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# The DP-E2F-like Gene *DEL1* Controls the Endocycle in *Arabidopsis thaliana*

**Kobe Vlieghe,[1] Véronique Boudolf,[1] Gerrit T.S. Beemster,[1] Sara Maes,[1] Zoltan Magyar,[1,2,3] Ana Atanassova,[1] Janice de Almeida Engler,[1,4] Ruth De Groodt,[1] Dirk Inzé,[1,*] and Lieven De Veylder[1]**

[1]Department of Plant Systems Biology
Flanders Interuniversity Institute for Biotechnology
Ghent University
Technologiepark 927
Gent B-9052
Belgium

[2]Biological Research Center
P.O. Box 521
Szeged H-6701
Hungary

## Summary

**Endoreduplication or DNA replication without mitosis is widespread in nature. Well-known examples are fruit fly polytene chromosomes and cereal endosperm. Although endocycles are thought to be driven by the same regulators as those that control the G1-S transition of the mitotic cell cycle, the molecular mechanisms that differentiate mitotically dividing cells from endoreduplicating ones are largely unknown. A novel class of atypical E2F-like proteins has recently been identified and is designated E2F7 in mammals [1, 2] and DP-E2F-like (DEL) in *Arabidopsis thaliana* [3–5]. We demonstrate that loss of *DEL1* function resulted in increased ploidy levels, whereas ectopic expression of *DEL1* reduced endoreduplication. Ploidy changes were correlated with altered expression of a subset of E2F target genes encoding proteins necessary for DNA replication. Because DEL1 proteins were postulated to antagonize the E2F pathway, we generated *DEL1-E2Fa-DPa* triple transgenics. DEL1 inhibited the endoreduplication phenotype, but not the ectopic cell divisions that resulted from the overexpression of both *E2Fa* and *Da*, illustrating that DEL1 specifically represses the endocycle. Because *DEL1* transcripts were detected exclusively in mitotically dividing cells, we conclude that DEL1 is an important novel inhibitor of the endocycle and preserves the mitotic state of proliferating cells by suppressing transcription of genes that are required for cells to enter the DNA endoreduplication cycle.**

## Results and Discussion

Whereas the E2F-DP transcription factors are well-known regulators of the G1-S transition, both in plants and mammals [6–8], the physiological role of E2F7 or DEL proteins remained unclear. E2F and DP proteins only contain a single DNA binding domain and need to dimerize for high-affinity, sequence-specific DNA binding. By contrast, DEL proteins hold two domains highly homologous to the DNA binding domain of E2Fs, which allows them to bind the canonical E2F binding site as monomers [4, 5]. To study the function of DEL1 (also known as EL3 [4] and E2Fe [5]) during plant development, we analyzed a T-DNA insertion mutation in the *DEL1* gene. The T-DNA of *del1-1* had been inserted between the two DNA binding domains of DEL1 (Figure 1A). Because E2F7 and DELs need to have both DNA binding domains to bind the E2F recognition sequence [1, 2, 4, 5], *del1-1* is most probably a null allele. The absence of full-length *DEL1* mRNA in the *del1-1* mutant was confirmed by reverse-transcriptase PCR analysis (Figure 1B). The *del1-1* mutant did not differ morphologically from wild-type plants. For example, 12-day-old cotyledons of wild-type and *del1-1* plants were comparable in number and size of abaxial epidermal cells (see Table S1 available with the Supplemental Data online). Similarly, no effects were seen on the first leaf pair. Obviously, *DEL1* function did not affect cell division. In contrast, DNA ploidy levels varied significantly between wild-type and *del1-1* plants. Wild-type cotyledons displayed a typical pattern with C values ranging from 2C to 16C, where the peaks higher than 2C resulted from endoreduplication. Cotyledons of *del1-1* plants had a significantly increased number of cells with 16C DNA content, as well as cells with a 32C DNA content; these cells are typically absent in wild-type plants (Figure 2A; Table S2). The effect on the endocycle was similar in hypocotyls (Figure 2B; Table S3) and roots (data not shown) but, interestingly, was less pronounced in leaves (Figure 2C; Table S3). The tissue specificity of the phenotype might be attributed to the presence of two *DEL1*-related genes in the *Arabidopsis* genome [3–5]; the functions of these genes might be redundant with those of *DEL1*, although the *DEL3* gene had no clear role in the endocycle [9].

