as seems likely, then we can understand why this variant spreads so efficiently. There is a clear possibility that, when a large payload of Delta virus is inhaled, it could evade or overwhelm local immunity in the URT, leading to breakthrough infections in vaccinated people, albeit of limited severity, that may be transmissible to other people. Antibodies to the spike protein are found in the URTs of mRNA vaccines, as judged by saliva assays, but in amounts that are quite low and perhaps inadequate to defeat Delta[16]. Systemic NAbs, however, keep the infections largely restricted to the URT in vaccinated people[14].

Ongoing assessments of how authorized vaccines perform against Delta in NHPs will be informative, adding to knowledge now accruing from monitoring individual humans and study cohorts. Although Beta is fading from the scene, future variants could combine its greater NAb-resistance properties with Delta's increased transmissibility. The more we know about how these viruses intersect with the human immune system, the more prepared we will be if that happens. Given the speed at which new strains are now appearing, that new variant may be the Nu variant. ❐

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Competing interests

The authors declare no competing interests

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IMMUNOMETABOLISM

The IRX(3)some factor in macrophages

Qiu and colleagues identify IRX3 as a driver of macrophage inflammatory cytokines, which can promote metabolic dysfunction.

Paul N. Moynagh and Andrew E. Hogan

Obesity is a major global healthcare concern, with over 600 million adults worldwide currently classified as living with the condition[1]. Obesity has been linked to numerous comorbid conditions ranging from type 2 diabetes mellitus and cardiovascular disease to a high percentage of cancers[2]. A core link between obesity and these comorbidities is chronic inflammation[3], and thus the quest to understand the initiators and drivers of this pathogenic process in people with obesity is critically important and may lead to future therapeutics. In this issue of *Nature Immunology*, Qiu and colleagues identify the transcription factor IRX3 as a key driver of pro-inflammatory cytokine production in macrophages, which in mouse models is associated with repression of lipolysis and thermogenesis, leading to increased bodyweight and poor metabolic health[4].

In 1993, seminal studies by Hotamisligil were the first to link inflammation to the development of obesity-related insulin resistance[5]. Ten years later, Weisberg and colleagues put the macrophage at the front and center of obesity-driven metabolic inflammation[6]. It is now well established that the macrophage is one of the dominant drivers of metabolic inflammation in obesity.

In 2007, a genome-wide search for metabolic disease susceptibility genes led to the identification of the *FTO* (fat mass and obesity associated) gene. Common variants in *FTO* were associated with increased bodyweight, although no direct connection between FTO and metabolism was found[7]. In subsequent studies by Smemo and colleagues in 2014, noncoding variants of *FTO* were linked to *IRX3* expression, and a direct link to bodyweight was identified, with IRX3-deficient animals displaying reduced adipose tissue mass owing to increased thermogenesis[8]. However, some inconsistencies remain with respect to the FTO–IRX3 circuitry, as other researchers have reported that activation of IRX3 results in increased thermogenesis[9,10].

Qiu and colleagues have now shed more light on the precise molecular and cellular mechanisms by which IRX3 controls bodyweight and metabolic health[4]. Using myeloid-specific deletion of *Irx3*, their work reveals a macrophage-intrinsic role for IRX3 as a transcriptional regulator of pro-inflammatory cytokines that repress lipolysis and thermogenesis in adipose tissue, resulting in decreased metabolic rate that manifests in obesity and poor metabolic health (Fig. 1).

Qiu and colleagues also provide important insight into the molecular mechanism by which pro-inflammatory stimuli, such as lipopolysaccharide (LPS), can employ IRX3 to induce expression of pro-inflammatory cytokines. LPS triggers the Toll-like receptor 4 (TLR4) pathway to positively target IRX3 by two pathways[4]. First, stimulation of macrophages with LPS inhibits the ubiquitination of IRX3 at a specific lysine residue, resulting in the stabilization of IRX3 and avoidance of proteasome-mediated degradation.

