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ORIGINAL RESEARCH

MGO3 and *GIP1* act synergistically for the maintenance of centromeric cohesion

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ABSTRACT

The control of genomic maintenance during S phase is crucial in eukaryotes. It involves the establishment of sister chromatid cohesion, ensuring faithful chromosome segregation, as well as proper DNA replication and repair to preserve genetic information. In animals, nuclear periphery proteins - including inner nuclear membrane proteins and nuclear pore-associated components - are key factors which regulate DNA integrity. Corresponding functional homologues are not so well known in plants which may have developed specific mechanisms due to their sessile life. We have already characterized the Gamma-tubulin Complex Protein 3-interacting proteins (GIPs) as essential regulators of centromeric cohesion at the nuclear periphery. GIPs were also shown to interact with TSA1, first described as a partner of the epigenetic regulator MGOUN3 (MGO3)/BRUSHY1 (BRU1)/TONSOKU (TSK) involved in genomic maintenance. Here, using genetic analyses, we show that the *mgo3gip1* mutants display an impaired and pleiotropic development including fasciation. We also provide evidence for the contribution of both *MGO3* and *GIP1* to the regulation of centromeric cohesion in Arabidopsis.

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Introduction

A tight regulation of DNA replication and mitosis in cycling cells ensures both the maintenance of genetic information integrity and an equational distribution of sister chromatids in daughter cells. Thus, accurate, efficient chromosome segregation is safeguarded by the maintenance of centromeric cohesion until anaphase. During S phase, DNA replication must deal with centromeric regions containing repetitive sequences and so, the cohesion between duplicated centromeres needs to be preserved. To properly monitor centromeric DNA replication, it was recently demonstrated that the slower dynamics of the replication forks did not activate the ATM- and Rad3-related (ATR) kinase involved in S phase DNA damage checkpoint.[1] In addition, the establishment of cohesion during S phase involves a chromosome transmission fidelity protein 7 (CTF7) which acetylates the structural maintenance of chromosome 3 (SMC3), a central component of the cohesion complex.[2] This step may also imply CTF18 and be coupled with the passage of the DNA replication fork.[2] This suggests that a mechanical link exists between cohesion establishment and DNA replication.

The regulation of DNA replication and sister chromatid cohesion remains poorly understood in plants. The *ctf7* mutants exhibit defects in both DNA repair and cell division.[3] Sister chromatid cohesion is impaired in the mutant of minichromosome maintenance helicase-binding protein E2F-target gene 1 (*ETG1*). Such a defect even extends the impact to centromeric regions when *CTF18* is simultaneously affected.[4]

Recently, we demonstrated that GIPs, initially found as regulators of the recruitment of microtubule-nucleation complexes, were also key players in the regulation of the nuclear architecture.[5,6] GIPs located on both sides of the Nuclear Envelope (NE) play a critical role in the maintenance of centromeric

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cohesion in the nuclei of cycling cells studied in *Arabidopsis* root meristems.[7,8] Interestingly, GIPs were identified as partners of TSA1[6] which was first described as TONSOKU (TSK)-associating protein1.[9] *TONSOKU* (*TSK*) is specifically expressed during S phase.[10] Allelic mutations in the epigenetic regulator *TSK*[11] also named *BRUSHY1 (BRU1)*[12-14] and *MGOUN3 (MGO3)*[15] led to a deregulation of various biologic processes: DNA damage response during DNA replication, cell cycle progression, heterochromatin organization, chromosomal subdomain architecture as well as meristem organization and flowering transition in *Arabidopsis*. TSA1 was also described as a partner of the COP9 signalosome subunit 1 (CSN1).[16] Both TSA1 and CSN1 may be involved in seedling development. Contrary to *gip* and *mgo3/bru1/tsk* mutants, the *tsa1* knocked-down mutant does not show strong growth alteration when growing under white light.[16] Therefore, we investigated the genetic interactions between *GIPs* and *MGO3/BRU1/TSK* in *Arabidopsis*. We established *gip1mgo3* and *gip2mgo3* lines, using the previously characterized *gip1, gip2* and *mgo3* mutants,[5,15] and compared the growth phenotypes of these mutants. We observed that *gip1mgo3* presented severe growth phenotypes as described previously for *gip1gip2*.[5] The defects of centromeric chromatin organization observed in *gip1mgo3* root nuclei indicate that *MGO3* contributes together with *GIP1* to the maintenance of centromeric cohesion in *Arabidopsis*. Therefore, our findings shed new light on the contribution of *MGO3*, in addition to *GIP1*, to a crosstalk between DNA replication and the establishment of sister chromatid cohesion, controlled at the nuclear periphery.

