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A234: GTP cyclohydrolase as a novel mechanism for tumour growth

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Background

Improvement of patient with cancer outcome can be achieved by identifying novel mechanisms that underlie cancer pathogenesis. GTP cyclohydrolase (GTPCH) is the rate-limiting enzyme for neopterin and tetrahydrobiopterin (BH4) synthesis. Elevated neopterin in patients associates strongly with cancer progression, while excessive BH4 favours tumour cell proliferation. We have recently found that GTPCH transforms normal fibroblasts and induces tumour angiogenesis; a similar role has been reported by another group in human colon and melanoma tumour xenografts. However, the mechanisms of GTPCH-driven tumour formation remain largely unknown.

Method

Immunohistochemistry (IHC) was used to investigate GTPCH expression in a variety of tumour tissue microarray (TMA). Gene microarray data were analyzed to correlate GTPCH elevation with prognosis of breast cancer patients. Cell cultures and mouse xenografts were models used to evaluate molecular effects of GTPCH expression in breast tumour cells.

Results

In screening TMA with IHC, GTPCH was found commonly highly expressed in breast, colon, lung and endometrium carcinomas and lymphomas. Analysis of a series of gene array data and interrogation of Oncomine showed a significant correlation of high GCH1 with worse prognosis and lower recurrence-free survival, particularly in the estrogen receptor (ER) or progesterone receptor (PR)-negative breast cancer in > 3,000 patients. In cell cultures, GTPCH transformed normal MCF10A epithelial cells and increased breast cancer BT474 malignancy; they displayed with an epithelial to mesenchymal transition phenotype. GTPCH increased MDA-MB231 cell proliferation and scratch wound healing, and upregulated RTK Tie2-associated Akt/ERK phosphorylation and spontaneously downregulated retinoblastoma tumour suppressor protein. In mouse xenotransplantation, GTPCH significantly increased tumour growth, angiogenesis and perfusion, and glycolytic metabolism pathway induction. These effects were attenuated by the GTPCH inhibitor.

Conclusion

Our study demonstrates a novel pathway by which GTPCH potentiates tumour growth, supporting further development of small molecule inhibitors and combination therapies most effective for clinical translation.

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