Balázs Csóka,[1,2] Pál Pacher,[3] Péter Bai,[4,5,6] and György Haskó[1,2,4]

New Piece in the Jigsaw Puzzle: Adipose Tissue–Derived Stem Cells From Obese Subjects Drive Th17 Polarization

Diabetes 2015;64:2341–2343 | DOI: 10.2337/db15-0437

The global epidemic of obesity is constantly growing and represents an enormous challenge for health care systems worldwide. Obesity fuels the development of metabolic syndrome that includes components such as elevated glucose levels, insulin resistance, elevated blood pressure, and increased levels of triglycerides (1). Obesity and metabolic syndrome increase the risk of metabolic diseases, such as type 2 diabetes (T2D), cardiovascular disease, and atherosclerosis, and contribute to a reduction in life expectancy (2). In the U.S., the obesity rate in adults has reached 36% and obesity affects more than 1 billion people worldwide (3). Currently, 9.3% of the U.S. population has diabetes. In adults, T2D accounts for 90–95% of all diagnosed cases of diabetes, and the estimated total economic burden of diabetes in the U.S. is $245 billion (4). Thus, it is imperative that we increase our understanding of the mechanisms that lead to the development of obesity-induced insulin resistance and T2D, which will help identify therapeutic targets to reduce the impact of these syndromes on morbidity and mortality.

The first piece of evidence that obesity, insulin resistance, and inflammation are interconnected was provided more than a century ago when Dr. R.T. Williamson (5) observed that the anti-inflammatory drug sodium salicylate improved glucose control in patients with diabetes. Almost 90 years later, Hotamisligil et al. (6) revisited this observation as they found that the neutralization of tumor necrosis factor (TNF)-α improved insulin resistance, and thus a link between inflammation and diet-induced insulin resistance was established. Subsequent studies elucidated that a complex immune cellular network regulates inflammation and insulin responsiveness in metabolic tissues. Recently, interleukin (IL)-1β antibodies in monotherapy or in combination with other antidiabetes agents show promise in patients with diabetes (7).

Adipose tissue is a perplexingly complicated endocrine organ that contains a multitude of cell types, such as adipocyte-derived stem cells (ASCs), adipocytes, vascular cells, and immune cells, that all play a role in obesity-induced inflammation. Although the pathogenesis of obesity-induced inflammation and insulin resistance remains incompletely understood, several key events have been identified. Excess calorie intake induces adipose tissue enlargement and causes adipocyte dysfunction. Enlarged adipocytes produce cytokines and chemokines that include TNF-α and chemokine (C-C motif) ligand-2, which, in turn, promote immune cell accumulation in the adipose tissue. Immigrated inflammatory immune cells enhance adipose tissue inflammation, which further exacerbates adipocyte dysfunction. TNF-α secreted by inflammatory cells interferes with insulin receptor signaling pathways in adipocytes and causes peripheral insulin resistance (8). While macrophages are preeminent in promoting proinflammatory conditions in the enlarged adipose tissue (9), recent data confirmed the harmful role of other innate immune cells as well as diverse T-cell subsets, such as $CD4^+$ T helper (Th)1 and $CD8^+$ T effector cells (10). Recently, a role for another Th-cell subset, Th17 cells, in obesity-induced inflammation was implicated based on the findings that the number of Th17 cells increases in obese subjects (11,12) and that IL-17A, the major Th17 cell product, inhibits adipogenesis and therefore promotes

[1]Department of Surgery, Rutgers New Jersey Medical School, Newark, NJ
[2]Center for Immunity and Inflammation, Rutgers New Jersey Medical School, Newark, NJ
[3]National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD
[4]Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[5]MTA-DE Lendület Laboratory of Cellular Metabolism Research Group, University of Debrecen, Debrecen, Hungary
[6]Research Center for Molecular Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
Corresponding author: Balázs Csóka, csokaba@njms.rutgers.edu.

See accompanying article, p. 2477.

insulin resistance (13). The exact mechanisms of Th17 cell development in the enlarged adipose tissue remain unknown.

