BLADDER CANCER

Measuring response to treatment

Cellular signalling involving the fibroblast growth factor (FGF) receptor FGFR3 is thought to have a role in bladder cancer pathogenesis, and is a target for the development of therapeutic drugs. Newly published research has confirmed that matrix metalloproteinases (MMPs) are regulated by FGFR3, and that MMPs have potential as pharmacodynamic markers of FGFR3 activity—inhibition of FGFR3 leads to measurable reductions in the elevated urinary levels of MMP-1 and pro-MMP-10 that are observed in patients with bladder cancer.

FGFR3 is a receptor tyrosine kinase that has been implicated as a potential oncogenic driver in the development of a range of human cancers. Activating mutations in *FGFR3* are present in 60–70% of low-grade, papillary, non-muscle-invasive bladder tumours, and in 11–16% of muscle-invasive bladder cancer tumours. High levels of wild-type FGFR3 are also found in >40% of muscle-invasive and metastatic bladder cancers. Several small-molecule inhibitors of FGFR3 are under clinical investigation for cancer therapy, so markers are required to assess pharmacodynamic modulation of FGFR3 expression and activity.

Researchers at Genentech have assessed the regulation of MMPs by FGFR3 in a series of preclinical and clinical investigations. In bladder cancer cell lines, *FGFR3* expression was inhibited using RNA interference, and transcription of genes encoding secreted proteins was measured by microarray and PCR. *MMP1* and *MMP10* were among the genes most affected, with 16-fold and fourfold reductions in mRNA levels, respectively. Similarly, inhibition of FGFR3 protein in these cells using the specific antibody R3Mab diminished secretion of MMP-1 and MMP-10, as well as its proprotein (pro-MMP-10), for which a more sensitive assay was available. Conversely, activation of FGFR3 using FGF-1 increased levels of MMP-1 and MMP-10 mRNA and secreted protein, an effect that was blocked by inhibition of the MEK–MAPK pathway, but not the PI3K–AKT pathway.

In mice bearing bladder cancer xenografts, weekly intraperitoneal administration of R3Mab induced dose-dependent suppression of tumour growth, and significantly reduced levels of MMP-1 and MMP-10 in tumour lysates and mouse serum. In humans, levels of MMP-1 and pro-MMP-10 were significantly higher in urine samples from 35 patients with bladder cancer than in 25 samples from healthy donors, but no differences were found in protein levels in corresponding serum samples.

R3Mab has been assessed in a Phase I dose-escalation trial in patients with relapsed or refractory, locally advanced or metastatic solid tumours, including 10 patients with bladder cancer. Clinical samples from this trial have now been analysed with respect to FGFR3 and MMPs. Levels of MMP-1 and pro-MMP-10 were significantly higher in pretreatment urine samples from patients with bladder cancer compared with other cancers. In serum samples, no differences were observed between cancer types. In eight evaluable pretreatment and post-treatment urine sample pairs from patients with bladder cancer, exposure to R3Mab reduced MMP-1 levels by >50%. In four of the eight sample pairs, pro-MMP-10 levels were also reduced. Whereas pro-MMP-10 reduction was only observed at maximal doses of R3Mab, MMP-1 was also affected by submaximal doses. Similar results were obtained with measurements of MMP-3 and MMP-9, identifying MMPs as a class of potential pharmacodynamic biomarkers for bladder cancer. However, no correlations were observed between baseline levels of any MMP and either FGFR3 or clinical response to R3Mab.

Bladder cancer is the second most common genitourinary tract malignancy, and development of therapeutic drugs for this condition will be expedited by availability of appropriate markers to indicate response to treatment. MMPs, which might, by their own activities, contribute to tumour growth, progression and metastasis, have now been shown to reflect FGFR3 responses in bladder cancers.

Robert Phillips

Original article Du, X. *et al.* MMP-1 and pro-MMP-10 as potential urinary pharmacodynamic biomarkers of FGFR3-targeted therapy in patients with bladder cancer. *Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-13-3336