Fractalkine activates a signal transduction pathway similar to P2Y12 and is associated with impaired clopidogrel responsiveness.

Fractalkine (FKN) activates a G(??) protein-coupled signaling pathway similar to the one activated by ADP via P2Y(12), which is the drug target of clopidogrel. FKN levels are increased under several disease conditions associated with impaired clopidogrel responsiveness. Blood samples were obtained from healthy volunteers and from 40 patients under chronic clopidogrel treatment. FKN reduced prostaglandin E1-induced vasodilator-stimulated phosphoprotein phosphorylation by \( \geq 25\% (P<0.01) \) at least partially mimicking the effect of ADP via P2Y(12). In vitro, FKN increased platelet reactivity index in clopidogrel-treated patients indicating potential activation of downstream targets of P2Y(12). When stratifying patients by their FKN levels, patients within the highest quartile of FKN (2042 ± 25 pg/mL) had the weakest response to clopidogrel (platelet reactivity index, 68 ± 4%), and patients within the lowest quartile (479 ± 50 pg/mL) had the strongest response (platelet reactivity index, 48 ± 7%; \( P=0.0106 \)). FKN by itself induced phosphoinositide 3-kinase activation leading to Akt phosphorylation at Ser(473) (\( P<0.01 \) versus basal). In addition to desensitizing platelets to prostaglandin E1 via G(??), FKN induces phosphoinositide 3-kinase-dependent Akt phosphorylation via a G(??) protein similar to ADP signaling through
P2Y(12). FKN increased the platelet ADP response in clopidogrel-treated patients. Once released from an atherosclerotic lesion, this mechanism could contribute locally to impaired clopidogrel responsiveness at the vulnerable plaque.