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Mammals regulate fat mass, so that in weight-stable individuals increases or reductions in adipose tissue activate responses that favor return to one's previous weight: A reduction in fat mass activates a system that increases food intake and reduces energy expenditure, and conversely, overfeeding and rapid adipose tissue expansion reduces food intake and increases energy expenditure. With the identification of leptin nearly two decades ago the central circuit that defends against reductions in body fat was revealed. Since then, the cellular and molecular pathways that leptin regulates in defense of body fat have been intensively and fruitfully studied. However, the systems that defend against rapid expansion of fat mass have been less well studied and characterized. Indeed, the key components remain largely obscure. During an effort to characterize the role that immune cells play in metabolism we uncovered a system that we believe limits fat mass expansion. The central component of this system is the activation of pro- apoptotic signaling in adipose tissue macrophages (ATMs). As adipose tissue expands, ATMs increase in number and accumulate large amounts of lipid, increasing cellular stress and their susceptibility to apoptosis. In studying strains of mice that vary in their susceptibility to high fat diet-induced obesity, we found that the size of the circulating natural killer (NK) cell population predicts adipose tissue NK cell content the size of the CD11c+ ATM population, and resistance to weight gain. Animals with the highest concentration of NK cells in their circulation and adipose tissue have fewer CD11c+ ATMs and are resistant to the development of obesity. Classically, NK cells recognize and induce apoptosis in malignant, virally infected and certain populations of stressed cells. We found that obesity increases the expression of an NK cell-recognized stress signal (RAET1e) in adipose tissue and specifically upregulates its expression in lipid-laden CD11c+ ATMs that are reduced in strains with high NK cells. These data suggested that NK cell targeted apoptosis of CD11c+ ATMs could limit fat mass expansion. Indeed, direct activation of apoptosis of CD11c+ ATMs in obese, but not in lean mice, reduces food intake and induces weight loss, without evidence of an inflammatory reaction or lipodystrophy. We propose to test (1) whether genetically decreasing or increasing NK cell targeted apoptosis of ATMs will predictable reduce or increase fat mass in high fat fed mice (2) whether weight loss induced by ATM apoptosis increases energy expenditure and requires leptin, and (3) whether overfeeding mice activates NK cell targeted apoptosis of ATMs to limit adipose tissue expansion. Achieving the goals of this application will identify potential therapeutic strategies to reduce or limit adipose tissue mass b targeted manipulation of adipose tissue immune cells.