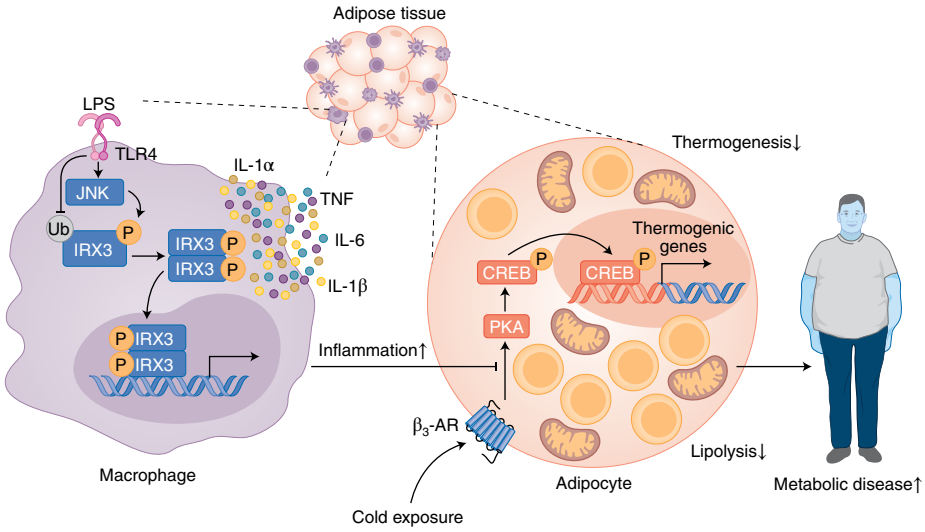

Fig. 1 | The role of IRX3 in macrophages and the effect of IRX3 on metabolic homeostasis. Stimulation of macrophages with LPS results in stabilization of IRX3 via the inhibition of ubiquitination. Janus kinase (JNK)-mediated phosphorylation results in the dimerization and translocation of IRX3 to the nucleus, where it drives the transcription of genes encoding pro-inflammatory cytokines. This IRX3-driven inflammation inhibits lipolysis and thermogenic gene expression in adipocytes, which collectively results in metabolic dysregulation and disease. β_3-AR, β3-adrenergic receptor; CREB, cAMP response element-binding protein; IL, interleukin; LPS, lipopolysaccharide; P, phosphate; PKA, protein kinase A; TLR, Toll-like receptor; TNF, tumor necrosis factor; Ub, ubiquitin.

Second, LPS can trigger activation of the JNK1/2 MAP kinases that phosphorylate IRX3, resulting in its dimerization and nuclear translocation, where it promotes transcriptional upregulation of pro-inflammatory genes. Thus, the authors demonstrate that the deletion of *Irx3* in macrophages reduces the abundance of interleukin-1α (IL-1α), IL-1β, IL-6 and tumor necrosis factor (TNF). They generated mouse models in which the *Irx3* gene was selectively deleted in macrophages and found that these mice showed increased adipocyte lipolysis and thermogenesis[4]. Consequently, their increased metabolic rate resulted in less weight gain and adiposity when the mice were kept on a high-fat diet, and this change translated into efficient glucose homeostasis and better metabolic health. It is well established that pro-inflammatory cytokines such as those driven by IRX3 can dysregulate metabolic processes including lipolysis and insulin signaling, resulting in metabolic diseases such as obesity and type 2 diabetes mellitus[3]. The present study by Qiu and colleagues provides further molecular detail about how macrophages can modulate adipose tissue homeostasis and metabolic health[4]. Importantly, the authors demonstrate cell specificity, with deletion of *Irx3* in neutrophils not phenocopying the pathophysiology of myeloid-specific deletion of *Irx3*.

The authors provide strong supporting evidence for IRX3 as a central regulator of macrophage-mediated inflammation in obesity, as well as prompting a number of outstanding questions to be addressed in the future studies[4]. Firstly, the present study was restricted to mouse models and in-vitro-derived human macrophages, and it will be important to address whether this regulatory mechanism translates to human adipose tissue and its control of metabolic health. Second, this novel mechanism promotes IRX3 as a potential target for therapeutic exploitation in the treatment of bodyweight or metabolic disease. To realize such potential to manipulate IRX3 in a therapeutic context, it would be valuable to understand the molecular basis for the regulation of IRX3 by pro-inflammatory stimuli such as LPS. The present study presents some data indicating that LPS can decrease the degree of ubiquitination of IRX3 and so promote its stabilization. The ubiquitination site is proposed to be lysine 409 and, while directly supporting data is absent, the proposed model implies that this site would be subject to Lys48-linked ubiquitination that would mark IRX3 for proteasome-mediated degradation. The mechanism by which LPS inhibits this ubiquitination, resulting in IRX3 stabilization, is not delineated, and it would be interesting to investigate whether this occurs through activation of a de-ubiquitinating enzyme or blockade of an E3 ubiquitin ligase. It would also be interesting to address the specificity of LPS in promoting IRX3 stabilization in the context of this mechanism. Many other TLR ligands can trigger the JNK1/2 pathway and share signal transduction pathways with TLR4, and so the present mechanism provides a potential explanation for how microbes may impinge on inflammation-associated obesity and metabolic health. The delineation of this mechanism may provide important clues about novel ways to manipulate the abundance of IRX3 that may have therapeutic value in the treatment of obesity-associated disease.

Overall, these findings by Qiu and colleagues[4] may have important implications for human obesity and the development of metabolic disease, and provide a strong rationale for further studies targeting macrophage IRX3. ❐

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Competing interests

The authors declare no competing interests.