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Zyxin-Siah2–Lats2 axis mediates cooperation between Hippo and TGF-β signalling pathways

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The evolutionarily conserved Hippo pathway is a regulator that controls organ size, cell growth and tissue homeostasis. Upstream signals of the Hippo pathway have been widely studied, but how microenvironmental factors coordinately regulate this pathway remains unclear. In this study, we identify LIM domain protein Zyxin, as a scaffold protein, that in response to hypoxia and TGF-β stimuli, forms a ternary complex with Lats2 and Siah2 and stabilizes their interaction. This interaction facilitates Lats2 ubiquitination and degradation, Yap dephosphorylation and subsequently activation. We show that Zyxin is required for TGF-β and hypoxia-induced Lats2 downregulation and deactivation of Hippo signalling in MDA-MB-231 cells. Depletion of Zyxin impairs the capability of cell migration, proliferation and tumourigenesis in a xenograft model. Zyxin is upregulated in human breast cancer and positively correlates with histological stages and metastasis. Our study demonstrates that Zyxin-Lats2–Siah2 axis may serve as a potential therapeutic target in cancer treatment.

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