In this issue of *Diabetes*, Eljaafari et al. (14) provide intriguing evidence that by coculturing human ASCs with human mononuclear cells (MNCs), ASCs from obese donors, but not from lean donors, drastically change the phenotype of MNCs. First of all, the researchers show that ASCs augment the differentiation of naïve $CD4^+$ T cells toward Th17 cells. In addition to promoting Th17 polarization, ASCs from obese patients inhibit Th1 cell development. Interestingly, the authors found that the presence of ASCs has a dual effect on interferon (IFN)γ secretion based on the IFNγ-producing populations examined: although ASCs inhibited IFNγ production by Th1 cells, they increased the secretion of IFNγ by Th17 cells. This observation brings up the question of by which mechanisms ASCs induce preferential Th17 differentiation over Th1 responses. One possible clue is indicated by the findings that IL-17A secretion was stimulated by both allogeneic and autologous ASCs, which suggests that ASCs might present a specific antigen to T cells to instigate Th17 differentiation. Future studies will clarify the precise mechanisms of how ASCs control $CD4^+$ cell fate in the expanding adipose tissue.

As Eljaafari et al. (14) also found elevated IL-1β and IL-6 production in coculture experiments using ASCs and MNCs, it was important to delineate the cellular origin of these cytokines. As monocytes are the main source of IL-1β and IL-6 production in MNCs, the authors depleted monocytes from MNCs and then they cocultured this depleted fraction of MNCs with ASCs. They observed that monocyte-depleted MNC fractions barely produced IL-1β, while monocyte depletion did not affect IL-6 production, suggesting that monocytes are the main source of IL-1β but not IL-6. Altogether, these results suggest that the triumvirate of monocytes, ASCs, and T cells controls Th17-specific adipose tissue inflammation.

Inflammasomes are caspase-1–containing multicomponent protein complexes, which proteolytically cleave IL-1β and IL-18 to induce the secretion of these cytokines by adipose tissue macrophages (15). Eljaafari et al. (14) reveal that caspase-1 activation and IL-1β secretion are important events in increasing IL-17A production by Th17 cells. While caspase-1 inhibition almost completely abrogated IL-17 production in ASC-MNC coculture experiments, anti–IL-1β antibody–mediated blockade alone only partially decreased IL-17A secretion by Th17 cells. These observations suggest that other inflammasome-regulated factors, including IL-18, also might be needed to trigger optimal IL-17A secretion. In addition, future studies are warranted to identify which specific inflammasome (i.e., NLRP1, NLRP3, NLRC4, and AIM2) is important for IL-17A production and what triggers inflammasome activation in obese adipose tissue. One candidate can be IL-17 itself as it has been shown that IL-17 stimulates IL-1β production by macrophages (16).

Eljaafari et al. (14) also address the molecular signaling mechanisms that lie behind ASC-induced Th17 differentiation. They provide evidence that PI3K and STAT3 are critical factors. Previous studies showed that whereas STAT3 activates IL-17A, STAT5 inhibits IL-17A transcription by binding to the same sites of the *IL-17A/F* locus (17). The authors of the current study demonstrate that this mechanism is also operational in the adipose tissue, as ASCs favored STAT3 over STAT5 dominancy at the *IL-17A/F* locus, therefore activating IL-17A transcription. As the authors did not assess what are the mechanisms by which ASCs differentially affect the transcription of IFNγ in Th1 and Th17 cells, this intriguing question will have to be addressed in the future.

In their working model, Eljaafari et al. (14) propose a complex network comprising ASCs, $CD4^+$ T cells, and monocytes (Fig. 1). In this model, ASCs obtained from obese subjects promote Th17 differentiation via increasing the transcription of IL-17A through activating the PI3K and STAT3 pathways. Increased IL-17 secretion by Th17 cells inhibits the differentiation of ASCs to adipocytes and thus the insulin responsiveness of the adipocytes. Furthermore, signals derived from ASCs or MNCs induce inflammasome activation and IL-1β secretion by monocytes, and this secreted IL-1β is required, at least partially, to maintain or further increase IL-17A production by Th17 cells. In summary, this work demonstrates that in addition to the known role of ASCs in affecting the

