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COMMENTARY

Is omega-3 key to unlocking inflammation in obesity?

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Low-grade inflammation has been identified as a key player in the development of the metabolic syndrome in obese subjects, leading the way to type 2 diabetes and cardiovascular diseases. Insulin resistance, a primary component of the metabolic syndrome, is characterised by chronically elevated concentrations of proinflammatory cytokines, acute phase proteins, and enhanced activation of proinflammatory signalling in insulin-responsive tissues of obese subjects.

The research effort thus far has established that, in obesity, the expanding adipose tissue makes a substantial contribution to the development of obesity-linked inflammation via the secretion of various proinflammatory cytokines, chemokines and adipokines. Recent investigations into the mechanisms responsible for this phenomenon have outlined a role for the macrophage [1–3]. In fact, macrophage accumulation in adipose tissue is positively correlated with adipocyte size and contributes to the expression of proinflammatory mediators of insulin resistance, such as TNF-α, IL-6 and inducible nitric oxide synthase (iNOS) [1, 2]. Furthermore, both inhibition of macrophage function, via myeloid-specific IκB kinase-β deletion [3], and prevention of macrophage accumulation in adipose tissue, via deletion of C–C motif chemokine receptor-2 [4], prevent the development of the inflammatory phenotype and insulin resistance with obesity. Hence, there is growing support for the current notion that macrophage infiltration into adipose tissue is central to obesity-related metabolic disorders.

Pioneering work by Storlien and colleagues has shown that long-chain omega-3 polyunsaturated fatty acids (LC*n*−3PUFA) can prevent the development of diet-induced insulin resistance in rats [5]. Furthermore, a growing number of studies support a link between this beneficial effect of LC*n*−3PUFA and an anti-inflammatory mechanism. LC*n*−3PUFA have been widely reported to have anti-inflammatory effects in a range of chronic inflammatory conditions, including rheumatoid arthritis and Crohn's disease [6, 7]. Treatment of obese subjects with LC*n*−3PUFA in a clinical setting has also been shown to reduce circulating levels of both proinflammatory cytokines and acute phase proteins [8, 9]. Whether these anti-inflammatory actions of LC*n*−3PUFA, and their positive influence on the metabolic syndrome, can be linked to local blunting of adipose tissue inflammation is not yet known.

In this issue of Diabetologia, Todoric et al. [10] present evidence that the inclusion of LC*n*−3PUFA in a high-fat diet prevents the development of an inflammatory gene expression profile and macrophage infiltration in the adipose tissue of obese diabetic *db/db* mice. Despite significantly enhancing weight gain, LC*n*−3PUFA treatment completely prevented the diet-induced adipose tissue switch to an inflammatory profile, attenuating the upregulation of an array of genes, notably those encoding the macrophage surface marker CD68, macrophage chemotactic protein-1, and the lipopolysaccharide receptor CD14. Incorporation of LC*n*−3PUFA into the high-fat diet also prevented the downregulation of genes involved in lipid metabolism, including those for fatty acid synthase and hormone-sensitive lipase, in adipose tissue of the obese mice. The anti-inflammatory effect of LC*n*−3PUFA was related to greatly diminished macrophage migration into

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adipose tissue and substantially enhanced circulating adiponectin levels. n−3PUFA as part of the high-fat diet also lowered circulating triglyceride to levels below those seen in chow-fed mice. Although these data suggest that improvement of metabolic status in obesity by LC*n*−3PUFA involves regulation of the adipose tissue gene expression profile and the prevention of macrophage infiltration into fat depots, further research is required to elucidate the exact mechanisms responsible.

Indeed, there are a multitude of potential mechanisms that could account for the anti-inflammatory actions elicited by LC*n*−3PUFA in this study (Fig. 1). For example, the competitive inhibition of arachidonate-derived proinflammatory leukotriene and prostaglandin production by LC*n*−3PUFA [11–13] could limit inflammation in adipose tissue. Negative modulation of monocyte function by LC*n*−3PUFA [14] could also account for the reduced macrophage infiltration. Interestingly, more recent studies have also identified LC*n*−3PUFA as precursors of two novel families of potent anti-inflammatory lipid mediators, the resolvins and protectins [15]. We may conjecture that these eicosanoids could contribute to the LC*n*−3PUFA-mediated inhibition of adipose tissue inflammation reported by Todoric and colleagues by favouring the resolution of the inflammatory process. Alternatively, LC*n*−3PUFA may blunt adipose tissue inflammation by acting as endogenous ligands for the peroxisome proliferator-activator receptors (PPARs) α, δ and γ, which have recently been recognised for their anti-inflammatory actions in adipocytes and macrophages [16–20].

