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BLADDER CANCER

Targeting oncofetal glycosaminoglycans

Patients with muscle-invasive bladder cancer (MIBC) typically receive cisplatin-based neoadjuvant chemotherapy, although many fail to respond to this approach. Now, the findings of a translational study reveal the potential of targeting oncofetal chondroitin sulphate glycosaminoglycans (ofCS) as an alternative approach.

Researchers initially found that 92% of bladder tumours from two cohorts of patients have detectable ofCS: furthermore, a notable change in distribution of ofCS expression was observed with the development of cisplatin-resistant disease, from within the tumour cells to expression on membrane proteoglycans. ofCS-containing proteoglycans were then targeted in seven different bladder cancer cells lines using VDC886, consisting of a hemiasterlin analogue (KT886) conjugated to the recombinant malarial protein rVAR2, which selectively binds to ofCS. All cell lines were sensitive to VDC886 in the nanomolar range.

The effectiveness of VDC886 was then explored in mice inoculated with UM-UC13 cells into the bladder wall, followed by exposure to cisplatin treatment, and the subsequent development of resistance, which was consolidated over multiple generations of mice. Among mice receiving VDC886, one mouse had a complete response, one had tumour regression, and four had stable disease, compared with no notable effects in mice receiving unconjugated forms of either rVAR2 protein or KT886.

These findings reveal the potential role of ofCS as a treatment target in patients with cisplatin-resistant MIBC, and suggest that the targeted delivery of cytotoxic agents might overcome resistance to platinum-based therapy.

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