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The quinoxaline di-N-oxide DCQ blocks breast cancer metastasis *in vitro* and *in vivo* by targeting the hypoxia inducible factor-1 pathway

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Background: Although tumor hypoxia poses challenges against conventional cancer treatments, it provides a therapeutic target for hypoxia-activated drugs. Here, we studied the effect of the hypoxia-activated synthetic quinoxaline di-N-oxide DCQ against breast cancer metastasis and identified the underlying mechanisms.

Methods: The human breast cancer cell lines MCF-7 (p53 wildtype) and MDA-MB-231 (p53 mutant) were treated with DCQ under normoxia or hypoxia. Drug toxicity on non-cancerous MCF-10A breast cells was also determined. *In vitro* cellular responses were investigated by flow cytometry, transfection, western blotting, ELISA and migration assays. The anti-metastatic effect of DCQ was validated in the MDA-MB-231 xenograft mouse model.

Results: DCQ selectively induced apoptosis in both human breast cancer cells preferentially under hypoxia without affecting the viability of non-cancerous MCF-10A. Cancer cell death was associated with an increase in reactive oxygen species (ROS) independently of p53 and was inhibited by antioxidants. DCQ-induced ROS was associated with DNA damage, the downregulation of hypoxia inducible factor-1 alpha (HIF-1alpha), and inhibition of vascular endothelial growth factor (VEGF) secretion. In MCF-7, HIF-1alpha inhibition was partially via p53-activation and was accompanied by a decrease in p-mTOR protein, suggesting interference with HIF-1alpha translation. In MDA-MB-231, DCQ reduced HIF-1alpha through proteasomal-dependent degradation mechanisms. HIF-1alpha inhibition by DCQ blocked VEGF secretion and invasion in MCF-7 and led to the inhibition of TWIST in MDA-MB-231. Consistently, DCQ exhibited robust antitumor activity in MDA-MB-231 breast cancer mouse xenografts, enhanced animal survival, and reduced metastatic dissemination to lungs and liver.

Conclusion: DCQ is the first hypoxia-activated drug showing anti-metastatic effects against breast cancer, suggesting its potential use for breast cancer therapy.

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