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CD8+ T cells drive adipose tissue inflammation – A novel clue for NASH pathogenesis?

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CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nishimura S, Manabe I, Nagasaki M, Eto K, Yamashita H, Ohsugi M, Otsu M, Hara K, Ueki K, Sugiura S, Yoshimura K, Kadowaki T, Nagai R. Nat Med 2009;15(8):914–20.

Abstract: Inflammation is increasingly regarded as a key process underlying metabolic diseases in obese individuals. In particular, obese adipose tissue shows features characteristic of active local inflammation. At present, however, little is known about the sequence of events that comprises the inflammatory cascade or the mechanism by which inflammation develops. We found that large numbers of CD8(+) effector T cells infiltrated obese epididymal adipose tissue in mice fed a high-fat diet, whereas the numbers of CD4(+) helper and regulatory T cells were diminished. The infiltration by CD8(+) T cells preceded the accumulation of macrophages, and immunological and genetic depletion of CD8(+) T cells lowered macrophage infiltration and adipose tissue inflammation and ameliorated systemic insulin resistance. Conversely, adoptive transfer of CD8(+) T cells to CD8-deficient mice aggravated adipose inflammation. Coculture and other in vitro experiments revealed a vicious cycle of interactions between CD8(+) T cells, macrophages and adipose tissue. Our findings suggest that obese adipose tissue activates CD8(+) T cells, which, in turn, promote the recruitment and activation of macrophages in this tissue. These results support the notion that CD8(+) T cells have an essential role in the initiation and propagation of adipose inflammation.

Non-alcoholic steatohepatitis (NASH) is rapidly becoming the leading cause of liver-related morbidity and mortality, largely in affluent societies. NASH may be present in 10–25% of patients with hepatic steatosis due to non-alcoholic fatty liver disease (NAFLD), a condition found in the majority of obese individuals (BMI $\geqslant$ 30 [1]). With obesity rates of ~30% in the US, and rising numbers in almost all countries of the world, prevention and treatment of NAFLD and especially NASH are urgently needed. NASH is considered the hepatic manifestation of a key feature of the metabolic syndrome, i.e., insulin resistance in conjunction with visceral adipose tissue inflammation [2]. In contrast, an increase in peripheral fat alone, i.e., white adipose tissue, is not associated with the metabolic syndrome or NASH. Thus, the insulin sensitizer Pioglitazone improves insulin sensitivity, fatty liver, and NASH, despite overall weight gain, due to redistribution of lipids from central stores to the peripheral (white) adipose tissue [3].

Chronic, low-grade inflammation is now considered to play a pivotal role in the development of metabolic syndrome in obesity [2]. In the August issue of Nature Medicine, three studies addressed different but related aspects of a previously unrecognized pathogenetic role of adaptive (T cell mediated) immunity in obesity-induced inflammation and insulin resistance in mice. Nishimura et al. [4] analyzed the dynamics of the inflammatory infiltrate in the visceral (epididymal) fat of C57Bl/6 mice with diet-induced obesity. They found that CD8+ T cells were recruited several weeks before the appearance of adipose tissue-associated macrophages (ATM), which are the hallmark and effectors of adipose tissue inflammation. Both antibody-mediated and genetic elimination of CD8+ T cells disrupted the vicious circle of adipose tissue inflammation, ATM recruitment and insulin resistance (Fig. 1), though mice continued to consume the high-fat diet and became obese. In the same volume, Winer et al. [5] and Feuerer et al. [6] confirmed an increase in the CD8+ to CD4+ T cell ratio in mice with diet-induced obesity. Moreover, both studies report (visceral) adipose tissue-restricted T cell receptor (TCR) rearrangements and an (oligo)-clonal CD8+ T cell expansion, pointing to the existence of yet unidentified "obesity" neoantigens. Finally, CD4+ Foxp3+ regulatory T cells and CD4+ Th2 T cells suppressed the proinflammatory CD8+ T cell response and prevented insulin resistance [6]. These groundbreaking studies are paving the way for rapid changes in our understanding of the metabolic syndrome, with direct implications on NASH pathogenesis.

In obesity, fat-laden hepatocytes and adipocytes share common features, such as storage of excess energy and important endocrine functions; physiological functions of both cell types are severely affected by obesity-related inflammation. Steatohepatitis in NASH is tightly linked to visceral adipose tissue inflammation in the context of the metabolic syndrome and may share common pathogenetic mechanisms. In addition, the liver plays a central role in the regulation of insulin sensitivity, because lack of insulin signaling in the liver alone was shown to be sufficient to cause systemic insulin resistance in mice [7].

Keywords: Non-alcoholic steatohepatitis; CD8+ T cells; Obesity; Metabolic syndrome; Insulin resistance; Inflammation; Adipose tissue; Macrophage.