To confirm the function of DEL1 as an inhibitor of the endocycle, we constructed transgenic *Arabidopsis* plants in which *DEL1* was expressed under control of the 35S promoter of the constitutive cauliflower mosaic virus (CaMV). Two independent lines that had a single T-DNA transgene insertion (*DEL1*$^{OE}$) and showed a moderate (line 2) or strong (line 4) increase in *DEL1* transcript levels were selected (Figure 1C). Homozygous *DEL1*$^{OE}$ lines were phenotypically similar to those of wild-type plants, although they had a smaller stature (Figure S1). The cotyledon size of 12-day-old plants was 15% (*DEL1*$^{OE}$ line 2) and 19% (*DEL1*$^{OE}$ line 4) reduced compared to that of wild-type plants as a result of a decrease in cell size (Table S1). Similarly, mature first leaves (22 days after sowing) were smaller (Figure 3A). To determine the cellular basis of this reduced size, we studied growth of the first leaf pair by using a kinematic growth analysis [10]. From day 4 until day 22 after sowing, leaves

*Correspondence: dirk.inze@psb.ugent.be
[3]Present address: School of Biological Sciences, Royal Holloway, University of London, Egham TW20 QEX, United Kingdom.
[4]Present address: Institut National de la Recherche Agronomique, Unité Interactions Plantes-Microorganismes et Santé Végétale, B.P. 2078, F-06606 Antibes Cedex, France.

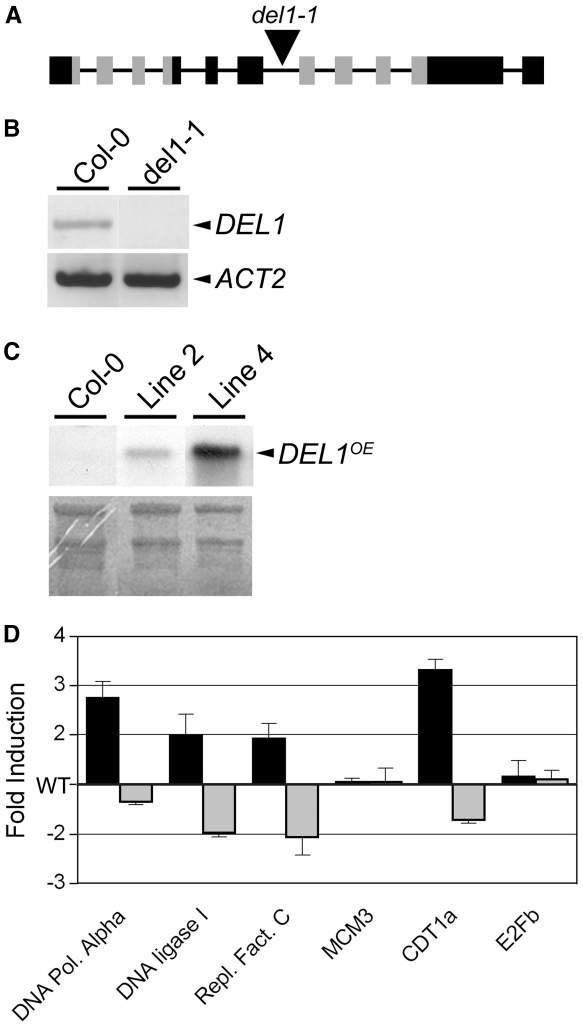


Figure 1. Molecular Analysis of *del1-1* and *DEL1$^{OE}$* *Arabidopsis* Plants

(A) *DEL1* gene structure. Black and gray boxes represent exons, and lines indicate introns. Regions that encode to the two DNA binding domains are in gray. The triangle corresponds to the T-DNA insert in the GABI-Kat 287D04 line (*del1-1*).

