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Combination of eribulin and aurora a inhibitor MLN8237 prevents metastatic colonization and induces cytotoxic autophagy in breast cancer

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Abstract

© 2016 American Association for Cancer Research.Recent findings suggest that the inhibition of Aurora A (AURKA) kinase may offer a novel treatment strategy against metastatic cancers. In the current study, we determined the effects of AURKA inhibition by the small molecule inhibitor MLN8237 both as a monotherapy and in combination with the microtubuletargeting drug eribulin on different stages of metastasis in triplenegative breast cancer (TNBC) and defined the potential mechanism of its action. MLN8237 as a single agent and in combination with eribulin affected multiple steps in the metastatic process, including migration, attachment, and proliferation in distant organs, resulting in suppression of metastatic colonization and recurrence of cancer. Eribulin application induces accumulation of active AURKA in TNBC cells, providing foundation for the combination therapy. Mechanistically, AURKA inhibition induces cytotoxic autophagy via activation of the LC3B/p62 axis and inhibition of pAKT, leading to eradication of metastases, but has no effect on growth of mammary tumor. Combination of MLN8237 with eribulin leads to a synergistic increase in apoptosis in mammary tumors, as well as cytotoxic autophagy in metastases. These preclinical data provide a new understanding of the mechanisms by which MLN8237 mediates its antimetastatic effects and advocates for its combination with eribulin in future clinical trials for metastatic breast cancer and early-stage solid tumors.

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