Results

Phenotypic growth characterization of gip1mgo3 *mutants*

We already showed that GIP deficiency in *gip1gip2* led to pleiotropic growth phenotypes and chromosomal instability[5] and that TSA1 interacted with both GIP1 and GIP2.[6] TSA1 was also shown to interact with MGO3/BRU1/TSK.[9] As *BRU1* is involved in genomic maintenance,[12] we investigated the relationships between MGO3/BRU1/TSK and GIPs. Among the several allelic mutants described in the literature, we used herein *mgo3–2*, further described as *mgo3*.[15] The *mgo3* mutant has a deletion of the 5′ coding region corresponding to a tetratricopeptide repeat-like domain (TPR-like) (Fig. S1).[15] First, we generated homozygous lines resulting from crosses between *gip1* or *gip2* and *mgo3* mutants, and characterized the growth of the different mutant seedlings. According to the genetic backgrounds of the mutants, Columbia (Col-0) for *gip1*, Wassilewskija (Ws) for *mgo3* and *gip2*, and Col-0Ws for *gip1mgo3* and *gip1gip2*, the wild type (WT) plants remained indistinguishable from each other (Fig. S2A). The *mgo3* mutant showed a reduced primary root growth compared with WT, *gip1* or *gip2* (Fig. S2A). While *gip2mgo3* showed a similar root growth phenotype as *mgo3*, the mean root growth of *gip1mgo3* was slower (Fig. 1, Fig. S2A). This was essentially due to the presence of high root length variability in *gip1mgo3*. Therefore, this prompted us to further split the *gip1mgo3* phenotypes into 2 subsets - type a (39.13% ± 4.09; n = 1219) resembling *mgo3* and type b (60.87% ± 4.09) which showed more severe and pleiotropic developmental phenotypes (Fig. S2A),

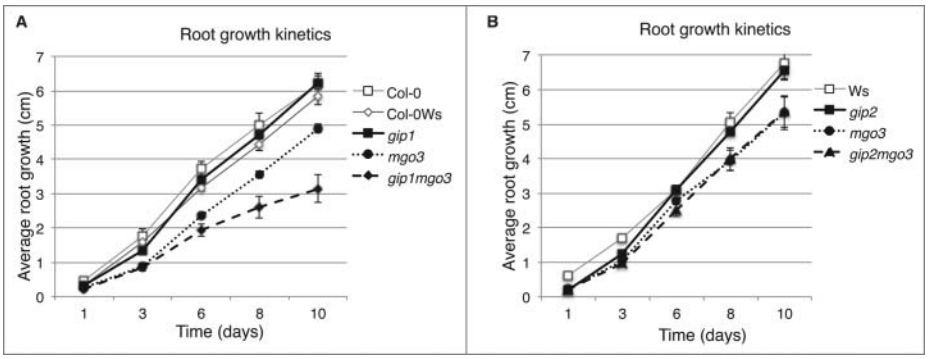

Figure 1. Comparative analysis of primary root growth of *gip1, gip2, mgo3, gip1mgo3* and *gip2mgo3 mutants* and WT. (A-B) Plantlets were grown on $^1/_2$ MS and growth was followed from day 1 to day 10 after germination. Three independent experiments were performed. SDs are indicated, n = 35, $P < 0.05$.

like those observed in *gip1gip2*.[5] At the level of their shoots, *gip2mgo3* were similar to *mgo3* but differed from *gip1mgo3* type a plantlets as these presented longer cotyledon petioles (Fig. S2B). Contrary to *gip1gip2*,[5] the *gip1mgo3* mutants remained fertile but exhibited fasciated inflorescences and stems with a much stronger phenotype compared with *mgo3* (Fig. S2C).[15] Such flattened shoots, as observed in *mgo3/bru1/tsk, fasciata 1, 2* and *tebichi* mutants, were functionally linked either to defects in chromatin assembly, DNA damage repair, DNA replication, or to meristem organization.[11,12,15,17-19] Thus, the increased fasciation observed in *gip1mgo3* suggests that GIP1 may contribute, together with MGO3, to these processes.