(B) Two-step RT-PCR analysis performed with equal amounts of total RNA prepared from 8-day-old wild-type and *del1-1* seedlings with primers that specifically amplify the *DEL1*-coding sequence flanking the T-DNA insertion site. The *actin 2* (*ACT2*) gene was used as a loading control.

(C) RNA gel blot analysis of wild-type (Col-0) and independent *DEL1$^{OE}$* lines. Equal loading of the gel was confirmed by methylene blue staining of the membrane (bottom panel).

(D) Change in transcript levels of replication genes (*DNA polymerase* $\alpha$*, DNA ligase I*, and *Replication factor c*), DNA replication licensing factors (*MCM3* and *CDT1a*), and *E2Fb* in *del1-1* (black) and *DEL1$^{OE}$* line 4 (gray). All measurements were performed on cotyledons of 10-day-old seedlings. Expression levels are compared with those found in wild-type (WT) cotyledons of the same age. Data represent average $\pm$ SE (n = 3).

of transgenic and wild-type plants grown side by side under the same conditions were harvested; leaf blade area and average cell area of abaxial epidermal cells were determined. The total number of epidermal cells was estimated as the ratio of leaf blade area and average cell area. Average cell division rates were calculated from the increase in cell number.

In the wild-type leaves, three developmental phases could be observed. First, until approximately 7 days after sowing, the cell number increased exponentially at maximal rates while cells retained a relatively constant cell size of approximately 80 $\mu m^2$ (Figures 3B and 3C), implying that expansion and division rates were balanced. In the second phase, between days 7 and 10, the division rate decreased (Figure 3D), testifying to the exit from the mitotic cell cycle. Simultaneously, average cell size started to increase (Figure 3C), indicating that the rate of cell expansion exceeded that of cell division. Between days 10 and 20, cell expansion continued in the absence of division, causing a 15-fold increase in cell size (Figure 3C). After day 20, leaves were mature and did not grow anymore (Figure 3A). When the development of the *DEL1$^{OE}$* and wild-type leaves was compared, cell size (Figure 3C) and cell number (Figure 3D) were very similar during the mitotic phase of leaf development. Cell division rates were comparable in wild-type plants and the *DEL1$^{OE}$* line 2 but were slightly lower in line 4. These data indicate that *DEL1* inhibits the mitotic cycle when it is expressed at high levels. In both *DEL1$^{OE}$* lines, cell division rates dropped at the same pace between days 7 and 10, but they did so somewhat more slowly than in wild-type plants, suggesting that DEL1 might control the timing of the mitosis-to-endocycle transition. In accordance with the later exit from mitosis, the average cell size decreased below that of the wild-type at day 9 (200 $\pm$ 16 $\mu m^2$ for wild-type, 112 $\pm$ 2 $\mu m^2$ for *DEL1$^{OE}$* line 2, and 125 $\pm$ 17 $\mu m^2$ for *DEL1$^{OE}$* line 4) and remained smaller during the later stages of leaf development (Figure 3C). At maturity, cell area was approximately 25% smaller in the leaves of both *DEL1$^{OE}$* lines. Taken together, these data show that the observed smaller leaf size in the *DEL1$^{OE}$* transgenic lines predominantly originates from an inhibition of cell growth.

