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IN BRIEF

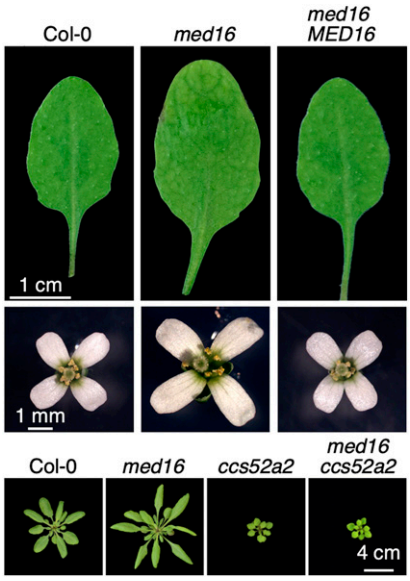
Mediator Skills: MED16 Controls Endoreduplication[OPEN]

The discovery of Mediator began with the observation that two transcriptional activators could interfere with each other's function in vitro, even though they did not bind to the same promoter (Kelleher et al., 1990). The hypothesis, since then well-validated, was that each transcription factor titrates components (i.e. Mediator) critical for the proper initiation of transcription away from the other transcription factor. The multisubunit protein complex, Mediator, is mobilized to promoters by transcription factors and in turn can recruit RNA polymerase II.

Core Mediator subunits are generally essential, but components mapping to the Mediator tail are not, and these interact with transcription factors to provide target gene specificity. Arabidopsis (*Arabidopsis thaliana*) *mediator* (*med*) tail mutants are associated with delayed flowering time and larger organs via increased cell expansion (*med25*), decreased tolerance to cold, disease resistance, and iron deficiency (*med16*), and reduced cell size and higher ploidy levels (*med14*) as compared with the wild type.

In their article, **Liu et al. (2019)** describe a new function for MED16 in the control of cell division, cell size, and DNA ploidy levels and identify the transcription factor and associated target genes responsible. During a forward genetic screen looking for mutants with enlarged leaves and flowers, the authors isolated a new allele of *med16*. Leaves, petals, and sepals from the mutant are larger, with larger cells, bigger nuclei, and increased DNA ploidy levels as compared with the wild type; these phenotypes are indicative of multiple rounds of DNA replication without cell division, i.e. endoreduplication (see figure). These results demonstrate a role for MED16 in modulating endoreduplication and cell growth (that is, cell division and expansion).

The authors then turned to a yeast two-hybrid screen and identified DP-E2F-LIKE 1/E2Fe (DEL1) as the transcription factor that recruits MED16 to chromatin, which solidified the link between MED16 and endoreduplication. Indeed, DEL1 targets are known: the *CELL CYCLE SWITCH 52* genes *CCS52A1* and *CCS52A2*, encoding activators of the Anaphase Promoting Complex (APC)/Cyclosome, an E3 ubiquitin ligase complex that degrades cell cycle proteins. This offered a testable model: DEL1 would bind to the *CCS52A1* and *CCS52A2* promoters and draw Mediator (via its MED16 subunit) to chromatin and establish transcriptional repression. Left unchecked, *CCS52A* expression would promote APC/Cyclosome activity and result in additional rounds of DNA replication.



DEL1 Recruits the Med Tail Subunit MED16 to Repress Endoreduplication.

Loss of MED16 function results in larger organs, but these effects are largely suppressed by mutations in the APC activator CCS52A2. (*Adapted from Liu et al. [2019] Figures 2 and 6 and Supplemental Figure 7.*)

Using chromatin immunoprecipitation assays, the authors confirmed that DEL1 and MED16 associate with cis-elements within the *CCS52A1* and *CCS52A2* promoters. In the case of MED16, this association is dependent on the presence of DEL1, which is consistent with the notion that DEL1 acts as a bridge between MED16 and DNA. Indeed, the expression levels of *CCS52A2* in leaves were low in Col-0 and higher in *del1* and *med16* single and double mutants. The expression of *CCS52A1* was also clearly increased in *med16* and *med16 del1*.

Genetic analyses corroborated these results: *med16* and *ccs52a2* single mutants had opposite phenotypes in terms of cell size and DNA ploidy levels, but the *ccs52a1* mutant almost completely suppressed the effects of *med16*, placing CCS52A1 downstream of MED16 and in the same pathway (see figure). Similarly, the *ccs52a1* mutant partially suppressed the higher ploidy levels of *med16*, also placing CCS52A1 downstream of MED16. Unfortunately, seedling lethality in *ccs52a1 ccs52a2* double mutants prevents the dissection of redundancy between *CCS52A* genes (Baloban et al., 2013).

MED16 is therefore clearly important for the repression of *CCS52A* genes by DEL1, but how this gene repression is exerted remains uncertain: Is RNA polymerase II recruited to DEL1 targets by Mediator/MED16, or does Mediator bound to *CCS52A* promoters include its (inactivating) kinase module?

Patrice A. Salomé
Department of Chemistry and Biochemistry
University of California
Los Angeles, 90095 California
salome@chem.ucla.edu
ORCID ID: 0000-0003-4452-9064

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