

GTSE1 leads cancer cells into CIN

Study reveals that protein regulates spindle microtubule dynamics by inhibiting microtubule depolymerase MCAK.

Mitotic cells must precisely regulate the dynamics of their spindle microtubules, particularly those that are attached to chromosomes via kinetochores. Kinetochores must be stable enough to capture chromosomes and align them at the equator of the spindle, yet not so stable that attachment errors, such as the merotelic attachment of a single kinetochore to microtubules emanating from both spindle poles, cannot be corrected. Cancer cells often have hyperstable kinetochore microtubules, leading to an increase in attachment errors and chromosome missegregation. This, in turn, causes cancer cells to frequently gain or lose chromosomes, a phenomenon known as chromosome instability (CIN) (1, 2). Bendre et al. reveal that microtubule hyperstabilization and CIN may be driven, in part, by the overexpression of a protein called GTSE1, which inhibits the microtubule depolymerase MCAK (3).

In interphase cells, GTSE1 promotes cell migration by binding to the microtubule plus end tracking protein EB1 (4), but, during mitosis, the protein is recruited to the spindle by a protein called TACC3 (5). What, if anything, GTSE1 does at the spindle is unknown, however, so Alex Bird and colleagues at the Max Planck Institute of Molecular Physiology in Dortmund, Germany, decided to deplete the protein from U2OS cancer cells (3). “We saw that essentially all the different microtubule populations within the spindle were destabilized in the absence of GTSE1,” Bird explains.

Astral microtubules, for example, were unstable in the absence of GTSE1, leading to defects in spindle positioning. Kinetochore microtubules were also destabilized, delaying chromosome alignment at the metaphase plate and the cells’ subsequent progression into anaphase. “But eventually the chromosomes align and segregate,” Bird says. “And when they do this, they actually

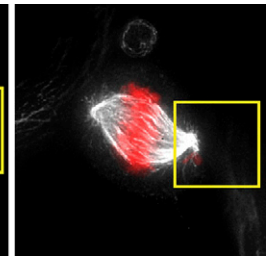
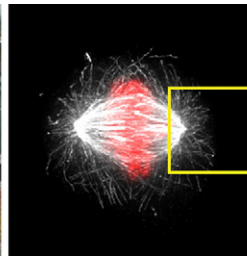


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segregate more accurately than usual.” U2OS cells normally show high levels of CIN but, in the absence of GTSE1, the frequency of chromosome missegregation was reduced, likely due to a decrease in merotelic microtubule-kinetochore attachments. The mitotic phenotypes associated with GTSE1 depletion are similar to the effects of overexpressing the microtubule depolymerase MCAK, suggesting that GTSE1 might stabilize microtubules by attenuating MCAK activity. Bird and colleagues previously found that GTSE1 associates with MCAK (5), and, in collaboration with Gary Brouhard’s laboratory at McGill University in Montreal, the researchers determined that, indeed, GTSE1 inhibits MCAK’s ability to depolymerize microtubules in vitro. Co-depleting MCAK largely rescued the mitotic phenotype of GTSE1-deficient cells; spindle microtubules were more stable, chromosomes aligned more efficiently, and chromosome segregation defects were returned to the levels seen in control U2OS cells. “So the GTSE1 depletion phenotype is caused by excess MCAK activity in the cell,” Bird explains.

Depleting GTSE1 also reduced chromosome missegregation in HeLa cells, which, like U2OS cells, usually show high levels of

CIN and express large amounts of GTSE1. This suggests that overexpression of GTSE1 might induce CIN. Bendre et al. tested this idea by overexpressing the protein in a cancer cell line—HCT116—that usually expresses low levels of GTSE1 and segregates chromosomes relatively accurately. “And we saw that these cells then had more segregation defects and increased levels of CIN,” Bird says.

GTSE1 is up-regulated in several different types of tumor, and its expression correlates with poor clinical outcome in breast cancer (4). Bendre et al. stress, however, that CIN likely arises from complex changes in entire cellular pathways, rather than from the elevated expression of *GTSE1* or any other single gene.

MCAK is also regulated by other factors including Aurora B kinase and the MCAK-binding protein NuSAP (6). Bird and colleagues now want to investigate precisely how GTSE1 inhibits MCAK activity and how its function is coordinated in time and space to ensure that spindle microtubule dynamics are at the right level to achieve both chromosome alignment and accurate segregation.

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“[Cells overexpressing GTSE1] had more segregation defects and increased levels of CIN.”