The observed decrease in cell size was accompanied by a reduced level of endoreduplication (Figures 2A–2C). Endoreduplication cycles from 4C to 8C and 16C were strongly repressed in the cotyledons and hypocotyls of *DEL1$^{OE}$* plants (Figures 2A and 2B; Tables S2 and S3). The number of cells with a 4C DNA content was also clearly reduced in leaves (Figure 2C; Table S4). Because endoreduplication is developmentally regulated, we investigated the effects of *DEL1* overexpression on the endocycle in leaves (Figure 2D). Ploidy levels of the first leaves were measured at discrete time intervals during development. In wild-type leaves, 70% of the cells had a 2C DNA content 8 days after sowing, the remainder being predominantly 4C (Figure 2D). Coinciding with the exit from mitosis at day 10, the 2C population decreased, whereas the number of cells with 4C DNA content increased and became the most abundant population from day 12 onward. Simultaneously, cells with 8C DNA content could be detected. Later during leaf development, a small, but reproducible, population of cells with 16C DNA content could be measured.

In the *DEL1$^{OE}$* lines, the ploidy distribution during the mitotic phase of leaf development, 8 days after sowing, resembled that found in wild-type plants. In contrast,

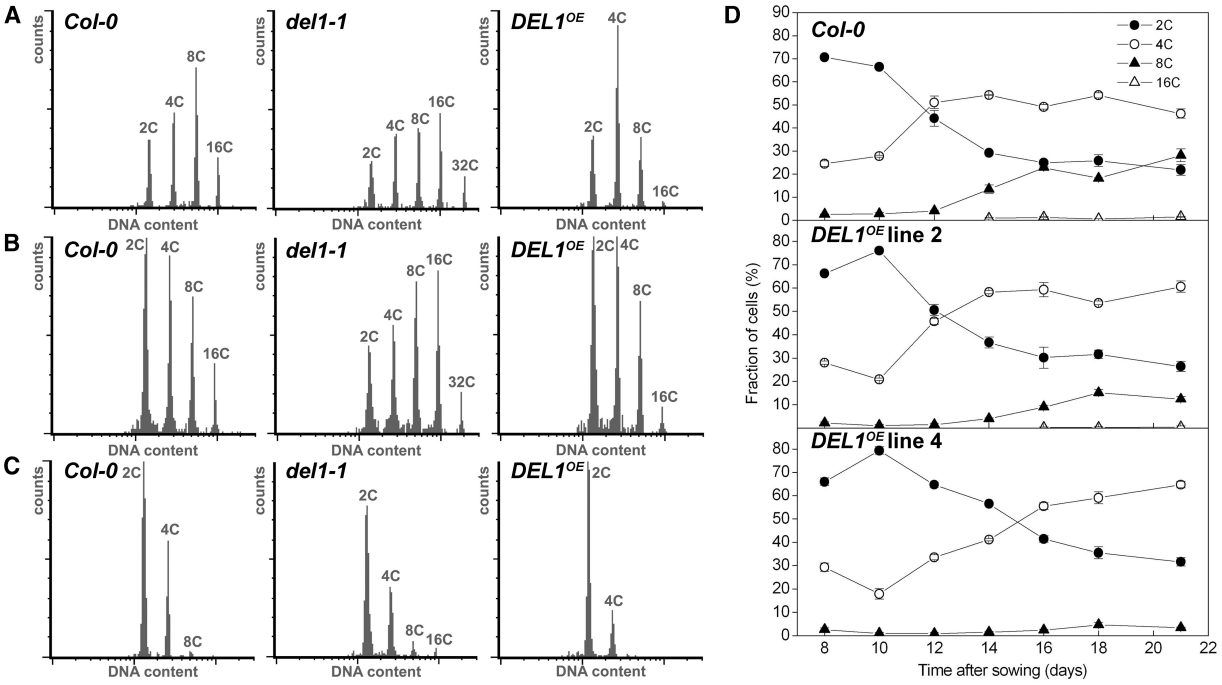


Figure 2. Control of the Endoreduplication Level by DEL1 in *Arabidopsis*

(A–C) DNA ploidy distribution measured by flow cytometry of untransformed control plants (left panels), *del1-1* (center panels), and *DEL1*$^{OE}$ line 4 (right panels) 12 days after sowing. (A) Cotyledons. (B) Hypocotyls. (C) Leaves. (D) Ploidy level distributions during development of the first leaf in wild-type and *DEL1*$^{OE}$ lines. Leaves were harvested at the indicated time points. Data represent average ± SD (n = 2).

