MECHANISM OF CANCER CELL KILLING BY MPS1 INHIBITORS

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MPS1, a mitotic kinase that is overexpressed in several human cancers, contributes to the alignment of chromosomes to the metaphase plate as well as to the execution of the spindle assembly checkpoint (SAC). In this study, we analyzed the impact of MPS1 inhibition on tumoral cells using three novel inhibitors of MPS1 of two independent structural classes, Mps-BAY1 (a triazolopyridine), Mps-BAY2a and Mps-BAY2b (two imidazopyrazines). By selectively inactivating MPS1, these small inhibitors can arrest the proliferation of cancer cells, causing their polyploidization and/or their demise. Cancer cells treated with Mps-BAY1 or Mps-BAY2a manifested multiple signs of mitotic perturbation including inefficient chromosomal congression during metaphase, unscheduled SAC inactivation, and severe anaphase defects. Videomicroscopic cell fate profiling of histone 2B-GFP-expressing cells revealed the capacity of MPS1 inhibitors to subvert the correct timing of mitosis as they induce a premature anaphase entry in the context of misaligned metaphase plates. Hence, in the presence of MPS1 inhibitors, cells either divided in a bipolar (but often asymmetric) fashion or entered one or more rounds of abortive mitosis, generating gross aneuploidy and polyploidy, respectively. In both cases, cells ultimately succumbed from the mitotic catastrophe-induced activation of the mitochondrial pathway of apoptosis. Of note, low doses of MPS1 inhibitors and paclitaxel synergized at increasing the frequency of chromosome misalignments and missegregations in the context of SAC inactivation. This resulted in massive polyploidization followed by the activation of mitotic catastrophe. A synergistic interaction between paclitaxel and MPS1 inhibitors could also be demonstrated *in vivo*, as the combination of these agents efficiently reduced the growth of tumor xenografts and exerted superior antineoplastic effects as compared to either compound employed alone. Altogether, these results suggest that MPS1 inhibitors may exert robust anticancer activity, either as standalone therapeutic interventions or combined with microtubule-targeting chemicals.