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The transcription factor p53 regulates adipose tissue macrophages' phenotype and their capacity to handle lipids.

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Abstract:

Background and aims: Obesity is a major risk factor for metabolic diseases including insulin resistance (IR) and Type 2 Diabetes (T2D). Excessive expansion of white adipose tissue (WAT) during obesity is accompanied by macrophage accumulation. Metabolic stress in obese adipose tissue (AT) modifies the function and fate of AT macrophages (ATMs), resulting in low-grade local and systemic inflammation contributing to the development of IR and T2D. However, the molecular mechanisms underlying this metabolic reprogramming of ATMs remain unknown. Transcription factors (TF) are crucial regulators of transcriptional programs involved in the polarization and adaptation of macrophages to their environment. Interestingly, the transcription factor p53, well known as a tumour suppressor, has been described in different cell types as a pivotal sensor of metabolic stress, playing an important role in the regulation of several metabolic pathways, and its dysregulation contributes to the development of metabolic diseases. We have shown increased expression and activation of p53 in obese ATMs. Thus, our aim was to investigate the role of p53 in macrophages polarization and metabolism, and to determine whether p53 dysregulation in ATMs during obesity could contribute to adipocyte dysfunction.

Materials and methods: We polarized control and p53-invalidated (KO) bone marrow-derived macrophages (BMDMs) into metabolically activated macrophages (MMe) with insulin, palmitate, and glucose, which phenocopy obese ATMs, and performed RNA-seq, RT-qPCR analyses, and measured cellular bioenergetics in real-time using Seahorse technology. We also treated adipocytes with conditioned media from macrophages and we studied the impact on adipocyte metabolism. Finally, to validate our *in vitro* data, we used particles to deliver siRNA against p53 specifically to ATMs in obese mice, and we explored the impact on their metabolic phenotype.

Results: We showed that MMe-polarized macrophages produced inflammatory mediators and expressed lipid handling genes. Invalidation of p53 potentiates MMe polarization with an increase in genes involved in lipid metabolism such as *Pparγ1*, *Cd36* and *Abca1*. Cellular respiration was increased in p53 KO MMe compared with control MMe, suggesting improved oxidative capacity, and mitochondrial respiration was more dependent on lipid oxidation. In contrast, p53 activation prior to MMe polarization decreased respiration compared with control MMe. Moreover, treatment of adipocytes with conditioned medium (CM) from p53-invalidated macrophages has less deleterious effects on insulin signaling than conditioned medium from control macrophages. Furthermore, adipocytes treated with CM from p53 KO MMe showed an increase in genes involved in lipogenesis. Finally, we showed that p53 invalidation specifically in ATMs improves glucose intolerance in obese mice and promotes the expression of lipid-handling genes at the expense of inflammatory genes in ATMs.

Conclusion: Our data suggest that activation of p53 in ATMs during obesity inhibits their ability to manage lipid, their oxidative capacity, and contributes to the secretion of factors altering insulin signalling in adipocytes. Thus, p53 dysregulation in ATMs during obesity could contribute to adipose tissue dysfunction and IR.

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