IMMUNOMETABOLISM

Inflammation brakes mitochondrial metabolism in obesity

A vicious cycle, linking obesity with chronic inflammation, fuels the development and exacerbation of metabolic syndrome and other disorders. Modulation of mitochondrial energy metabolism via interleukin-1β signaling establishes a runaway positive-feedback loop that brings about and reinforces the sequelae of a high-fat diet.

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Obesity is rapidly becoming a global health hazard[1]. According to the World Health Organization, in recent years, the prevalence of obesity worldwide has reached epidemic proportions[2]. The societal ramifications of this grim development are wide ranging, given that obesity is also a major risk factor for, and is tightly associated with, devastating human pathologies, including cardiovascular diseases, type 2 diabetes mellitus, cancer, metabolic disorders, dementia and accelerated aging, among others[2]. Thus, understanding the intricate signaling pathways and molecular mechanisms underlying and sustaining the complex physiology of obesity is becoming a pressing priority.

Being overweight has long been known to induce a variety of inflammatory responses[3,4]. The reverse link has also been postulated; chronic systemic inflammation is a condition that can facilitate the development of metabolic syndrome and obesity[5]. However, the cellular and molecular underpinnings of this latter association have remained largely elusive. In this issue of *Nature Immunology*, Zhou and colleagues[6] identify a signaling cascade that is triggered by the proinflammatory cytokine interleukin (IL)-1β to ultimately downregulate energy generation and expenditure in adipocyte mitochondria (Fig. 1). This newfound association essentially establishes a positive-feedback loop, whereby a high-fat diet (HFD) drives obesity and induces low-level chronic inflammation, which in turn impedes mitochondrial energy metabolism to further enhance fat accumulation and weight gain.

Consistent with previous reports linking inflammation with obesity, the authors found that IL-1β levels are much higher in the adipose tissue of HFD-fed mice versus control animals fed a low-fat diet. Elevated IL-1β interfered with mitochondrial oxidative phosphorylation by suppressing respiratory chain supercomplex formation, without affecting other aspects of mitochondrial physiology and homeostasis such as mitophagy, reactive oxygen species (ROS) production, calcium leakage or cytochrome *c* release. Organization of respiratory chain complexes I–IV into supercomplexes in the inner mitochondrial membrane (IMM) is important to establish and maintain the proton gradient required to generate energy. Consequently, ATP production and the associated oxygen consumption, as well as fatty acid oxidation (FAO), are diminished in adipocytes upon IL-1β stimulation.

How are these alterations in adipocyte mitochondrial energy metabolism brought about by IL-1β? The interleukin 1 receptor (IL-1R) is activated by IL-1β and recruits MyD88, an innate immunity signal

