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LETTER

Plasma fetuin-A triggers inflammatory changes in macrophages and adipocytes by acting as an adaptor protein between NEFA and TLR-4

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Abbreviation
TLR4 Toll-like receptor 4

To the Editor: We read with interest the research letter entitled 'Plasma fetuin-A does not correlate with monocyte TLR4 in humans' by Jialal and colleagues [1]. The authors state that: 'Studies using animal models, largely the work of Pal et al [2], have elegantly demonstrated that fetuin-A is the endogenous ligand for Toll-like receptor 4 (TLR4) via which lipids such as fatty acids induce insulin resistance, but there are no data in support of this in humans'. This is not, in fact, the case: in the paper referred to [2], our group provided data on human adipocytes from both diabetic and non-diabetic participants showing that fetuin-A acts as an endogenous ligand of TLR4 to induce insulin resistance. In another recent review, Stefan and Häring observed a significant correlation between circulating fetuin A and insulin resistance in humans [3].

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Jialal et al also state: 'Based on our findings, we propose that until larger studies report significant correlations between TLR4 expression in monocytes/adipose tissue and circulating fetuin-A in humans with obesity, the metabolic syndrome or diabetes, the relationship between these two proteins demonstrated in animals might not translate to humans'. In our *Nature Medicine* paper [2], we have clearly shown a significant correlation between plasma fetuin-A and TLR4 expression in adipocytes from abdominal subcutaneous adipose tissue of obese human subjects with type 2 diabetes.

We have shown that circulating NEFA stimulates the production of fetuin-A by the liver via NF-κB. Fetuin-A then forms a dimer with NEFA by acting as its binding protein. The NEFA–fetuin-A dimer finally binds to TLR-4 present on the surface of adipocytes and macrophages, resulting in the formation of a ternary complex that triggers a local inflammatory response in the adipose tissue. Upon stimulation by circulating fetuin-A, white adipose tissue attracts circulating M2 macrophages that undergo proinflammatory polarisation to M1 under the influence of fetuin-A generated locally by the inflamed adipocytes [4, 5]. Jialal et al drew conclusions based on their studies on circulating monocytes, which are not the most appropriate model to study the NEFA–fetuin-A–TLR4 relationship [1]. Such interactions have only been reported to take place in the adipose tissue, not only by our group but also by others. In a recent paper, Trepanowski et al proposed a model wherein they suggest that: 'Fetuin-A originating from hepatocytes and adipocytes sends chemoattractant signals that induce macrophage infiltration into adipose tissue and subsequent conversion to a classically activated M1 subtype. Fetuin-A then presents fatty acids to the TLR4 receptors on both M1 macrophages and adipocytes, thereby propagating the release of proinflammatory cytokines' [6]. Moreover, our hypothesis concerned TLR4 activation and NOT expression,

which Jialal et al went on to study [1]. Finally, their concluding remarks on fetuin-A and TLR4 expression in monocytes/adipose tissue goes against the existing literature on the subject and unnecessarily creates a lot of confusion.

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