an increase of 2C cells was seen in the *DEL1*$^{OE}$ lines (Figure 2D), whereas the 2C population of wild-type leaves decreased at day 10. This reproducible increase probably reflects the accumulation of G1 cells that have exited the G2 phase of the mitotic cycle, whereas part of the nuclei of the wild-type leaves had already entered the first endocycle. Later during leaf development, the 2C DNA population of *DEL1*$^{OE}$ plants decreased more slowly than that of wild-type leaves. In the strongest *DEL1*$^{OE}$ line, 2C cells remained the prevailing population for 15 days after sowing (Figure 2D). Moreover, almost no cells had a DNA content higher than 4C, even at the latest time point analyzed. Also in the *DEL1*$^{OE}$ line 2, a clear effect on the endocycle was observed, as illustrated by the strong decrease in 8C cells (12.4 ± 1.1%) compared to that of wild-type leaves (28.1 ± 2.8%). The results obtained from the leaf kinematic growth analysis, in combination with those of the ploidy measurements, strongly indicate that DEL1 operates as a specific repressor of the endocycle. Only when the *DEL1* gene is expressed highly above the endogenous level, the mitotic cell cycle is inhibited as well.

DEL proteins have been postulated to act as negative regulators of the E2F pathway [1–5]. Overexpression of both *E2Fa* and *DPa* (*E2Fa-DPa*$^{OE}$) genes in *Arabidopsis* resulted in a dual phenotype: Ectopic cell division occurred in certain cells, whereas others underwent excessive endoreduplication [11]. To test whether DEL1 was able to suppress these phenotypes, we crossed an *E2Fa-DPa*$^{OE}$ line with either a *DEL1*$^{OE}$ (line 4) or an untransformed control plant (Col-0). Offspring plants were first analyzed by flow cytometry. As observed before, *E2Fa-DPa*$^{OE}$ plants displayed an increased number of cells with a 16C DNA content together with two additional endocycles, whereas the number of 2C cells was strongly reduced (Table 1). Expression of *DEL1*$^{OE}$ in the *E2Fa-DPa*$^{OE}$ background resulted in a reduced endoreduplication, illustrating that DEL1 inhibits the endoreduplication phenotype induced by E2Fa-DPa. To address the question of whether DEL1 could also suppress the ectopic cell division phenotype caused by E2Fa-DPa, we counted the number of abaxial epidermal pavement cells of 6-day-old cotyledons (Table 2). Pavement cells of *E2Fa-DPa*$^{OE}$ transgenic plants were significantly smaller than those of control plants. Despite their smaller size, cotyledons of *E2Fa-DPa*$^{OE}$ plants had approximately 5-fold more epidermal cells. Cotyledons of *DEL1-E2Fa-DPa*$^{OE}$ triple transgenic lines had a reduced cell size and an increased cell number that did not differ from those of *E2Fa-DPa*$^{OE}$ lines. These results show that DEL1 does not suppress the ectopic cell divisions caused by overexpression of both *E2Fa* and *DPa* and again illustrate that DEL1 specifically inhibits the endocycle.

DEL1 could repress the endocycle by preventing either mitotically dividing cells from endoreduplicating or post-mitotic cells from initiating the endocycle. To distinguish between these possibilities, we examined the spatial expression of *DEL1* by in situ hybridization of sections from a 5-day-old etiolated hypocotyl (Figure S2), which is a well-characterized model system for DNA endoreduplication in plants [12–14]. In contrast to *E2Fa*, no *DEL1* transcripts could be detected in cortex cells that undergo extensive endoreduplication but no mitotic

