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TITLE

IMATINIB RESISTANCE IN CHRONIC MYELOID LEUKEMIA: ROLE OF COX-2, MDR-1 AND HDACS

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The development of imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) represented a major success for target-directed cancer chemotherapy and a breakthrough in the management of chronic myeloid leukemia (CML). Although showing high rates of hematologic and cytogenetic responses, primary refractory disease and secondary resistance have been observed in a proportion of patients on imatinib monotherapy. Studies have suggested that resistance to imatinib originates from Bcr-Abl gene amplification, overexpression of Bcr-Abl protein or point mutations in the Bcr-Abl gene. However, several groups suggested that there might be other forms of Bcr-Abl-independent imatinib resistance. More recently, attention has been laid on the drug bioavailability, as a result of variation in the efflux and influx proteins, in the development of resistance to imatinib.

Aberrant transcription due to altered expression or mutation of genes that encode Histone acetyltransferases (HATs), histone deacetylases (HDACs) or their binding partners, is a key event in the onset and progression of cancer. In humans at least eighteen different HDACs have been reported. Studies have shown that certain oncogenes repress transcription by recruitment of HDACs. Studies also suggest that changes in HDACs expression in leukemic cells might be involved in chromatin-independent mechanisms of abnormal cellular proliferation, leading to acquired drug resistance of the cells. It has been reported that imatinib resistance in some CML patients is associated with activation of histone deacetylases (HDACs) signaling pathway mediated through loss of kinase target dependence. Therefore, further understanding of Bcr-Abl-independent imatinib resistance may be required to develop new therapeutic modalities for imatinib-resistant chronic myelogenous leukemia.

We have previously generated one imatinib-resistant K562 (IR-K562) cell line by culturing K562 cells gradually in increasing concentrations of imatinib. These IR-K562 cells showed severe modulation in cyclooxygenase-2 (COX-2) and multidrug resistance protein-1 (MDR1) expression with no altered expression of Bcr-Abl compared with parental K562 cells (*Leukemia Research*, 32, 855-864). Further, we have shown that celecoxib, a selective COX-2 inhibitor, overcomes imatinib resistance in these cells. However, the exact mechanism of induction of COX-2 and MDR1 leading to imatinib resistance in these cells has not been studied. Understanding the molecular mechanisms regulating COX-2 and/or MDR1 expression could add insight into cellular signaling pathways leading to resistance, which could become potential targets for pharmacological intervention. Here we show that HDACs (HDAC1, 2, 3, 4 and SIRT1) are upregulated in IR-K562 cells thereby modulating the expression of COX-2 via CREB transcription factor. COX-2, in turn induced MDR1 expression via PGE2-cAMP-PKC pathway. Furthermore, decreased Bax and increased Bcl2 expression in IR-K562 cells caused attenuation of p53-mediated apoptosis thus leading to Bcr-Abl independent resistance to imatinib.