Centromere organization is impaired in gip1mgo3 *mutants*

In meristematic root cells, nuclei are enlarged in both *gip1mgo3* type b and *gip1gip2* (Fig. 2A), while interphasic cortical microtubule organization is not significantly altered in these mutants nor in *gip1mgo3* type a, *gip1* and *mgo3* mutants (Fig. 2A, Fig. S3). More specifically, while chromocentres which mainly correspond to pericentromeric heterochromatin at the nuclear periphery,[20] reach the number of 10 in Arabidopsis WTs (either ecotypes Ws, Col-0 or Col-0Ws), far more than 10 heterochromatin signals are present in about 20% of *gip1mgo3* type b plantlets compared with *gip1mgo3* type a, *gip1* or *mgo3* (less than 5%).

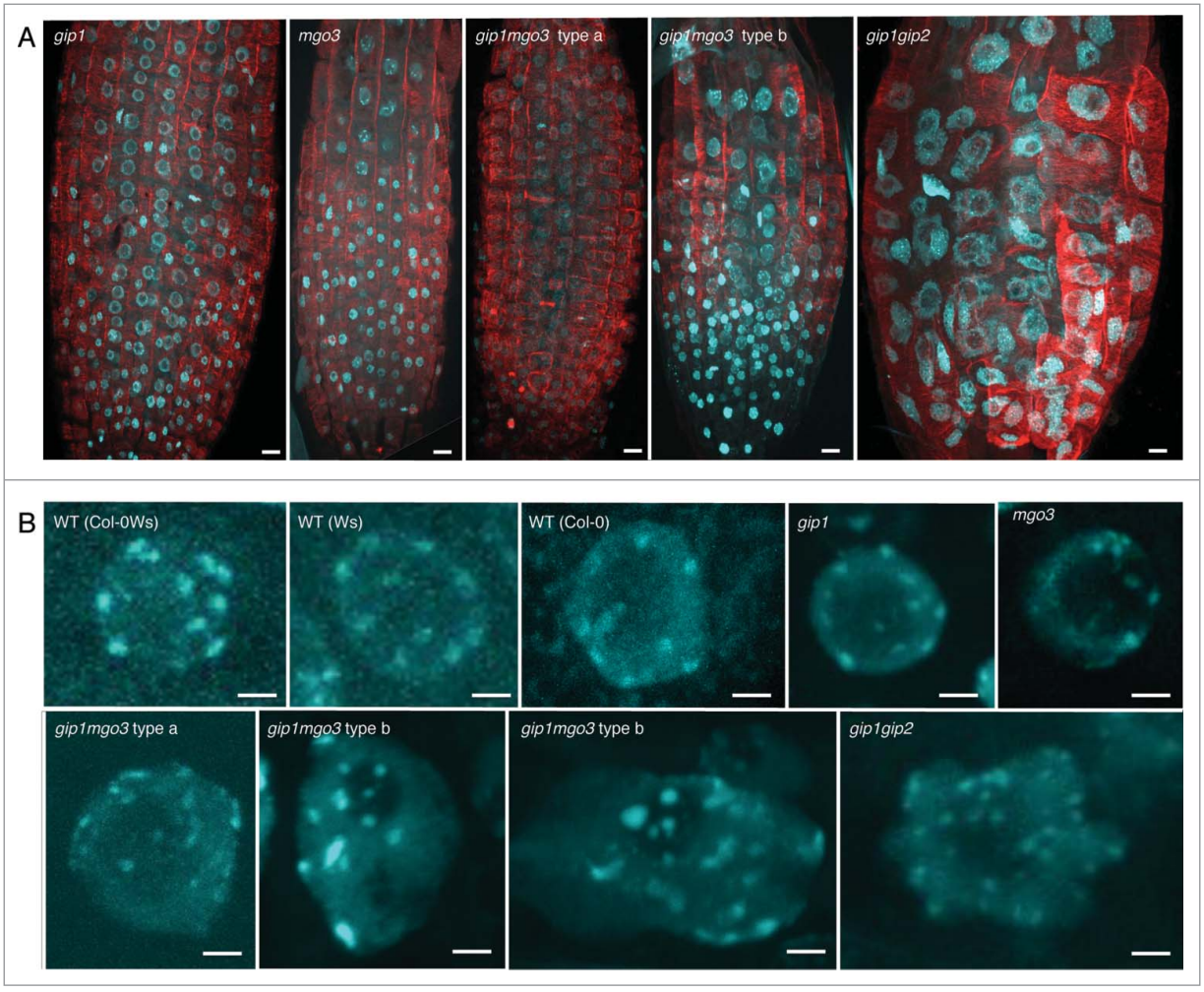

Figure 2. Analysis of root meristematic nuclei from *gip1, mgo3, gip1mgo3* compared with *gip1gip2*. (A) Detection of chromatin by DAPI staining (blue) and microtubules by immuno-labeling with antibodies directed against α-tubulin (red) performed on whole mount meristems of the different seedlings (*gip1, mgo3, gip1mgo3* and *gip1gip2*). Images were captured by confocal microscopy and correspond to Z-stack projections of focal planes. Bars = 10 μm. (B) Meristematic nuclei representative for different WT backgrounds (Ws Col-0), Col-0Ws) were compared with *gip1, mgo3, gip1mgo3* type a and b and *gip1gip2*. Images were captured by confocal microscopy and correspond to Z-stack projections of focal planes. Bars = 2 μm. For Z-stacks, slides were acquired in 0.35 μm intervals.

Thus, the *gip1mgo3* type b phenotype was similar to that described previously for *gip1gip2* (Fig. 2B).[7] For a more accurate description of the centromere defect, we evaluated the number of centromeric signals in 4C flow sorted nuclei, using the FISH centromere-specific pAL probe. While in WT the number of pAL signals did not exceed 10, we observed more than 10 signals in 6 to 7% of the nuclei in the *gip1* and *mgo3* mutants as well as in the *gip1mgo3* type a mutants (Fig. 3A). This percentage increased up to 19% in the *gip1mgo3* type b mutants. A similarly increased number of pAL signals was observed for the less affected *gip1gip2* type1 mutants.[7] These data argue for a synergistic contribution of *MGO3* and *GIP1* to centromeric cohesion. In addition, we observed an irregular distribution of pAL signals in the nuclei of both *gip1mgo3* type a

