The present study tested the hypothesis that endogenous prostaglandin E2 (PGE2) suppresses inflammation in fat by activating EP4 receptors. In mouse adipose tissue, PGE2 (5-500nM) attenuated lipopolysaccharide-induced mRNA and protein expression of chemokines, including interferon-γ-inducible protein 10 and macrophage-inflammatory protein-1α. A selective EP4 antagonist (L161,982) reversed, and structurally different selective EP4 agonists [CAY10580 and CAY10598] mimicked these actions of PGE2. Adipose tissue derived from EP4-deficient mice did not display the same response to PGE2. These findings established the involvement of EP4 receptors in the anti-inflammatory effect of PGE2 in adipose tissue. The latter was mimicked by 8-bromo-cyclic adenosine monophosphate, but was insensitive to H98 (protein kinase A inhibitor). Experiments performed on adipose tissue from high-fat–fed mice demonstrated EP4-dependent attenuation of inflammation during diet-induced obesity. Furthermore, adipose tissue and systemic inflammation was enhanced in high-fat-fed EP4-deficient mice compared to wild-type littermates, and in high-fat fed untreated C57BL/6 mice compared to mice treated with EP4 agonist. The latter findings provide in vivo evidence that PGE2-EP4 signaling modulates inflammation. Thus, the present results demonstrate that PGE2, via activation of EP4 receptors, functions as an endogenous anti-inflammatory mediator in adipose tissue, and suggest that targeting EP4 may mitigate inflammation in that tissue.