Acentrosomal spindle organization renders cancer cells dependent on the kinesin HSET

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Centrosomes represent the major microtubule organizing centres (MTOCs) of animal somatic cells and orchestrate bipolar spindle assembly during mitotic cell division. In meiotic cells, the kinesin HSET compensates for the lack of centrosomes by focusing acentrosomal MTOCs into two spindle poles. By clustering multiple centrosomes into two spindle poles, HSET also mediates bipolar mitosis in cancer cells with supernumerary centrosomes. However, although dispensable in non-transformed human cells, the role of HSET in cancer cells with two centrosomes has remained elusive. In this study, we demonstrate that HSET is required for proper spindle assembly, stable pole-focusing and survival of cancer cells irrespective of normal or supernumerary centrosome number. Strikingly, we detected pronounced acentrosomal MTOC structures in untreated mitotic cancer cells. While in most cancer cells these acentrosomal MTOCs were rapidly incorporated into the assembling bipolar spindle, some cells eventually established bipolar spindles with acentrosomal poles and free centrosomes. These observations demonstrate that acentrosomal MTOCs were functional and that both centrosomal and acentrosomal mechanisms were required for bipolar spindle organization. Our study shows that HSET is critical for clustering acentrosomal and centrosomal MTOCs during spindle formation in human cancer cells with two bona fide centrosomes. Furthermore, we show that in checkpoint-defective cancer cells, acentrosomal spindle formation and HSET-dependence are partially mediated by a constitutive activation of the DNA damage response. In summary, we propose that acentrosomal spindle assembly mechanisms are hyperactive in cancer cells and promote HSET, a key driver of acentrosomal spindle organization, as an attractive target for cancer therapy.
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