

Chronic exposure to hypoxia facilitates chemotherapy sensitivity with downregulation of MDR1.

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Chemotherapy is widely applied to various cancers. However, the tumor acquires resistance to such cytotoxic compounds. Especially, the facilitation of drug efflux often causes therapeutic failure, which is known as multidrug resistance. Multidrug resistance protein1 (MDR1, also known as p-glycoprotein) is a typical transporter relevant to the adaptive drug resistance. Rapid progression of tumors exceeds oxygen demand, resulting in a hypoxic microenvironment. It has been believed to be a cause of multidrug resistance, however, there is almost no chronic study. Thus the current study aims to reveal the chronic effects of hypoxia on sensitivity to chemotherapy using Caco2 cells and doxorubicin. Cytotoxicity of doxorubicin was smaller when cells were exposed to hypoxia in twelve hours indeed, but it was enhanced when exposed longer duration than three days with the accumulation of doxorubicin in the cells. In accordance, the expression of MDR1 was once increased in twelve hours but suppressed after one day in response to the oxygen availability. In conclusion, prolonged hypoxia should facilitate sensitivity to chemotherapy by reducing the expression of MDR1 in spite of its acute upregulation.