Transient resistance to DNA damaging agents is associated with expression of microRNAs-135b and -196b in human leukemia cell lines

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The acquisition of resistance to anticancer drugs is widely viewed as a key obstacle to successful cancer therapy. However, detailed knowledge of the initial molecular events in the response of cancer cells to these chemotherapeutic and stress responses, and how these lead to the development of chemoresistance, remains incompletely understood. Using microRNA array and washout and rechallenge experiments, we found that short term treatment of leukemia cells with etoposide led a few days later to transient resistance that was associated with a corresponding transient increase in expression of ABCB1 mRNA, as well as miR-135b and miR-196b. This phenomenon was associated with short-term exposure to genotoxic agents, such as etoposide, topotecan, doxorubicin and ionizing radiation, but not agents that do not directly damage DNA. Further, this appeared to be histiotype-specific, and was seen in leukemic cells, but not in cell lines derived from solid tumors. Treatment of leukemic cells with either 5-aza-deoxycytidine or tricostatin A produced similar increased expression of ABCB1, miR- 135b, and miR-196b, suggesting a role for epigenetic regulation of this phenomenon. Bioinformatics analyses revealed that CACNA1E, ARHGEF2, PTK2, SIAH1, ARHGAP6, and NME4 may be involved in the initial events in the development of drug resistance following the upregulation of ABCB1, miR-135b and miR-196b. In summary, we report herein that short-term exposure of cells to DNA damaging agents leads to transient drug resistance, which is associated with elevations in ABCB1, miR-135b and miR-196b, and suggests novel components that may be involved in the development of anticancer drug resistance.

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