Of the three known mammalian PPAR isoforms, LC*n*−3PUFA appear to bind most efficiently with PPARγ [21]. On the basis of current literature, this latter target of LC*n*−3PUFA appears to be the most plausible mechanistic explanation for the findings of Todoric and colleagues. Accordingly, PPARγ agonists have been reported to inhibit macrophage activation [22] and infiltration into adipose tissue [2]. Moreover, a very recent study using the PPARγ inhibitor bisphenol A diglycidyl ether (BADGE) demonstrated that treatment with LC*n*−3PUFA augments circulating adiponectin levels via a PPARγ-dependent mechanism [17]. Given that adiponectin is known to exert anti-inflammatory effects and enhance insulin sensitivity [23, 24], it is conceivable that LC*n*−3PUFA could impede the adipose tissue switch to an inflammatory gene expression profile in response to obesity via a PPARγ- and adiponectin-dependent mechanism.

In accord with this theory, the use of PPARγ agonists is characterised by enhanced weight gain [25] similar to that seen with LC*n*−3PUFA treatment in this study. However, it should be noted that not all studies using LC*n*−3PUFA reported increased weight gain. Indeed, to the contrary, the prevention of weight gain in insulin resistance prevention studies is often reported following treatment with LC*n*−3PUFA [26]. This heterogeneity as regards the influence of LC*n*−3PUFA on weight gain may stem from differences in the animal models used, the mode of treatment (e.g. use for prevention or reversal of insulin resistance), or might result from differential degrees of LC*n*−3PUFA signalling through the PPARγ and PPARα receptors in these studies [25].

In conclusion, these mechanisms remain to be explored and it is very likely that the results presented in the article by Todoric and colleagues reflect a combination of the pleiotropic functions of LC*n*−3PUFA at multiple sites within the adipose

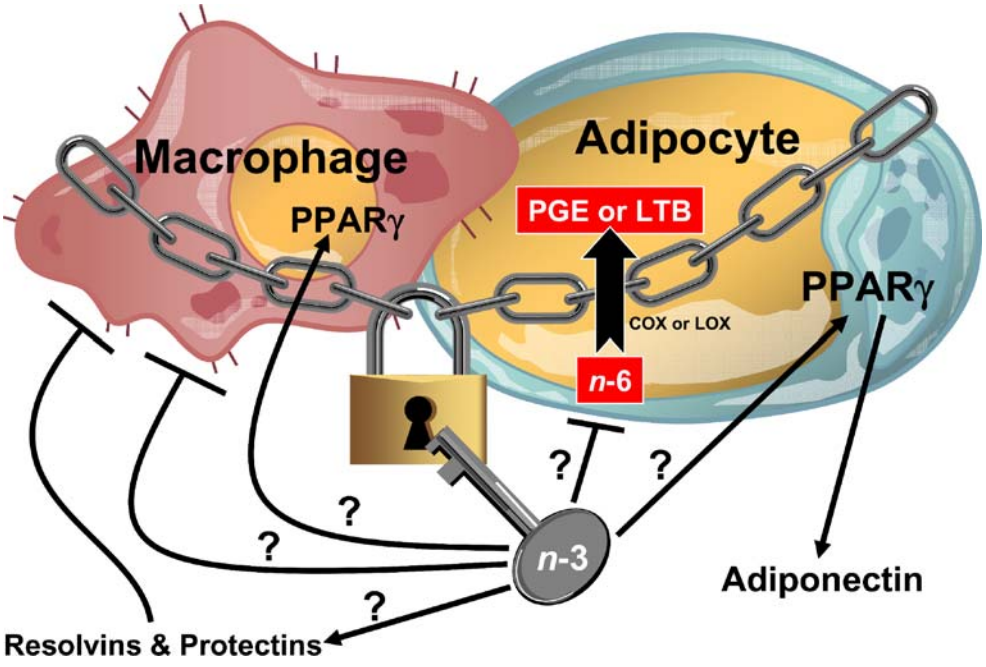

Fig. 1 Proposed mechanisms for the anti-inflammatory actions of LC*n*−3PUFA in adipose tissue. *COX* Cyclooxygenase, *PGE* prostaglandin, *LOX* 5-lipoxygenase, *LTB* leukotriene

tissue. Additional studies are certainly warranted to examine whether such effects of LC*n*−3PUFA are present in other insulin-sensitive tissues, including liver and skeletal muscle, and to elucidate the underlying mechanisms. It now seems critical to determine whether the adipose-specific blunting of an inflammatory profile is the principal mechanism by which LC*n*−3PUFA prevent diet-induced insulin resistance.

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