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TARGETING EPIGENETIC MODIFYING ENZYMES FOR CANCER THERAPY

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G9a is an epigenetic regulator that methylates H3K9 generally causing repression of gene expression and participate in diverse cellular functions. G9a is genetically deregulated in a variety of tumour types, and can silence tumour suppressor genes and therefore is important for carcinogenesis. Although hypoxia is recognised to be an adverse factor in tumour growth and metastasis, the role of G9a in regulating gene expression in hypoxia has not been described extensively. Here, we show that G9a protein stability is increased in hypoxia via reduced proline hydroxylation and hence inefficient degradation by the proteasome. This leads to an increase in H3K9me2 at its target promoters. Blocking the methyltransferase activity of G9a inhibited cellular proliferation and migration in vitro and tumor growth in vivo. Furthermore, an increased level of G9a is a crucial factor in mediating the hypoxic response by down-regulating the expression of specific genes, including *ARNTL, CEACAM7, GATA2, HHEX, KLRG1* and *OGN*. This down-regulation can be rescued by a small molecule inhibitor of G9a. Based on the hypothesis that the changes in gene expression would influence patient outcomes, we have developed a prognostic G9a-suppressed gene signature that can stratify breast cancer patients. Together, our findings provide a new insight into the role G9a plays as an epigenetic mediator of hypoxic response which can be used as a diagnostic marker and proposes G9a as a therapeutic target for solid cancers.

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