The function and phenotype of immune cells are powerfully modulated by their biological milieu and immunologic context. Identifying the signals responsible for regulating context-specific function has provided key insights into immune regulation (1). Obesity induces an immune response with a strong inflammatory phenotype, in which adipose tissue expression and production of classic inflammatory molecules, including TNF-α, interferon-γ, inducible nitric oxide synthase, and IL-1β, are increased and implicated in the development of metabolic disease (2). A central feature of the inflammatory phenotype of adipose tissue in obese individuals is the recruitment and accumulation of a distinct macrophage population, adipose tissue macrophages (ATM) (3, 4). Lumeng et al. (5), several years ago, noted two large subpopulations of ATM defined by their expression of the integrin CD11c. They found that the majority of ATM in obese individuals was CD11c+, whereas those found in lean adipose tissue were primarily CD11c−. They proposed that during the development of obesity, CD11c+ ATM accumulate in adipose tissue and expressed the markers of classically activated, M1-polarized, macrophages. Conversely, they proposed that resident ATM are CD11c− and alternatively activated, M2-polarized cells that exert an antiinflammatory effect by secreted factors, including IL-10 (5). These findings strongly argue, not unexpectedly, that adipose tissue from obese individuals provides a unique context for macrophages to develop and function. The signals within this milieu that lead to recruitment and activation have not been completed delineated. However, data argue that adipocyte death, ER stress, hypoxia, and lipolysis can regulate ATM recruitment.

Studies of human forms of lipodystrophy, including those that occur in HIV-infected individuals treated with antiretroviral therapy, have also revealed that impaired adipose tissue development and function lead to adipose tissue recruitment of macrophages and up-regulation of inflammatory gene expression and circulating cytokines (6, 7). However, a previous report by Shoelson and co-workers (8) demonstrated that in a mouse model of chronic, congenital lipodystrophy, the inflammation was both qualitative and functionally distinct. They found that the adipose tissue was still on balance inflammatory, but the pattern of inflammatory and anti-inflammatory gene expression differed substantially between obese and lipodystrophic animals, and that anti-inflammatory strategies that reduced insulin resistance in obese mice had no effect on systemic metabolism in congenital lipodystrophy (8).

In their current study, Fischer-Posovszky (9) use an inducible transgenic mouse model of lipodystrophy, in which a modified form of the apoptosis-inducing protein caspase-8 is expressed under the aP2-promoter in adipocytes. Treatment of adipocytes expressing the modified caspase-8 with a dimerizing agent activated apoptosis and within days led to the involution of adipose tissue and nearly complete absence of lipid in remnant depots in treated, transgenic mice. Previously, the authors had demonstrated that induced adipocyte apoptosis leads to the influx of macrophages (10). In their current report, they find that the phenotype of the ATM is distinct from those seen in obesity and the more chronic forms of lipodystrophy. Acute lipodystrophy and the near complete absence of adipocytes leads to the recruitment of CD11c+ macrophages that surprisingly express markers of alternatively activation, including CD301 and CD206. Consistent with the expression of these markers the authors find that induction of adipocyte apoptosis increases adipose tissue expression of IL-10 with no effect on the expression of several genes encoding classic M1, inflammatory pro-
teins, including interferon-γ and inducible nitric oxide synthase.

What explains the alternatively activated phenotype of ATM in this form of lipodystrophy and what does it tell us about the functions of ATM? The authors suggest that a key difference between their model of lipodystrophy and other settings, in which ATM accumulate in adipose tissue, is the relative lack of adipocytes. They suggest that the death of nearly all adipocytes removes from their model adipocyte-derived signals, and therefore, they hypothesize that although adipocyte death is a key recruitment factor for ATM, factors released from stressed adipocyte are likely to be the key regulators of ATM inflammatory state. Alternatively, the apoptotic death that occurs in the inducible model of lipodystrophy may differ from the death of adipocytes in HIV-associated and congenital forms of lipodystrophy. Nonetheless, understanding adipocyte function remains central to identifying the factors that regulate the immune response to obesity.

Acknowledgments

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Disclosure Summary: The author has nothing to disclose.

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