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Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance.
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Toll-like receptor 4 (TLR4) has a key role in innate immunity by activating an inflammatory signaling pathway. Free fatty acids (FFAs) stimulate adipose tissue inflammation through the TLR4 pathway, resulting in insulin resistance^{1–7}. However, current evidence suggests that FFAs do not directly bind to TLR4^{8,9}, but an endogenous ligand for TLR4 remains to be identified. Here we show that fetuin-A (FetA) could be this endogenous ligand and that it has a crucial role in regulating insulin sensitivity via Tlr4 signaling in mice. *FetA* (officially known as *Ahsg*) knockdown in mice with insulin resistance caused by a high-fat diet (HFD) resulted in downregulation of Tlr4-mediated inflammatory signaling in adipose tissue, whereas selective administration of FetA induced inflammatory signaling and insulin resistance. FFA-induced proinflammatory cytokine expression in adipocytes occurred only in the presence of both FetA and Tlr4; removing either of them prevented FFA-induced insulin resistance. We further found that FetA, through its terminal galactoside moiety, directly binds the residues of Leu100–Gly123 and Thr493–Thr516 in Tlr4. FFAs did not produce insulin resistance in adipocytes with mutated Tlr4 or galactoside-cleaved FetA. Taken together, our results suggest that FetA fulfills the requirement of an endogenous ligand for TLR4 through which lipids induce insulin resistance. This may position FetA as a new therapeutic target for managing insulin resistance and type 2 diabetes.



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