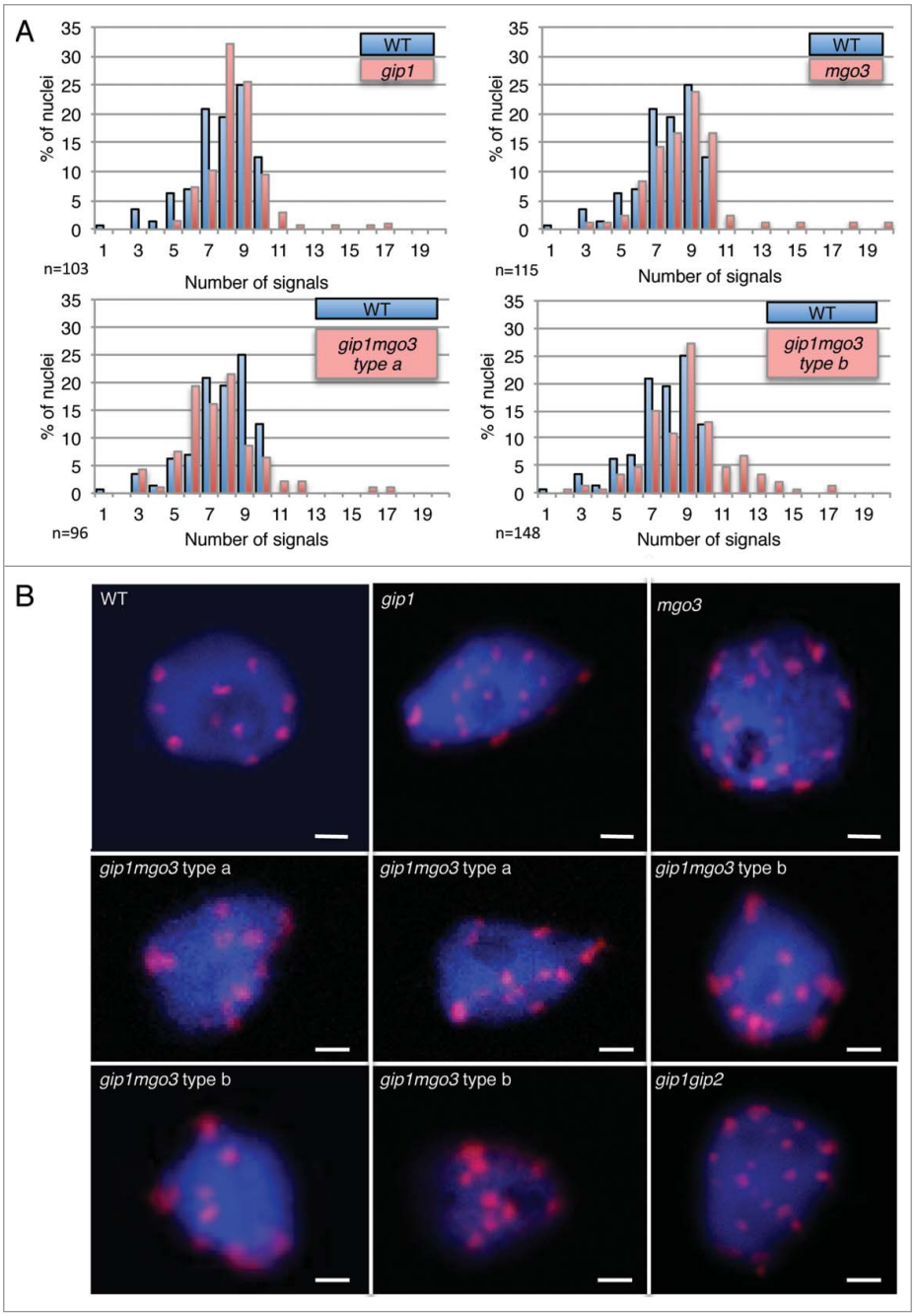

Figure 3. The *gip1*, *mgo3* and *gip1mgo3* mutants exhibit centromeric cohesion defects. (A) Number of pAL signals in 4C flow-sorted nuclei from WT, *gip1*, *mgo3* and 2 seedling phenotypes (types a and b) of *gip1mgo3* mutants. A Student t-test was used to calculate the confidence of values for signals >10. $P < 0.05$ (B) FISH detection of centromeric pAL signals in 4C nuclei from WT, *gip1*, *mgo3*, *gip1mgo3* type a and b compared with *gip1gip2* mutants. The image stacks of nuclei were collected with a Z-step size of 0.34 μm. Bars = 2 μm.

(8.6%; n = 93) and b (22%; n = 77) mutants compared with WT (Fig. 3B). The centromeric histone H3 variant (CENH3) signals, detected using immunolabelling, confirmed these results (Fig. S4). This indicates that *MGO3*, together with GIP1, may contribute to the spatial centromeric chromatin organization.

Discussion

In the present study, we have analyzed the genetic interactions between *MGO3* and *GIP1* in the control of centromeric chromatin. Previously, we showed the involvement of both GIP1 and GIP2 at the nuclear interface[7] and herein, the contribution of GIP1 together with MGO3 to the maintenance of centromeric cohesion.

MGO3/BRU1/TSK plays a role in stalling replication forks[12] as described for its homolog in humans, Tonsoku-Like (TONSL),[21,22] acting as a reader of new epigenetic marks linked to new histone incorporation at the post-replicative state.[23] Beside their role in centromeric cohesion, GIPs must also be involved in the loading/maintenance of CENH3 at centromeres.