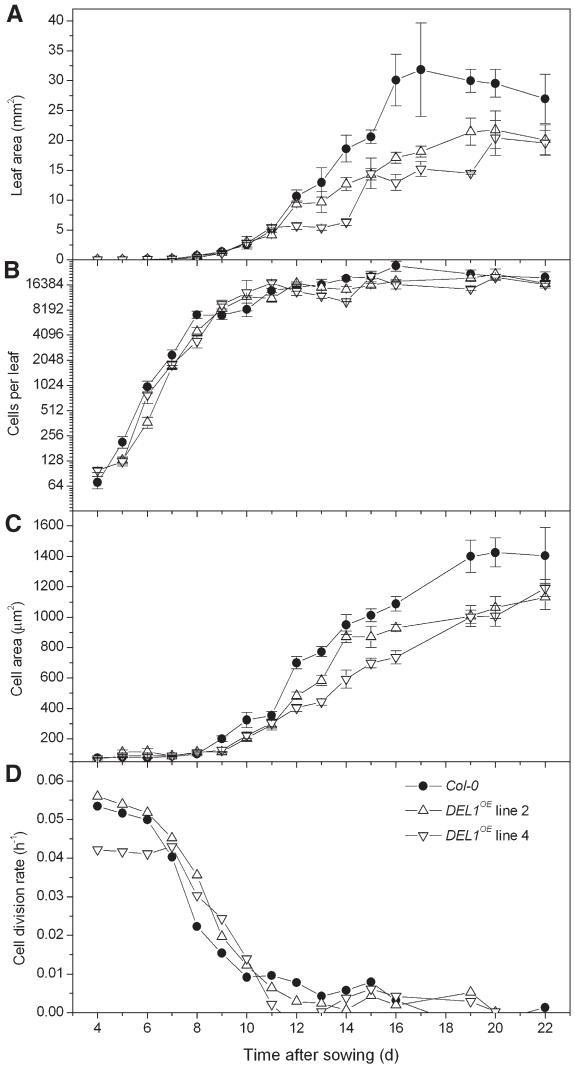


Figure 3. Kinematic Analysis of Leaf Growth of the First Leaf Pair of Wild-Type (Col-0) and *DEL1*$^{OE}$ Plants

(A) Leaf blade area.
(B) Epidermal cell number on the abaxial side of the leaf.
(C) Epidermal cell size on the abaxial side of the leaf.
(D) Average cell division rates of the epidermal cells on the abaxial side of the leaf. Error bars give standard errors (n = 5).
Symbols in (A), (B), and (C) are as in (D).

cell divisions. The *DEL1* hybridization signal was entirely confined to the vascular tissue that divides mitotically, as demonstrated by the expression of the mitosis-specific, cyclin-dependent kinase gene *CDKB1*. The presence of *DEL1* transcripts in dividing cells and its absence in cells undergoing DNA endoreduplication supports a role for DEL1 as repressor of the endocycle in mitotically dividing cells.

DEL1 resides in the nucleus and associates with the promoter of genes that contain the E2F consensus binding site [4, 5]. Consequently, DEL1 most probably represses the endocycle directly at the transcriptional level. Because *DEL1* is specifically expressed in proliferating cells, DEL1 might preserve the mitotic state of dividing cells by repressing the transcription of genes required for the endocycle. Previously, the mammalian homolog of DEL1, E2F7, has been demonstrated to regulate the expression of only a subset of E2F-dependent genes [2]. By quantitative PCR, we tested whether the transcript levels of DNA replication genes containing an *E2F-cis*-acting element in their promoter were altered in 10-day-old cotyledons of *del1-1* and *DEL1*$^{OE}$ plants. Of all six analyzed genes, which are regulated by *E2Fa-DPa* ([11, 15]; unpublished data), four had increased transcript levels in the *del1-1* mutant, whereas their expression was reduced in the *DEL1*$^{OE}$ lines (Figure 1D). In contrast, *MCM3* and *E2Fb* transcript levels did not change in response to altered *DEL1* levels. These data suggest that DEL1, like its mammalian counterpart, regulates only a subset of the E2F target genes. Because the DEL1 protein specifically inhibits the endoreduplication program, genes with an altered expression level in the *del1-1* and *DEL1*$^{OE}$ lines presumably play a role in the endocycle, whereas genes with unaltered transcript levels might be specific for the mitotic cell cycle.