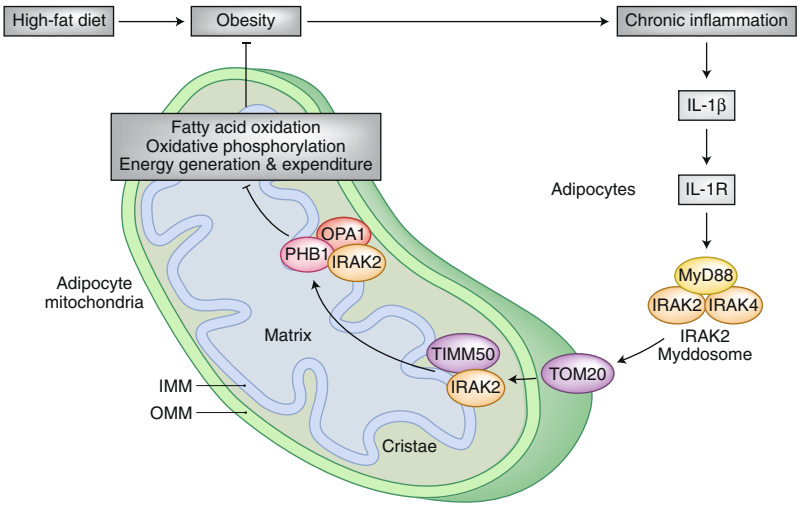

Fig. 1 | Reprogramming of mitochondrial metabolism. Obesity-induced inflammation attenuates energy generation and expenditure in adipocyte mitochondria, further aggravating obesity. IL-1β inflammatory cytokine signaling via IL-1R recruits the IRAK2–Myddosome to mitochondria, where it associates with the mitochondrial import receptor subunit TOM20 on the outer mitochondrial membrane. IRAK2 then translocates to the inner mitochondrial membrane, where it interacts with the inner membrane translocase subunit TIMM50. While at the inner mitochondrial membrane, IRAK2 binds the prohibitin complex subunit PHB1. Association with PHB1 facilitates the interaction of IRAK2 with the mitochondrial dynamin-like GTPase OPA1. Binding of IRAK2 to PHB1 and OPA1 alters the morphology of inner mitochondrial membrane cristae and interferes with respiratory complex formation and function. As a result, oxidative phosphorylation and fatty acid oxidation in adipocytes are diminished. In addition, uncoupled mitochondrial respiration that contributes to thermogenesis becomes impaired, reducing energy expenditure in brown adipose tissue cells. Thus, IRAK2 is a key component of a positive-feedback mechanism that shunts mitochondrial energy metabolism to ultimately augment fat accumulation and obesity.

transduction adaptor that binds both IL-1R and Toll-like receptor (TLR) complexes[7]. Elimination of IL-1R in adipocytes alleviated the impact of IL-1β treatment on adipocyte mitochondria. In addition, mice lacking MyD88 specifically in adipose tissue exhibited improved resistance to the detrimental effects of HFD. These animals were leaner and showed increased brown adipose tissue (BAT) thermogenic capacity, with less lipid accumulation and elevated FAO in adipocytes. Remarkably, depletion of MyD88 elicits extensive remodeling of the IMM in adipocytes, with increased cristae formation and concomitant enhanced respiratory chain supercomplex assembly. These findings indicate that IL-1β signaling triggers mitochondrial adaptations that diminish energy expenditure in adipocytes.

IL-1 signals are propagated downstream of IL-1R via the formation of the Myddosome, a multiprotein complex comprising MyD88 and the IL-1R-associated kinases (IRAK) 1, 2 and 4, among other protein components[8]. IRAK1 has already been implicated in mediating HFD-induced metabolic pathology, including glucose intolerance and insulin resistance[9]. Zhou and colleagues now report that, upon IL-1β stimulation, MyD88, IRAK2 and IRAK4, but not IRAK1, translocate to the outer mitochondrial membrane (OMM) in adipocytes[6]. Depletion of MyD88 blocks translocation, indicating that Myddosome formation is required for this step. However, only IRAK2, not MyD88 or IRAK4, enters the mitochondrial intermembrane space and localizes to the IMM. Indeed, IRAK2 possesses a functional mitochondrial localization signal and interacts both with the translocase of outer mitochondrial membrane protein TOM20 and the translocase of inner mitochondrial membrane, TIMM50. These surprising and insightful findings offer a potential path via which proinflammatory IL-1β signaling could directly modulate mitochondrial energy metabolism. In this scenario, IRAK2 provides the critical missing link. Consistently, severing this link by knocking down IRAK2 or impairing its mitochondrial localization abolished the attenuation of mitochondrial energy metabolism imposed by IL-1β treatment in adipocytes. By contrast, IRAK2 deficiency did not interfere with inflammatory responses triggered by IL-1β in adipocytes, indicating a specific role for this kinase in the regulation of mitochondrial activity.

Mice lacking IRAK2 were considerably more resistant to the harmful HFD. These animals recapitulated MyD88-deficient mutants with regard to weight gain, insulin sensitivity and adipose tissue physiology. Likewise, they displayed elevated FAO and thermogenic gene expression, in addition to expansion of the cristae, in adipose tissue mitochondria. Furthermore, removal of either MyD88 or IRAK2 promoted respiratory chain supercomplex formation and increased energy expenditure, particularly in BAT mitochondria, where most thermogenesis takes place by uncoupling the electron transport chain from ATP production and dissipating the electrochemical proton gradient energy as heat[10]. As a result, these animals showed higher body temperature and reduced lipid accumulation. Collectively, these observations indicate that HFD puts the brakes on mitochondrial energy metabolism via MyD88 and IRAK2, which further exacerbates obesity.