[7] The current challenge is to untangle the dynamics of these processes and to characterize the chaperones involved in CENH3 loading.[8] In animals, a dual role was described for the histone chaperone nucleosome assembly protein 1 (NAP1) controlling sister chromatid separation independently of its function in nucleosome assembly.[24] It is worth noting that human TONSL was shown to be an H3–1/H4 chaperone needed for nucleosome assembly after the restart of stalled replication forks,[25] but its role in the control of centromeric replication has not been investigated so far.

In interphase cells, GIPs were found on both sides of the NE. TSA1 and GIP1 exhibited a similar spotty appearance at the NE periphery,[6,11] while BRU1–EGFP fusion proteins, detected in the nucleus, were partially excluded from the nucleolus.[13] Nuclear localization of GIPs at the centromeres may contribute, together with MGO3, to the control of centromeric cohesion during S phase as previously suggested.[26] Interestingly, the minimal domain of interaction of TSK was partly overlapping with that of GIP1 in the C-terminal region of TSA1.[6,9] These data argue for a spatiotemporal regulation of GIP1, TSA1 and MGO3 interactions to properly ensure centromere cohesion. In addition, in *tsk* mutants, a stabilization of TSA1 was observed without any changes in the *TSA1* transcript level,[16] contrary to *mgo3* in which we showed that *TSA1* was upregulated (3 to 4 times, Fig. S5). This corroborates that a tight regulation exists between *TSA1* and *MGO3*.

