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‡ 8Ÿ>8 Cancer Fights Back: Hypoxia and HIF Signalling in the Development of Chemoresistance in Cancer Cells

1n Œ>8 Dr. Kian Leong LEE (Cancer Science Institute of Singapore, National University of Singapore, Singapore)

Numerous drug treatment regimes have been developed over the decades for the therapeuti management of diverse cancers. However, one of the unintended consequences of drug use is th subsequent development of chemoresistance in patients resulting in disease relapse. The mechanisms by which cancer cells become refractory to previously effective drugs remain poorly understood and this presents a persistent hurdle in the eradication of the disease. Here we show that hypoxia and the HI signalling pathway are important drivers of chemoresistance through the induction of the cell cycle and survival response in two unrelated cancer types. In chronic myeloid leukemia patients, several cases developed resistance against the frontline tyrosine kinase inhibitor drug imatinib. We show that hypoxia, which is a key microenvironment parameter in the bone marrow that harbours leukemic stem cells, drives their maintenance with the transcriptional regulation of survival genes. Separately, our attempts at developing a therapeutic strategy for the treatment of breast cancer cells via inhibition of the oncogenic G9A H3K9 methyltransferase led to the unexpected finding that this upregulates the hypoxia inducible factors (HIFs) and derepresses a number of hypoxia target genes many of which are also implicated in cell survival. Hypoxia itself, was able to promote an improved cell cycle response against G9A inhibitor drugs. Together, these studies suggest that the hypoxia/HIF pathway is an important mediator of chemoresistance in cancers of different origins, and future therapeutic targeting may necessitate the concurrent inhibition of the HIF pathway for effective implementation of cancer treatments.

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