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Abstract:

Signaling via the Pyk2-Src-Cbl complex downstream of integrins contributes to the assembly, organization, and dynamics of podosomes, which are the transient adhesion complexes of highly motile cells such as osteoclasts and dendritic cells. We previously demonstrated that the GTPase dynamin is associated with podosomes, regulates actin flux in podosomes, and promotes bone resorption by osteoclasts. We report here that dynamin associates with Pyk2, independent of dynamin's GTPase activity, and reduces Pyk2 Y402 phosphorylation in a GTPase-dependent manner, leading to decreased Src binding to Pyk2. Overexpressing dynamin decreased the macrophage colony-stimulating factor- and adhesion-induced phosphorylation of Pyk2 in osteoclastlike cells, suggesting that dynamin is likely to regulate Src-Pyk2 binding downstream of integrins and growth factor receptors with important cellular consequences. Furthermore, catalytically active Src promotes dynamin-Pyk2 association, and mutating specific Src-phosphorylated tyrosine residues in dynamin blunts the dynamin-induced decrease in Pyk2 phosphorylation. Thus, since Src binds to Pyk2 through its interaction with phospho-

Y402, our results suggest that Src activates a negative-feedback loop downstream of integrin engagement and other stimuli by promoting both the binding of dynamin to Pyk2-containing complexes and the dynamin-dependent decrease in Pyk2 Y402 phosphorylation, ultimately leading to the dissociation of Src from Pyk2.

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