The question now becomes, how does IRAK2 exert its regulatory function on mitochondrial respiratory chain supercomplex assembly? The authors identified the mitochondrial scaffold protein prohibitin 1 (PHB1) as an interactor of IRAK2 on the IMM[6]. PHB1 and the related protein prohibitin 2 (PHB2) are subunits of a large, ring-like macromolecular structure at the IMM, implicated in processes ranging from mitochondrial biogenesis to insulin–insulin-like growth factor 1 (IGF1) signaling, cancer and aging[11,12]. Importantly, prohibitins are also involved in cristae morphogenesis by regulating the processing of optic atrophy protein 1 (OPA1), a dynamin-like GTPase serving as a component of the mitochondrial fusion machinery[13]. Association of IRAK2 with PHB1, upon IL-1β stimulation, also recruits OPA1 to the complex. As a consequence of OPA1 sequestration by IRAK2 and PHB1, cristae become destabilized and respiratory chain supercomplex formation is diminished. In this context, PHB1 facilitates the interaction of IRAK2 with OPA1. Accordingly, loss of PHB1 alleviates the IRAK2-mediated moderation of mitochondrial energy metabolism caused by IL-1β stimulation in adipocytes.

The fusogenic function of OPA1 is primarily regulated by the ATP-independent metalloprotease OMA1, which shows overlapping activity with the m-AAA protease[13]. Both OMA1 and the m-AAA protease are sequestered in IMM microdomains, bounded by ring-like prohibitin complexes[14]. Interestingly, OPA1 deficiency was previously shown to fortify against HFD-induced obesity and insulin resistance, albeit via a different mechanism involving ER stress responses and fibroblast growth factor 21 (FGF21) signaling in muscle cells[15]. By contrast, OMA1-depleted mice exhibit increased body weight, coupled with reduced energy expenditure and thermogenesis[16]. While these studies are ostensibly at odds with the findings of Zhou and colleagues[6], it should be noted that the function of OPA1 in mitochondrial fusion can be decoupled from its capacity to organize and preserve IMM cristae[17]. Therefore, the overarching role of OPA1 in mitochondrial energy metabolism at the organismal level is rather intricate and entails the integration of multiple effects in diverse tissues. Nevertheless, given the requirement for OPA1 oligomerization, but not GTPase activity, in cristae formation[17], it is tempting to hypothesize that interaction with both IRAK2 and PHB1 interferes with OPA1 oligomer assembly at the IMM, and thus, cristae maintenance in adipocytes. In agreement with this notion, the authors find that IRAK2 is still required for impeding mitochondrial metabolism following IL-1β stimulation of adipocytes that overexpress PHB1[6]. Be that as it may, further dissection of cristae formation mechanics and the contribution of interactions between IRAK2 and PHB1 and OPA1 therein will provide deeper insight relevant to the rewiring of mitochondrial metabolism by proinflammatory signals.

Notably, phosphorylation of IRAK2 is necessary for its proper localization with TIMM50 at the IMM and for interaction with PHB1 and OPA1. Inactivation of the kinase function of IRAK2 eliminated the impact of IL-1β treatment on mitochondrial energy metabolism. While the kinase-inactive variant still associates with TOM20 and enters mitochondria upon IL-1β stimulation, IRAK2 phosphorylation is abolished, suggesting that IRAK2 becomes autophosphorylated. This modification is a prerequisite for interaction with TIMM50 and for interfacing with PHB1–OPA1. As such, it is essential for IRAK2-suppressive functions in mitochondria. The phenotype of kinase-inactive IRAK2 mutant animals fully corroborates this chain of events and, to a large extent, resembles that of IRAK2 knockout mice. When subjected to a HFD, these animals are leaner and less insulin resistant. Moreover, they exhibit elevated FAO activity and respiratory chain supercomplex formation, as well as higher body temperature, indicative of boosted thermogenesis and energy expenditure in BAT.

Combined, the findings of Zhou and colleagues reveal an unexpected signaling axis that determines mitochondrial activity in adipocytes by relaying proinflammatory IL-1β signals via the Myddosome and IRAK2 to modulate respiratory chain supercomplex formation, thus impacting energy generation and expenditure.

Importantly, this transduction cascade establishes a positive-feedback loop that amplifies the detrimental effects of HFD and aggravates obesity (Fig. 1). A similar molecular mechanism may govern mitochondrial energy metabolism in human adipose tissue. Indeed, HFD causes low-level inflammation and secretion of proinflammatory cytokines, including IL-1, in humans[18]. In addition, consistent with other studies[19], the authors find that *IL1B* gene expression is higher in the adipose tissue of patients with diabetes[6]. Hence, the study by Zhou and colleagues provides ample scope for investigating potential intervention strategies targeting IRAK2 and other components of the newly discovered pathway in adipocytes, with the aim of ameliorating obesity and related metabolic disorders in humans. ❐

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Competing interests

The author declares no competing interests.