In conclusion, we have identified DEL1 as a novel and specific repressor of the endocycle. Recently, we have demonstrated that the decision of cells to divide mitotically or to endoreduplicate is dictated by the activity of the mitosis-specific CDKB1;1 [16]. Therefore, it will be interesting to test whether DEL1 inhibits the endocycle by regulating the expression level of genes determining CDKB1;1 activity. In addition, because *DEL1* is closely related to the mammalian *E2F7* gene, it would be important to see whether the role of the DEL1/E2F7 proteins has been conserved evolutionarily. It has been noted before that E2F7 is to be found at a chromosomal location whose deletion has been associated with poor prognosis for pancreas cancer patients, marking *E2F7* as a possible tumor suppressor gene [2]. Because aneuploidy predisposes cells to oncogenic transformation, E2F7 might play a crucial role in maintaining the normal euploid state of the cell.

Table 1. Ploidy Levels in 6-Day-Old Wild-Type and Transgenic Seedlings

| Line | 2C (%) | 4C (%) | 8C (%) | 16C (%) | 32C (%) | 64C (%) |
|---|---|---|---|---|---|---|
| Col-0 | 27.4 ± 2.1 | 35.0 ± 1.1 | 29.7 ± 3.6 | 6.2 ± 2.3 | | |
| *DEL1*$^{OE}$ × Col-0 | 33.8 ± 3.3[a] | 40.2 ± 2.6[a] | 18.3 ± 0.9[a] | 4.9 ± 1.0[a] | | |
| Col-0 × *E2Fa-DPa*$^{OE}$ | 19.6 ± 2.6 | 34.0 ± 2.7 | 22.1 ± 2.0 | 14.6 ± 1.6 | 5.7 ± 0.7 | 0.9 ± 0.2 |
| *DEL1*$^{OE}$ × *E2Fa-DPa*$^{OE}$ | 34.4 ± 4.3[b] | 36.5 ± 0.8[b] | 17.2 ± 1.2[b] | 7.1 ± 0.9[b] | 2.3 ± 0.5[b] | 0.2 ± 0.1[b] |

Data represent average ± SD (n=5 to 8).
[a] $p < 0.01$ (comparison with Col-0).
[b] $p < 0.01$ (comparison with Col-0 × *E2Fa-DPa*$^{OE}$).
p-values were derived from two-tailed Student's t-tests.

Table 2. Size and Number of Abaxial Pavement Cells in Cotyledons of *E2Fa-DPa*$^{OE}$ and *DEL1-E2Fa-DPa*$^{OE}$ Lines

| Line | Cotyledon size (mm$^2$) | Abaxial Pavement Cells | |
|---|---|---|---|
| | | Size ($\mu$m$^2$) | Estimated Number |
| Col-0 | 2.4 ± 0.2 | 1954 ± 149 | 1307 ± 103 |
| *DEL1*$^{OE}$ × Col-0 | 1.8 ± 0.1[a] | 1210 ± 55[a] | 1478 ± 73 |
| Col-0 × *E2Fa-DPa*$^{OE}$ | 1.6 ± 0.1 | 265 ± 32 | 6820 ± 855 |
| *DEL1*$^{OE}$ × *E2Fa-DPa*$^{OE}$ | 1.9 ± 0.2 | 291 ± 58 | 7228 ± 833 |

All measurements were performed on cotyledons harvested 6 days after sowing. The indicated values are means ± SE (n = 9 to 15).
[a] $p < 0.01$ (comparison with Col-0).
p-values were derived from two-tailed Student's t-tests.

**Supplemental Data**

Supplemental Data including Experimental Procedures, two figures, and four tables are available with this article online at http://www.current-biology.com/cgi/content/full/15/1/59/DC1/.

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