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Abstract

An Unveiled Cell Death Mechanism Exclusive to Human Cancer Cells †

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Abstract: The modified phenanthridine PJ34 blocks the post-translational modifications of specific proteins highly expressed in human malignant cells. This exclusively arrests mitosis in human malignant cells by inserting flaws in their mitotic spindle structure. Cancer cells were efficiently eradicated by Mitotic Catastrophe cell death, while similarly treated healthy proliferating cells were spared and continued to proliferate as untreated cells. This cytotoxic effect was examined in a variety of human epithelial cancer cells in tissue culture and in xenografts. Three affected proteins were identified out of all tested proteins implicated in mitosis in epithelial malignant cells compared to healthy epithelial cells. Two kinesins, KifC1/HSET and Kif18A, as well as NuMA were identified. The identified kinesins are already examined for their potential implication in cancer therapy. Blocking the post-translational modifications of NuMA by PJ34 exclusively prevented the protein binding capacity of NuMA in cancer cells. This prevented its clustering in the spindle poles, which stabilizes the spindles and enables alignment of chromosomes in spindle mid-zone. Un-aligned chromosomes and dispersed NuMA and centrosomes were detected in distorted spindles of human cancer cells treated with PJ34. Mitosis was arrested in the anaphase and this lead to cell death via cytochrome-c leakage from the mitochondria membrane. Thus, the cytotoxic activity of PJ34 unveiled a new mechanism causing self-eradication of human cancer cells during mitosis, including cancer cells that are not responsive to current therapies and regardless of specific mutations. The more rapidly cells proliferate, the more rapidly they are eradicated.

Keywords: mitotic spindle; cancer cells; NuMA; kinesins; Mitotic Catastrophe cell death

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Reference

1. Cohen-Armon, M. Exclusive modifications of NuMA in malignant epithelial cells: A potential therapeutic mechanism. *Drug. Dis. Today* **2022**, *27*, 1205–1209. [CrossRef] [PubMed]