HYPOXIA

A breath of fresh air

> expression of a set of hypoxia-induced genes is strongly indicative of poor prognosis

The association of hypoxia with cancer is two-way: tumours typically experience low oxygen levels that lead to a hypoxia response, and mutations that cause an inappropriate hypoxia response can lead to cancer. Now, Chi *et al.* have shown that expression of a set of hypoxia-induced genes is strongly indicative of poor prognosis.

Cells respond to hypoxia through the hypoxia-inducible transcription factors (HIFs). Under normal conditions the HIF α-subunit is degraded by polyubiquitylation, but in normal hypoxic conditions and in tumours the rate of degradation decreases.

The authors set out to define a hypoxia gene-expression signature in primary cultured normal cells to compare it with expression in tumour cells. Because the hypoxia response varies widely between cell types, they used several different epithelial and mesenchymal samples. They obtained expression profiles from each cell type at several time points over a 24-hour response to hypoxia. Clustering analysis showed classes of genes that were up- or down-regulated in response to hypoxia, some of which were common and some of which were cell-type specific.

As carcinomas are derived from epithelial cells, the authors used the data from the epithelial cell cultures to define a set of 168 genes that were consistently induced by hypoxia. Using several previously published data sets from breast and ovarian cancer they found that tumours with high expression of hypoxia-response genes were of higher grade, were more likely to have p53 and oestrogen-receptor deficiencies, and, most importantly, correlated with significantly shorter survival times.

For the simple analysis of new tumour samples, the authors defined a 'hypoxia-response score' from the average expression of the hypoxia-induced genes. This score was compared with other prognostic indicators using the data from one of the breast cancer studies. It was found to be a better indicator of survival than traditional factors such as age, tumour size, tumour grade or response to chemotherapy. The addition of the hypoxia-response score increased the prognostic power of a multivariate analysis by 10%. Also included in the analysis was a similar signature for the wound-healing response. The two signatures showed only a weak correlation with each other, and between them accounted for 40% of the predictive power of the analysis.

DNA METHYLATION

Methylation gastronomy

The bacterium *Helicobacter pylori* is bad news for the stomach — in particular because it is responsible for at least half of all gastric cancers. But how *H. pylori* causes cancer is not clear. In their recent paper, Maekita and colleagues explore the association between *H. pylori* and aberrant DNA methylation in the gastric mucosa.

The researchers measured the levels of DNA methylation at certain CpG islands of individuals who were, or who were not, infected with *H. pylori*. CpG islands are often aberrantly methylated in cancers, and in gastric cancer cells, tumour suppressors (specifically, *INK4a* (also known as cyclin-dependent-kinase inhibitor 2A, or p16), *CDH1* (also known as E-cadherin) and *MLH1*) are inactivated by DNA methylation more often than they are through mutation.

Maekita and colleagues used methylation-specific PCR to determine levels of methylation in eight regions of the genome — two regions in a CpG island associated with *INK4a* and six regions in CpG islands associated with *LOX* (lysyl oxidase, which is also a tumour suppressor), HRAS-like suppressor and *THBD* (both of which are putative tumour suppressors), and *p41ARC* (also known as actin-related protein-2/3 complex, subunit 1B), *HAND1* and *FLNC* (which are frequently methylated in gastric cancers).

They found that individuals who were infected with *H. pylori* (but who did not have gastric cancer) had high levels of abnormal methylation at all eight CpG islands. The same CpG islands were also aberrantly methylated in patients with gastric cancer (but no existing *H. pylori* infection). From this, the authors suggest that *H. pylori* might increase the risk of cancer by inducing aberrant methylation in the gastric mucosa, and they discuss possible mechanisms for this. Previous studies indicate that *de novo* DNA methylation can be induced by cell proliferation, which is a feature of *H. pylori* infection. The researchers also speculate that the strong, chronic inflammation could be responsible. Whatever the mechanism, these findings indicate that measuring levels of methylation at specific CpG islands could be used as a mechanism of risk assessment for gastric cancer.

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ORIGINAL RESEARCH PAPER Maekita, T. *et al.* High levels of aberrant DNA methylation in *Helicobacter pylori* — infected gastric mucosae and its possible association with gastric cancer risk. *Clin. Cancer Res.* **12**, 989–995 (2006)

> *H. pylori* might increase the risk of cancer by inducing aberrant methylation in the gastric mucosa