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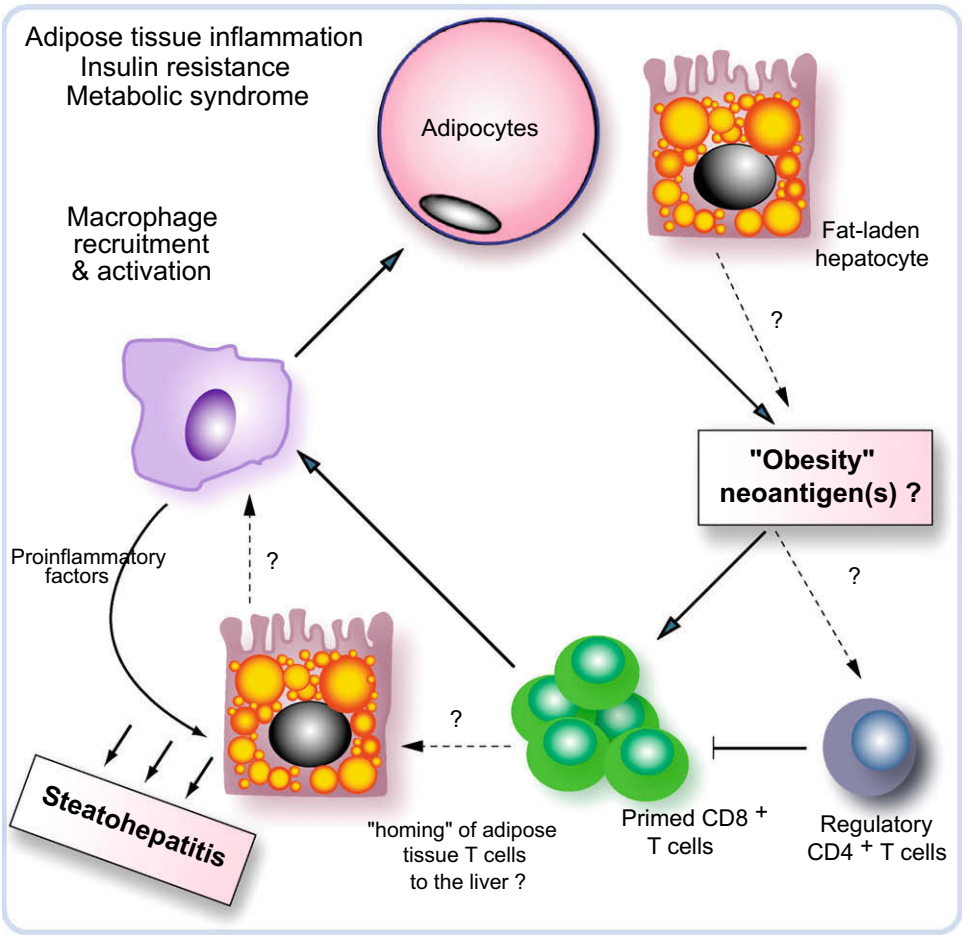

Fig. 1. The study by Nishimura et al. [4] proposes a vicious circle between adipocytes, CD8+ T cells, and adipose tissue macrophages. Hypothetical implications for the immunology of steatohepatitis is illustrated.

Since the discussed papers demonstrate that adaptive (antigen restricted T cell) immunity is a central trigger (CD8+ T cells) or suppressor (CD4+ regulatory or Th2 T cells) of the metabolic syndrome, the conventional view of NASH pathogenesis as fatty liver which suffers a "second (or third) hit" specific to the liver (such as certain drugs, genetic predisposition related to oxidative stress or insulin sensitivity, primary iron overload, or infection with the hepatitis B or C virus) may have to be broadened. In light of the novel data it cannot be excluded that reduction in hepatic inflammation in NASH patients treated with the glitazones might be attributable to inhibition of inflammatory T cells [8] rather than their insulin-sensitizing properties. These novel studies provide a framework for new research into the immune-pathogenesis of NASH (Fig. 1), which may finally lead to novel T cell-directed therapies for steatohepatitis.

Clearly, identification of the putative visceral adipose tissue neoantigen(s) and the relevant antigen-presenting cell(s) become the next challenges in the obesity field and could lead to groundbreaking discoveries and novel therapies. The potential impact of these groundbreaking developments on the Hepatology field is indeed hard to overestimate. Clinical and experimental studies exploring the role of adaptive immunity in NASH pathogenesis are urgently needed. The following questions remain to be addressed:

(1) What is the nature and function of T cells in NASH liver biopsies, in visceral adipose tissue of patients with NASH, and in small animal models of NASH? While the T cell presence and involvement in NASH remains completely unexplored, inflammatory macrophages infiltrating the liver have already been identified as contributors to human [9] and rodent steatohepatitis [10].

(2) Is there homing to the liver of the same CD8(+) T cells that are activated in the visceral adipose tissue, causing hepatic macrophage recruitment, with subsequent low-grade inflammation and NASH? Of note, a pathological role of CD8+ T cells has been suggested earlier in hepatic inflammation and fibrogenesis in mice [11].

(3) Is there a similarity in TCR rearrangement in the visceral adipose tissue and the liver of NASH patients (and of NASH animal models), which would implicate common neoantigens in the adipose tissue and the steatotic liver?

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