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PERSPECTIVE

Trimming Trem2 and possible impacts on the metabolic syndrome

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Obesity is associated with chronic low-grade inflammation characterized by activation of immune cells and inflammatory signals that may lead to systemic metabolic derangements. One such signal is the triggering receptor expressed on myeloid cells 2 (Trem2) that is overexpressed in lipid-associated macrophages and adipocytes of mice and humans during obesity and insulin resistance (Jaitin et al., 2019; Sharif et al., 2021). The *Trem2* gene encodes an immunoglobulin transmembrane receptor that binds various anionic molecules, including phospholipids, DNA, toll-like receptor ligands such as bacterial lipopolysaccharides, and pro-inflammatory cytokines such as interferon-gamma. Apart from obesity, activation of *Trem2* in myeloid cells has been implicated in non-alcoholic fatty liver disease, atherosclerosis, carcinogenesis and Alzheimer's disease (Deczkowska et al., 2020).

Previous studies have suggested that mice lacking *Trem2* ($Trem^{-/-}$) and fed with a high-fat diet (HFD) to induce obesity exhibited a reduction in crown-like structures surrounding the adipocytes, accompanied by prominent adipocyte hypertrophy (Jaitin et al., 2019; Liu et al., 2019; Sharif et al., 2021). Importantly, those studies have demonstrated conflicting findings. Two studies (Jaitin et al., 2019; Liu et al., 2019) found that $Trem^{-/-}$ mice display exacerbated weight gain and adiposity in response to HFD feeding, but these findings were not recapitulated by another study using the same conditions (Sharif et al., 2021). Likewise, inconsistent results were noted between these studies with regard to the effect of Trem2 on systemic glucose tolerance (Jaitin et al., 2019; Liu et al., 2019; Sharif et al., 2021). Moreover, mice over-expressing *Trem2* also displayed exacerbated weight gain, along with aggravated glucose intolerance and insulin resistance, similar to $Trem^{-/-}$ mice (Park et al., 2015).

In this issue of *The Journal of Physiology*, Winn et al. (2022) aimed to reconcile some of these discrepancies. While they confirm that *Trem2* ablation drives adipocyte hypertrophy and reduction in adipose tissue macrophages, as previously reported, they do not observe a *Trem2*-dependent increase in body weight or adiposity under HFD or regular diet feeding. Importantly, in an elegant set of stringent experiments, Winn et al. (2022) exclude the possibility that these conflicting results stem from differences in gender, routes of glucose administration (oral *versus* intraperitoneal), duration of fasting (5 *versus* 15 h), types of carbohydrate challenge (mixed meal *versus* glucose tolerance tests), duration of diet-induced obesity (following HFD feeding for 12 or 16 weeks), and housing temperatures (22°C or 28°C). Under all of these conditions, and in contrast to previous observations (Jaitin et al., 2019; Liu et al., 2019; Sharif et al., 2021), *Trem2* deletion neither impacted glucose tolerance, circulating insulin levels and glucose dispersion following insulin administration in an insulin tolerance test, nor did it affect exercise tolerance. Based on their findings, Winn et al. (2022) conclude that *Trem2* impacts adipose tissue remodelling, adipocyte size and accumulation of macrophages in adipose tissue during obesity; however, whole-body loss of *Trem2* is insufficient to disrupt systemic metabolic homeostasis.

The discrepancies between the study by Winn et al. (2022) and previous studies may stem from genetic differences between the mouse strains used in these respective studies. Winn et al. (2022) utilized a mouse line featuring a deletion in exon 2, while the other groups used $Trem2^{-/-}$ mice designed to delete a portion of the transmembrane and cytoplasmic domains encoded by exons 3 and 4. A targeted deletion of different exons of the same gene is not unlikely to result in phenotypic differences, as alternative splicing may enable restoration of the disrupted reading frame by exon skipping, resulting in the translation of a functional protein. Additional possibilities include unrecognized genetic or environmental signals impacting these results across mice and vivaria. For example, non-*Trem2*-related off-target gene-editing effects, genetic colony drifts, or gut microbiome differences between mouse strains in different animal vivaria may explain some of these metabolic differences and merit further study. Such phenotypic differences may be exploited as a means of studying the combined impacts of genes and the environment on metabolic outcomes, and merit future head-to-head investigations across diets, vivaria and microbiome perturbations.

The global rise in the prevalence of metabolic morbidity necessitates timely recognition of potential targetable cellular processes that may modulate body weight gain, hyperlipidaemia and hyperglycaemia. Trem2 constitutes one such candidate for potential metabolic interventions; hence delineating its metabolic effects across genetic and environmental contexts can be important both scientifically and medically. To this aim, it would be interesting to dissect the tissue- and cell-specific roles of *Trem2* by generating a specific conditional knockout of *Trem2* in adipocytes, hepatocytes or myeloid cells. Alternatively, pharmacological inhibition via neutralizing antibodies (Park et al., 2015) or small molecules (Deczkowska et al., 2020) that modulate Trem2 signalling may provide insights into Trem2 function while avoiding genomic manipulations. The elegant study by Winn et al. (2022) adds important insights into this quest,

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while highlighting the complexity and variability that are the hallmarks of metabolic phenotypes, which should be accounted for, in striving to develop effective metabolic interventions.

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Additional information

Competing interests

None declared.

Author contributions

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