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BLADDER CANCER

Context is key: dual roles of ANGPTL4

> increased ANGPTL4 plasma levels were associated with reduced disease-free survival

Angiopoietin-like 4 (ANGPTL4) could have oncogenic and/or tumour-suppressive roles in urothelial carcinoma, according to new data published in *Oncogene*. Moreover, recombinant circulating ANGPTL4 level could be a minimally invasive biomarker of tumour progression in this disease.

Results of preliminary research showed that gene and protein expression of ANGPTL4 is downregulated in urothelial cancer cell lines. Further analysis revealed that the *ANGPTL4* promoter region had high levels of promoter methylation, and treatment with a demethylating agent and/or a histone deacetylase inhibitor restored ANGPTL4 expression.

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Ectopic expression of ANGPTL4 in urothelial carcinoma cell lines suppressed migration, reduced colony formation, and increased susceptibility to cisplatin. Cells overexpressing *ANGPTL4* exhibited upregulation of genes involved in RAS signalling and circadian entrainment and downregulation of genes involved in cell adhesion and cAMP signalling.

In vivo, *ANGPTL4*-overexpressing xenografts were considerably smaller than control xenografts. Furthermore, these *ANGPTL4*-overexpressing xenografts had reduced cell numbers and increased numbers of apoptotic cells.

In tumour tissue samples, *ANGPTL4* promotor methylation was significantly higher than in adjacent normal tissue. Furthermore, *ANGPTL4* expression was reduced, which was positively associated with increased pathological stage.

In vitro, treatment with exogenous recombinant circulating ANGPTL4 promoted urothelial carcinoma cell line proliferation in a dose-dependent and time-dependent manner and also significantly increased migration in these cells. Moreover, treatment with exogenous circulating ANGPTL4 increased ERK and, subsequently, FAK activation in these cells.

In vivo, exposure to recombinant circulating ANGPTL4 resulted in xenografts that were considerably larger than xenografts that had not been exposed to this protein.

In patient tumour samples, ANGPTL4 expression was reduced in muscle-invasive urothelial carcinoma tissue, but expression was observed in stroma and also in tumour-infiltrating lymphocytes. Analysis of plasma showed that levels of recombinant circulating ANGPTL4 in samples from patients with urothelial carcinoma were significantly higher than those from people without this disease. Receiver operating characteristic analysis resulted in a cut-off plasma level of recombinant circulating ANGPTL4 of 75.98 ng/ml with a sensitivity of 85.26% and a specificity of 73.68% for distinguishing patients with urothelial carcinoma from people without. Moreover, increased ANGPTL4 plasma levels were associated with reduced disease-free survival.

These data suggest that ANGPTL4 could have dual oncogenic and tumour-supressing roles in urothelial carcinoma, depending on the context of expression. These results also indicate that an interaction between the tumour and the tumour microenvironment occurs. Furthermore, levels of recombinant circulating ANGPTL4 could serve as a noninvasive biomarker for patients with this disease.

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ORIGINAL ARTICLE Hsieh, H.-Y. *et al.* Epigenetic silencing of the dual-role signal mediator, ANGPTL4 in tumor tissues and its overexpression in the urothelial carcinoma microenvironment. *Oncogene* http://dx.doi.org/10.1038/onc.2017.375 (2017)