SA, Kim JK, Flavell RA, Davis RJ: **JNK expression by macrophages promotes obesity-induced insulin resistance and inflammation**. *Science.* 2013, **339:**218-222.

Signalling through JNK in insulin-sensitive tissues leads to decreased glucose tolerance and diabetes onset. Mechanistically, JNKs promote insulin resistance by phosphorylating the insulin receptor substrate (IRS) adaptor proteins, hampering efficient signaling downstream of the insulin receptor. JNK signaling in the central nervous system also favors insulin resistance by promoting obesity. The authors of this study now provide evidence that JNKs contribute to insulin resistance by favoring the differentiation of macrophages into the pro-inflammatory M1 subtype. Macrophage-specific JNK deficiency was found to be associated with secretion of anti-inflammatory cytokines by epididymal adipose tissue and improved overall glucose tolerance. These results point towards a pivotal role played by macrophages in modulating adipose inflammation and peripheral insulin sensitivity. It was suggested earlier that targeting the JNK MAPK pathway could be efficacious against obesity and insulin resistance development by restoring insulin sensitivity in the central nervous system, skeletal muscles and adipocytes. The present study indicates that inhibiting JNK MAPK signaling in another cell type – the macrophages - also contributes to the prevention of obesity-induced insulin resistance by limiting inflammation in adipose tissues. Hence, JNK inhibitory drugs may generate independent beneficial actions against obesity-mediated dysfunctions by targeting, insulin-sensitive tissues, neurons, and cells that control inflammation.

Further recommended reading

[*] Johnson AM, Olefsky JM: **The origins and drivers of insulin resistance**. *Cell* 2013, **152:**673-684.

How overnutrition triggers inflammation and the mechanisms by which FFAs produce their deleterious so-called “lipotoxic” effects are thoroughly treated in this perspective article. The causal link between gastrointestinal microbiota and the development of insulin resistance is also discussed in detail.