Identification of Quinolinols as Activators of TEAD-Dependent Transcription

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Authors

Ajaybabu V. Pobbati, Tom Mejuch, Sayan Chakraborty, Hacer Karatas, Sakshibeedu R. Bharath, Stéphanie M. Guéret, Pierre-Alexis Goy, Gernot Hahne, Axel Pahl, Sonja Sievers, Ernesto Guccione, Haiwei Song, Herbert Waldmann, Wanjin Hong

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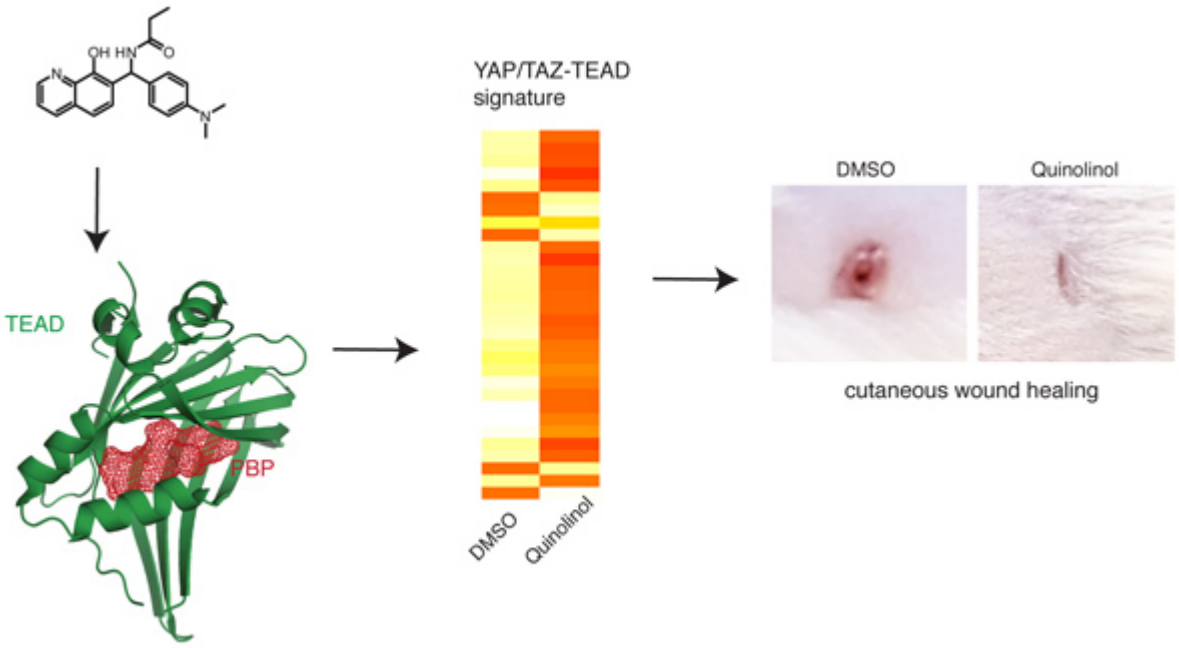
Abstract

The transcriptional co-regulators YAP (Yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif) are the vertebrate downstream effectors of the Hippo signaling pathway that controls various physiological and pathological processes. YAP and TAZ pair with the TEAD (TEA domain) family of transcription factors to initiate transcription. We previously identified a tractable pocket in TEADs, which has been physiologically shown to bind palmitate. Herein, a TEAD–palmitate interaction screen was developed to select small molecules occupying the palmitate-binding pocket (PBP) of TEADs. We show that quinolinols were TEAD-binding compounds that augment YAP/TAZ–TEAD activity, which was verified using TEAD reporter assay, RT-qPCR, and RNA-Seq analyses. Structure–activity relationship investigations uncovered the quinolinol substituents that are necessary for TEAD activation. We reveal a novel mechanism where quinolinols stabilize YAP/TAZ protein levels by

occupying the PBP. The enhancement of YAP activity by quinolinols accelerates the in vivo wound closure in a mouse wound-healing model. Although small molecules that occupy the PBP have been shown to inhibit YAP/TAZ–TEAD activity, leveraging PBP to activate TEADs is a novel approach.

Figure



Legend for image: TEAD family of transcription factors facilitates cells to repair damaged tissues. We identify that certain quinolinols occupy the palmitate-binding pocket of the TEADs and activate gene expression. TEAD activation by quinolinols improves wound healing in a mouse model.