In plants so far, only the *etg1ctf18* mutants which are affected in DNA replication and sister chromatid cohesion, respectively,[4] have been described to impair centromeric cohesion, but to a lesser extent than for *gip1gip2* or *gip1mgo3*. Our study highlights MGO3 and GIP1 as key actors whose dynamic interplay may allow the coordination of DNA replication[12] and centromeric cohesion at the NE periphery, although the underlying mechanisms remain to be elucidated.

In addition, as observed in *ctf7*,[3] post-replicative repair is affected in the *etg1* mutants and leads to the formation of endogenous Double Strand Breaks as well as the activation of the DNA damage response.[4] Similarly, mutations in the structural maintenance of chromosome 5/6 complex (SMC5/6) lead to defects in sister chromosome cohesion as well as impaired DNA repair in *Arabidopsis*.[27] All these data argue for a tight control between DNA replication, DNA repair and sister chromatid cohesion. As postreplicative DNA repair is impaired in *bru1*,[12] we need to further investigate this aspect in relation with GIPs and the nuclear periphery.

Altogether, our data reveal a particular network at the nuclear periphery involved in centromeric cohesion establishment/maintenance. This sustains proper chromosome segregation which is crucial for cell division and plant development. A further characterization of the dynamic interplay between GIP1 and MGO3 may help to understand the functional crosstalks taking place at the nuclear envelope periphery in plants. Since both GIP and MGO3 are conserved in humans as MOZART1[28] and TONSL, respectively, this may allow the investigation of their roles in defects of nuclear architecture[29] and chromatid cohesion in humans[30] linked to cancer progression.

Materials and methods

Plants and growth

gip1, gip2, gip1gip2 and *mgo3* mutants have been described previously.[5,15] The *Arabidopsis* lines were grown *in vitro* on Murashige and Skoog medium (SERVA Electrophoresis) at 20°C with a 16h photoperiod (70 μmol m-2 s-1 fluorescent lighting).

Homozygous T-DNA insertion lines of *gip1* and *gip2* were crossed with *mgo3–2* to produce the *gip1mgo3* and *gip2mgo3* mutants. All the investigations were performed on homozygous F3 lines. For genotyping, we used the same primers as described previously.[5,15]

Whole mount root tip immunostaining

7-day-old *Arabidopsis* seedlings were fixed as described.[5] We used the primary monoclonal antibody anti-α-tubulin (clone DM1A; Sigma-Aldrich, 1/5000) and the Alexa 568–conjugated goat anti-mouse IgG secondary antibody (1:300) (Molecular Probes). Root tips were mounted in antifade Vectashield (Vector Laboratories), with DAPI (2 μg/ml).

Immunocytochemistry

7-day-old *Arabidopsis* seedlings were placed for 20 min on ice in 4% paraformaldehyde in PEM buffer (50 mM PIPES, 5 mM EGTA, 5 mM $MgSO_4$, pH 6.9) and processed as described.[7] Primary anti-CENH3 polyclonal antibodies (Novus Biologicals; 1/500) were used in overnight incubation at 4°C; signals were detected using Alexa 568 fluor dye-conjugated secondary antibodies (1:300, Life Technologies) and counterstained with 2μg/ml DAPI.

Flow sorting of nuclei

The nuclei of 7-day-old plantlets were isolated and flow-sorted according to their endoploidy level after formaldehyde fixation using a FACS Aria (BD Biosciences), as described previously.[31]

FISH

The pAL plasmid[32] was used for the detection of the 180 bp centromeric tandem repeats. Probes were labeled with Orange 552 dUTP (Enzo Life Sciences (Els) Ag,) using the nick translation DNA labeling system (Enzo Life Sciences (Els) Ag). Slides were processed as described[7] previously and incubated with 20 μl of pAL probe per slide. After denaturation at 80°C for 2 min, hybridization was performed overnight at 37°C. After successive washes at 42°C in 2xSSC, in 50% formamide in 2xSSC and then 2xSCC, the material was mounted in Vectashield (Vector Laboratories) containing DAPI (2 μg/ml). The different frequencies of sister chromatid cohesion were tested for significance, using the 2-sided Fisher exact test.

Confocal microscopy

Confocal images were acquired with a Zeiss LSM 780 microscope equipped with 20x/0.8 or 63x/1.4 oil objectives. pAL centromeric signals as well as DAPI were observed using a laser beam with the excitation wavelengths of 405 and 488 nm, respectively.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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