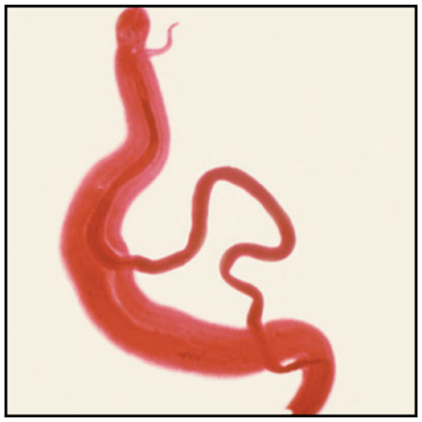
Cell

The Many Faces of Insulin Resistance

Low-grade inflammation in the liver and adipose tissue drives systemic insulin resistance. Recent reports, discussed in this Select, identify new pathways used by immune cell populations to modulate chronic metabolic inflammation that results from obesity-associated insulin resistance.



Photograph of adult schistosomes from the CDC DPDx image library. Image courtesy of Donald. A. Harn

What Do Helminths and Breast Milk Have in Common?

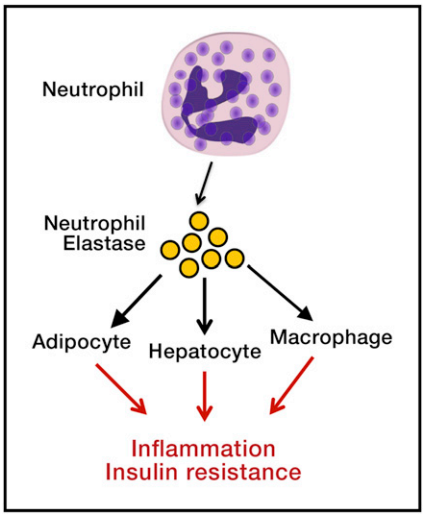
Parasitic worms such as helminths and human breast milk express immunomodulatory glycans recently shown to improve glucose tolerance and insulin sensitivity. During infection with *Schistosoma mansoni*, parasite eggs trapped in host tissues initiate a cascade of events that results in attenuated immune responses by the host (hence prolonged parasite survival). Bhargava et al. (2012) demonstrate that the LewisX trisaccharide, part of the glycan lacto-N-fucopentaose III (LNFPIII), that is secreted from a saline-soluble homogenate of helmith eggs or human breast milk is effective in reducing the chronic inflammation seen in diabetes induced by a high-fat diet (HFD), thus resulting in improved metabolic function. Specifically, LNFPIII increases interleukin-10 (Il-10), a cytokine that has been shown to improve metabolic homeostasis. Mice treated with LNFPIII have less proinflammatory M1 and more anti-inflammatory M2 macrophage-specific gene expression in white adipose tissue (WAT), resulting in enhanced insulin signaling, reduced WAT inflammation, and improved systemic glucose homeostasis. An interesting observation is that although the immunomodulatory activity of LNFPIII in WAT is Il-10 dependent, the glycan also has critical Il-10-independent functions. The authors show that LNFPIII has beneficial effects in liver because it can protect against diet-induced lipid accumulation and hepatosteatosis. LNFPIII affects de novo lipogenesis by reducing expression of hepatic lipogenic enzymes, including the master lipogenic transcription factor SREBP-1C. These effects are Il-10 independent, and the LNFPIII-mediated reduction is partly driven by the upregulation of the negative SREBP-1C regulator and nuclear receptor FXRa via an ERK-AP1-FXRa axis. Collectively, LNFPIII treatment shifts the immune profile to an anti-inflammatory state, which warrants further exploration of its therapeutic potential.

Bhargava et al. (2012). Nat. Med. 18, 1665–1672.

