The role of histone lysine demethylases in cancer cells’ resistance to tyrosine kinase inhibitors

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Abstract

Current cancer therapies are often associated with treatment failure and reduced patients’ survival due to drug resistance. There are various mechanisms involved in the acquisition of cancer drug resistance, including the selection of advantageous mutations, overexpression of transporter proteins and epigenetic alterations. In this context, epigenetic alterations refer to chromatin-mediated regulation of gene expression that results in heritable changes in the cellular phenotype. There is an ever-growing body of evidence suggesting that epigenetic mechanisms play an important role in bringing about drug resistance in cancer cells. While the relationship between chemotherapy and epigenetics has been widely discussed, emerging evidence indicates that specific epigenetic effectors are also crucial for the development of resistance to tyrosine kinase inhibitors (TKIs). One particular gene that encodes the histone lysine demethylase KDM5A is overexpressed in several cancers. In breast cancer tissues, cells with KDM5A gene amplification were found to be more resistant to erlotinib, an inhibitor of the tyrosine kinase epidermal growth factor receptor (EGFR), when compared to cells without the same amplification. KDM5A was also shown to mediate resistance to a second EGFR inhibitor called gefitinib, in EGFR-mutant lung cancer cell lines. This evidence indicates that KDM5A could activate alternative survival pathways involved in overcoming EGFR inhibition. In line with these results, another histone demethylase (i.e., KDM1A) promotes liver cancer cells’ resistance to the TKI sorafenib. Current evidence provides a suitable rationale to consider the use of specific KDMs inhibitors to sensitize cells to tyrosine kinase targeted therapies and thus, presents an opportunity to prevent the further development of drug resistance. This review discusses the involvement of histone lysine demethylases in the development of resistance to TKI and highlights the importance to develop new cancer treatment regimens to counteract this phenomenon.

Keywords: Epigenetics, drug resistance, cancer