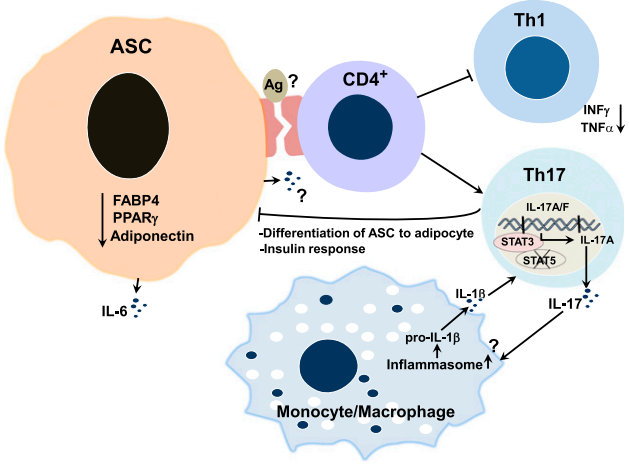

Figure 1—ASCs induce Th17 polarization. ASCs obtained from obese subjects inhibit Th1 polarization and production of IFNγ and TNF-α by Th1 cells. Moreover, ASCs, predominantly through direct cell-cell contact probably with an unidentified antigen (Ag) or cell surface molecule, promote Th17 differentiation and augment IL-17A transcription through activating PI3K and STAT3 pathways. Signals derived from ASCs or MNCs induce inflammasome activation and IL-1β secretion by monocytes and macrophages. Afterward, IL-1β secreted by monocytes and macrophages further increases the production of IL-17A by Th17 cells. Elevated IL-17 secretion by Th17 cells inhibits differentiation of ASCs to adipocytes and insulin response of these cells.

function of Th1 cells (18), ASCs are also active players in regulating Th17-mediated inflammation in the obese adipose tissue. In conclusion, the study by Eljaafari et al. (14) supports the argument that we need to better understand the relationships among the various cell populations that reside in the adipose tissue and their potential contribution to insulin resistance.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Grundy SM. Use of emerging lipoprotein risk factors in assessment of cardiovascular risk. JAMA 2012;307:2540–2542
2. Leal J, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. Eur Heart J 2009;30:834–839
3. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012; 307:491–497
4. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA, U.S. Department of Health and Human Services, 2014
5. Williamson RT. On the treatment of glycosuria and diabetes mellitus with sodium salicylate. BMJ 1901;1:760–762
6. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91
7. Dinarello CA, Donath MY, Mandrup-Poulsen T. Role of IL-1beta in type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2010;17:314–321
8. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444: 860–867
9. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175–184
10. Cildir G, Akıncılar SC, Tergaonkar V. Chronic adipose tissue inflammation: all immune cells on the stage. Trends Mol Med 2013;19:487–500
11. Sumarac-Dumanovic M, Stevanovic D, Ljubic A, et al. Increased activity of interleukin-23/interleukin-17 proinflammatory axis in obese women. Int J Obes (Lond) 2009;33:151–156
12. Fabbrini E, Cella M, McCartney SA, et al. Association between specific adipose tissue CD4+ T-cell populations and insulin resistance in obese individuals. Gastroenterology 2013;145:366–374.e1–3
13. Ahmed M, Gaffen SL. IL-17 inhibits adipogenesis in part via C/EBPα, PPARγ and Krüppel-like factors. Cytokine 2013;61:898–905
14. Eljaafari A, Robert M, Chehimi M, et al. Adipose tissue–derived stem cells from obese subjects contribute to inflammation and reduced insulin response in adipocytes through differential regulation of the Th1/Th17 balance and monocyte activation. Diabetes 2015;64:2477–2488
15. Esser N, L'homme L, De Roover A, et al. Obesity phenotype is related to NLRP3 inflammasome activity and immunological profile of visceral adipose tissue. Diabetologia 2013;56:2487–2497
16. Jovanovic DV, Di Battista JA, Martel-Pelletier J, et al. IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. J Immunol 1998;160:3513–3521
17. Yang XP, Ghoreschi K, Steward-Tharp SM, et al. Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nat Immunol 2011;12:247–254
18. Hoogduijn MJ, Crop MJ, Peeters AM, et al. Human heart, spleen, and perirenal fat-derived mesenchymal stem cells have immunomodulatory capacities. Stem Cells Dev 2007;16:597–604