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CANCER

Integrated epigenomic analysis sheds light on role of *BMP4* in regulating cisplatin sensitivity in gastric cancer

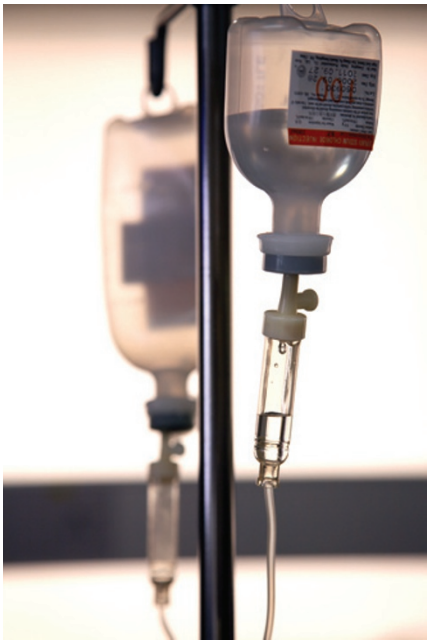
Bone morphogenetic protein 4 (*BMP4*) is involved in the development and progression of gastric cancer—a finding that could lead to targeted gastric cancer treatment and alternative treatment strategies for patients with tumours resistant to cisplatin.

Although some mechanisms by which different cancers evoke cisplatin resistance have been elucidated, there is currently no way to determine accurately which patients with gastric cancer are most likely to respond to cisplatin. "Our overall goal was to identify biomarkers that might aid clinicians in tailoring gastric cancer treatments … and highlight novel targeted strategies for overcoming cisplatin resistance in gastrointestinal cancer," explains Patrick Tan, corresponding author.

The team's first step was to treat 20 gastric cancer cell lines with increasing cisplatin concentrations. The cell lines varied greatly in their level of cisplatin sensitivity, and extending drug incubation times generated similar results. Comparing the gene expression profiles of the four most cisplatin-sensitive and four most cisplatin-resistant cell lines identified 291 differentially expressed genes.

The identification of such a large number of genes, and the proposal that aberrant DNA methylation patterns can serve as molecular markers predictive of prognosis and sensitivity to chemotherapy, motivated Tan and colleagues to study CpG (cytosine–phosphate–guanine) methylation levels across the cell lines. 1,505 CpG sites corresponding to 807 genes were quantified and the results validated. Combining the lists of differentially methylated and differentially expressed genes between the cisplatin-sensitive and cisplatin-resistant cell lines revealed five genes (*BMP4*, *CD9*, *DSC2*, *CDH17* and *TFPI2*) that were both differentially expressed and differentially methylated.

Focusing on *BMP4*—which encodes a member of the TGFβ superfamily—the team found that its methylation



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–199 bp and –123 bp (*BMP4*$^{-199}$ and *BMP4*$^{-123}$) from the transcription start site was inversely correlated with *BMP4* expression in the cisplatin-sensitive and cisplatin-resistant cell lines and across the original 20 cell lines (the correlation was strongest for *BMP4*$^{-199}$). *BMP4* methylation was also inversely correlated with cisplatin resistance and *BMP4* expression levels positively correlated with cisplatin resistance.

Additional work with the gastric cancer cells lines further elucidated the role of *BMP4*: its expression is probably regulated by methylation of its promoter; high *BMP4* expression levels at baseline in cisplatin-resistant cell lines can activate downstream components of the BMP signalling pathway; suppression of cell proliferation and invasion (by *BMP4* silencing) and their enhancement (by *BMP4* overexpression) support a pro-oncogenic effect of *BMP4* in gastric cancer; and reciprocal regulation of mesenchymal genes by *BMP4* silencing and overexpression suggests *BMP4* expression could aid the epithelial–mesenchymal transition in gastric cancer cells.

Moving to the clinical setting, the team confirmed that *BMP4* expression was significantly upregulated in primary gastric cancers compared with nonmalignant gastric tissue. Analysis of a subset of tumours designated as having 'low' or 'high' *BMP4* expression showed that *BMP4* methylation significantly correlated with *BMP4* expression. High *BMP4* expression levels were also found to correlate with poor patient survival. Several gene sets were found to be enriched in *BMP4* 'high' tumours, including some related to the epithelial–mesenchymal transition (for example, TGF-β signalling) and others related to cisplatin resistance (for example, nucleotide excision repair).

In the final part of their study, Tan and colleagues considered the therapeutic implications of their findings. They found that targeted inhibition of *BMP4* signalling could be one way to sensitize gastric cancer cells to cisplatin. Encouragingly, they also found that cisplatin-resistant cell lines did not exhibit resistance to oxaliplatin and had the same response as cisplatin-sensitive cell lines.

The researchers are now validating the utility of *BMP4* as a cisplatin resistance marker in a series of patient cohorts. One aspect of their continuing efforts involves prospectively collecting gastric cancer samples from patients receiving a fluorouracil prodrug plus either cisplatin or oxaliplatin as part of an ongoing phase II clinical trial. "Analysis of the genomic profiles of these samples upon completion of the trial should allow us to correlate *BMP4* expression levels to cisplatin and oxaliplatin responses, respectively," they conclude.

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