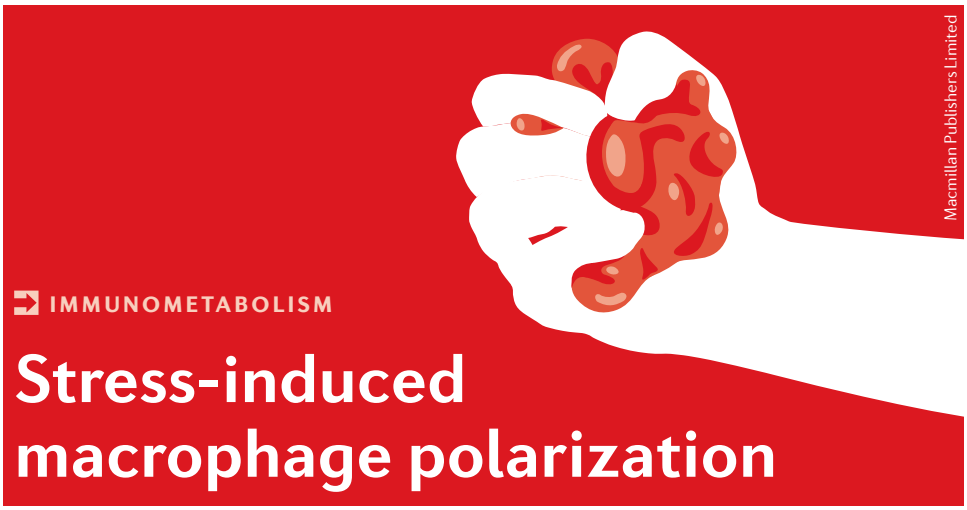
Nature Reviews Immunology | Published online 10 Apr 2017; doi:10.1038/nri.2017.41



IMMUNOMETABOLISM

Stress-induced macrophage polarization

> lack of IRE1α enhances energy expenditure and heat production through adaptive thermogenesis

Obesity is associated with chronic low-grade inflammation of adipose tissue, primarily mediated by adipose tissue macrophages (ATMs) of an M1 phenotype (classically activated, pro-inflammatory macrophages). M1 polarization of ATMs is thought to promote insulin resistance and type 2 diabetes through effects on cellular energy metabolism. The endoplasmic reticulum (ER) stress pathway mediated by inositol-requiring enzyme 1α (IRE1α)–X box binding protein 1 (XBP1) is also known to be hyperactivated in obese adipose tissue, but the connection between ER stress, macrophage polarization and energy homeostasis has been unclear. This study shows a role for IRE1α in ATMs in suppressing the alternative M2 polarization of macrophages and hence impairing adaptive thermogenesis.

In the white adipose tissue (WAT) of obese mice fed a high-fat diet (HFD) — and specifically in resident ATMs — there were increased levels of *Xbp1* mRNA splicing and increased expression of ER stress markers compared with mice fed a normal chow diet, which is in line with previous studies showing that excess nutrient handling activates the IRE1α–XBP1 pathway. Mice with a myeloid-specific knockout of IRE1α (*Ern1*$^{f/f}$;*Lyz2*-Cre mice; created by the authors) were resistant to HFD-induced obesity, having lower body weight and adiposity, decreased hyperinsulinaemia and improved insulin sensitivity; this observation couples the ER stress response of macrophages to obesity-associated metabolic dysfunction.

Oxygen consumption and core body temperature were significantly higher in HFD-fed *Ern1*$^{f/f}$;*Lyz2*-Cre mice than in control mice, which is indicative of increased energy expenditure in the absence of IRE1α. Indeed, increased expression of mitochondrial uncoupling protein 1 (UCP1) and of other key thermogenic genes was observed in the brown and beige adipose tissue of HFD-fed *Ern1*$^{f/f}$;*Lyz2*-Cre mice compared with control mice, which suggests that lack of IRE1α enhances energy expenditure and heat production through adaptive thermogenesis. In keeping with this conclusion, *Ern1*$^{f/f}$;*Lyz2*-Cre mice could maintain their body temperature at higher levels than control mice in response to cold stress. Macrophage depletion in WAT markedly decreased UCP1 induction in *Ern1*$^{f/f}$;*Lyz2*-Cre mice after cold exposure.

Further analysis of this macrophage-specific effect showed that HFD-fed *Ern1*$^{f/f}$;*Lyz2*-Cre mice had significantly decreased expression of M1 marker genes and increased expression of M2 marker genes in WAT, together with decreased levels of pro-inflammatory cytokines, compared with HFD-fed control mice. Therefore, loss of IRE1α in ATMs seems to correct the M1–M2 imbalance induced by HFD by favouring M2 polarization. Loss of IRE1α was sufficient to promote interleukin-4 (IL-4)-induced M2 polarization of bone marrow-derived macrophages (BMDMs) and inhibit lipopolysaccharide-induced M1 polarization in a cell-autonomous manner. Specifically, IRE1α ablation increased IL-4-induced expression of interferon regulatory factor 4 (IRF4) and Krüppel-like factor 4 (KLF4), which are crucial regulators of M2 polarization.

Finally, the authors showed that IL-4-induced M2 macrophages increased the expression of *Ucp1* by brown adipocytes in co-culture and that this effect was increased for *Ern1*$^{f/f}$;*Lyz2*-Cre BMDMs compared with control BMDMs. In summary, the results suggest a pathway by which the activation of macrophage IRE1α in response to excess nutrients enhances M1 polarization and suppresses M2 polarization, which limits the attempt to restore energy balance through adaptive thermogenesis and results in adipose tissue inflammation and insulin resistance.

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ORIGINAL ARTICLE Shan, B. *et al.* The metabolic ER stress sensor IRE1α suppresses alternative activation of macrophages and impairs energy expenditure in obesity. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3709 (2017)