Discovery of small-molecular inhibitors for the Jasmonate-related major transcription factor MYC and chemical regulation of plant hormone crosstalk

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Plant hormone-related transcription factors (TFs) are key regulators for plant life cycles including growth, differentiation, or defense. Since these TFs play pivotal roles, they are often genetically redundant to be robust against unexpected mutations. Furthermore, many TFs are involved in plant hormone crosstalk regulatory system, making analysis difficult. Therefore, selective chemical tools for plant TFs are expected to be effective in analyzing plant hormone signaling, although the molecular design of chemical tools has been challenging so far.

Jasmonoyl-L-isoleucine (JA-Ile) is an essential phytohormone in defense responses against insects or pathogens.[1] More than 25 TFs in the JA signaling are coded in the genome of the model plant *Arabidopsis thaliana* with a high genetic redundancy, although the details remain unclear.[2] We herein focus on a master regulator TFs MYCs in JA signaling, which regulates anti-insect responses as well as growth inhibition. MYCs are repressed by interactions with JAZ repressors and activated by transcriptional mediator MED25.[3] Based on these protein-protein interactions (PPIs), we established a high-throughput screening (HTS) system to identify MYC inhibitors, and successfully obtained 18 hit compounds for MYC3 from existing drug library (Figure 1). Subsequently, we conducted more refined assays *in vitro* as well as *in vivo*, and finally identified three efficient MYC3 inhibitor candidates. These inhibitors also showed similar inhibitory effects for MYC2/4, redundant homologues for MYC3, but not for other TFs such as EIN3, another master regulators for defense against pathogen infection in JA signaling. By using *in silico* docking study, we aimed to optimize the structure of one candidate. Our new endeavor should provide various useful tools for understanding plant signaling pathways in the future.

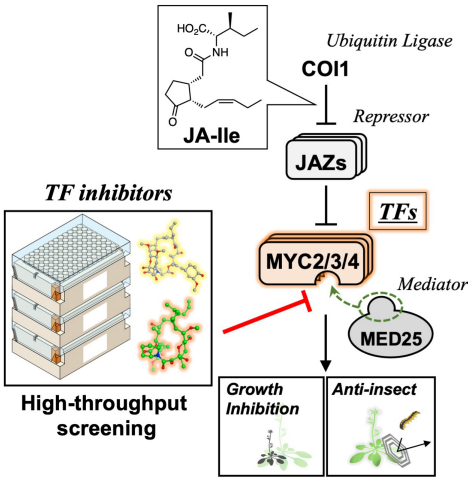

Figure 1. JA signaling pathway and the screening of MYC inhibitors.

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