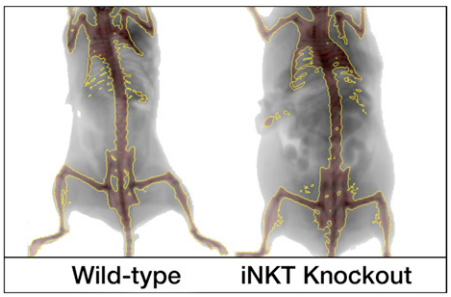
The Secret Life of Secreted Elastase

Neutrophils, which comprise about 90% of granulocytes, are enriched in the adipose of mice fed a HFD. This begs the question, do neutrophils play a role in initiating the inflammatory cascade seen in obesity? In a series of elegant experiments, Talukdar et al. (2012) show that neutrophils contribute to the etiology of inflammation-induced insulin resistance and that elastase, a serine protease secreted by neutrophils, plays a crucial mechanistic role in the process. Indeed, elastase expression and activity increase in the adipose and liver of mice, concomitant to HFD-induced neutrophil infiltration, and chemical inhibition of the enzyme improves glucose intolerance, whereas treatment with recombinant elastase has the opposite effect. Moreover, genetic deletion of elastase in mice results in substantially higher glucose tolerance and lower fasting insulin concentration in both liver and adipose tissue, as highlighted by increased levels of insulin receptor substrate 1 (IRS1) (an interesting twist based on the ability of extracellular neutrophil elastase to gain access to the intracellular space and mediate its degradation) and AKT phosphorylation. The authors next show that the proinflammatory effects of elastase are dependent on TLR-4 signaling and NFκB activation and suggest that this action by secreted elastase possibly results in recruitment and polarization of adipose macrophages (M1) and also, as part of a feed-forward secondary mechanism, additional neutrophil accumulation. Thus, the secret life of secreted elastase is revealed, and neutrophils can be added to the list of immune cells mediating the low-grade inflammation seen in insulin resistance driven by obesity.

Talukdar et al. (2012). Nat. Med. 18, 1407–1412.



Neutrofil elastase is a mediator of the low-grade inflammation seen in insulin resistance. Image courtesy of Dayoung Oh.



Dual energy X-ray absorptiometry scan shows that iNKT-deficient mice have significantly more body fat than wild-type mice, but lean mass is unchanged. Image courtesy of Linda Lynch.

Multipurpose Natural Killer T Cells

In the management of obesity-induced insulin resistance, adapting proven therapies for other disorders would be highly desirable. A report by Lynch et al. (2012) suggests just such an approach. They identify an innate T lymphocyte population of invariant natural killer T (iNKT) cells that are protective against the development of HFD-driven insulin resistance. iNKT cells are enriched in the fat depots of lean humans, get depleted in obesity, and reappear after bariatric surgery. Similarly, in the mouse, iNKT are severely depleted in the leptin-deficient (ob/ob) mouse model, progressively decline to markedly reduced numbers during HFD feeding, and bounce back when the mice are switched to a chow diet. The authors show that this unique immune repertoire of fat-derived iNKT cells produces more anti-inflammatory IL-10 after stimulation with the prototypical lipid antigen alpha-galactosylceramide (αGC), which is intriguing because IL-10 promotes a phenotype switch toward the M2 anti-inflammatory macrophage population. Compelling data from mice with iNKT cell deficiency show a correlation with increased metabolic syndrome and insulin resistance that worsens on a HFD and increased M1 macrophage infiltration in the adipose. Interestingly, adoptive transfer of iNKT cells to obese mice not only improves glucose homeostasis but also triggers significant fat loss. The next burning question of course is, what is the effect of αGC on the insulin-resistance profile of these mouse models? Indeed, αGC injection causes a significant decrease in adipose mass and cell size, improves glucose homeostasis, and results in markedly increased iNKT cell numbers. As αGC is already used as a treatment in multiple cancer settings, and it does not cause hypoglycemia in the diabetic and euglycemic murine models, it is a matter of time before its effect on humans with insulin resistance is determined.

Lynch et al. (2012). Immunity 37, 574–587.

Finding the Mysterious TLR-4 Ligand

Free fatty acids (FFAs) mediate activation of the TLR-4/NFκB pathway to promote insulin resistance. However, how FFAs activate TLR-4 has remained elusive. The paper by Pal et al. (2012) addresses this conundrum and suggests that fetuin is the mysterious ligand. This is intriguing because fetuin, a liver secretory glycoprotein and major carrier of FFAs in the circulation, has already been labeled as a marker of low-grade metabolic inflammation because it stimulates production of cytokines and chemokines from adipocytes and macrophages. The authors show that fetuin fits the role of a TLR-4 ligand because it can recapitulate many of the effects seen previously that linked TLR-4 action to insulin resistance. For example, mice with fetuin and TLR-4 knockdown or hepatectomized rats (another means for reducing fetuin expression) are protected from HFD-induced insulin resistance and NFκB activation. Restoring fetuin expression in the knockdown mouse model results in lipid-induced insulin resistance, whereas infusion of the proinflammatory lipid palmitate, a FFA with maximum binding to fetuin but not to TLR-4, fails to activate TLR-4 in mice with fetuin knockdown. The authors show that FFA-mediated activation of TLR-4 and subsequent NFκB phosphorylation requires intact fetuin, and the lipotoxicity-driven insulin resistance involves not only the presence of FFAs, fetuin, and TLR-4 but also their physical interaction. Indeed, two leucine-rich repeats on TLR-4 are crucial for fetuin binding, and FFAs induce insulin resistance, whereas the terminal β-galactosidase moiety of fetuin is the candidate site for TLR-4 binding. Thus, fetuin acts as an adaptor protein and endogenous presenter of FFAs to TLR-4 and represents a new therapeutic target in the management lipid-induced insulin resistance.

Pal et al. (2012). Nat. Med. 18, 1279–1285.

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