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## Adipose tissue inflammation and ectopic fat accumulation

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### Abstract

Obesity may be viewed as a state of chronic, low-grade inflammation, which plays an important role in the development of the metabolic syndrome. Indeed, unbalanced production of pro- and anti-inflammatory adipocytokines seen in visceral fat obesity plays a critical role in the pathophysiology of the metabolic syndrome. Recent evidence has revealed that adipose tissue macrophages may participate in obesity-induced chronic inflammation, thereby contributing to the pathogenesis of metabolic derangements of multiple organs. We have demonstrated that a paracrine loop involving saturated fatty acids (FAs) and tumor necrosis factor- $\alpha$  derived from adipocytes and macrophages, respectively, aggravates obesity-induced adipose tissue inflammation. Saturated FAs, which are released from hypertrophied adipocytes via the macrophage-induced lipolysis, activate macrophages through Toll-like receptor 4 (TLR4). Moreover, TLR4-signal deficient C3H/HeJ mice are protected against obesity-induced adipocytokine dysregulation and insulin resistance. These observations suggest the role of saturated FAs in adipose tissue inflammation.

Storing excessive energy as triglyceride is also a fundamental function of adipose tissue. Evidence has accumulated suggesting that reduced capacity of lipid storage in adipose tissue leads to ectopic fat accumulation in the liver and skeletal muscle, where lipotoxicity impairs their metabolic functions. We have recently reported that Mincle, a novel pathogen sensor for *Mycobacterium tuberculosis* and pathogenic fungus *Malassezia*, is selectively upregulated in adipose tissue macrophages in obesity. We also found that saturated FAs induce Mincle expression through TLR4. Mincle-deficient mice were protected against obesity-induced insulin resistance although there was no significant difference in body weight between the genotypes. Histological analysis in adipose tissue revealed that reduced interstitial fibrosis and increased adipocyte size in Mincle-deficient mice on a high-fat diet (HFD) compared to wildtype mice on a HFD. Moreover, ectopic fat accumulation in the liver was markedly attenuated in Mincle-deficient mice on a HFD compared to wildtype mice on a HFD. On the



other hand, there was no apparent difference in histological examinations and metabolic parameters between the genotypes on a standard diet. These observations suggest that Mincle, a novel regulator of adipose tissue inflammation, plays a role in ectopic fat accumulation in obesity. Collectively, chronic inflammation induces insulin resistance, adipocyte lipolysis, and interstitial fibrosis in adipose tissue, which may reduce lipid-storage capacity of adipose tissue, thereby leading to ectopic fat accumulation.