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LETTER

Plasma fetuin-A does not correlate with monocyte TLR4 in humans

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Abbreviation
TLR4 Toll-like receptor 4

To the Editor: We read with great interest the '50 years forward' commentary by Iroz, Couty and Postic, which discussed hepatokines, including fetuin-A [1]. In our study on patients with the metabolic syndrome (n=28), we found that fetuin-A secretion from subcutaneous adipose tissue was increased, even after adjusting for adiposity, and that secreted levels of adipose tissue derived fetuin-A correlated with a measure of insulin resistance [2]. We also reported an increase in fetuin-A mRNA and protein in obese mice. In addition, Chatterjee et al have reported an increase in adipose tissue fetuin-A in visceral adipose tissue of obese diabetic individuals (n=5) and mice [3]. Thus, based on these recent publications, in addition to being a hepatokine, fetuin-A needs to be considered as an adipokine, since fetuin-A mRNA and protein are present in adipose tissue [2, 3], and fetuin-A contributes to insulin resistance.

Studies using animal models, largely the work of Pal et al [4], 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. Hence, in a preliminary analysis of the patients with the metabolic syndrome included in our study, in whom we had previously shown increased monocyte TLR4 activity that correlated with insulin resistance, NEFA and endotoxin levels [5], we assayed fetuin-A in remaining frozen plasma samples. All participants gave informed consent to participate in the original study and the protocol was approved by the UC Davis Institutional Review Board. In this smaller cohort, both plasma fetuin-A (controls: 199±19 ug/ml and metabolic syndrome: 246±39 ug/ml, p<0.001) and monocyte TLR4 (controls: 28±16 mean fluorescence intensity [MFI]/10,000 cells and metabolic syndrome: 48±23 MFI/10,000 cells; p<0.01) were increased. We did not find a significant correlation between plasma fetuin-A and TLR4 (r=0.25, p=0.29, n=19), but there was a significant correlation between endotoxin and TLR4 (r=0.55, p=0.04, n=14) in this smaller sample size. In addition, we found a strong correlation between NEFA and fetuin-A (0.84, p=0.0006, n=12).

Thus, in this preliminary analysis, while endotoxin correlated with TLR4, and fetuin-A correlated with NEFA, fetuin-A did not correlate with TLR4 on monocytes. 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. Thus, fetuin-A could induce insulin resistance by mechanisms other than activation of TLR4 [6, 7].

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