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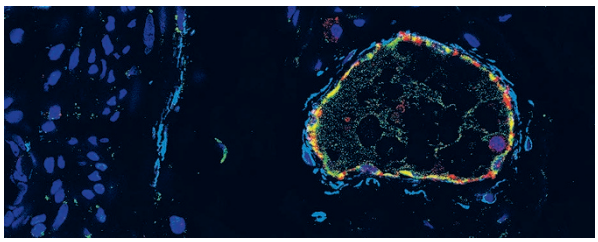
COLORECTAL CANCER

CRC endothelial regulation

SPARCL1, a secreted antiangiogenic protein, can be differentially regulated in colorectal cancers (CRCs) with disparate tumour microenvironments, according to new research.

The tumour microenvironment is shaped by bidirectional interactions between stromal and tumour cells. Tumour endothelial cells (TECs) have been extensively targeted in CRC on the basis that angiogenesis is required for tumour growth, yet anti-angiogenic treatments are only effective in some patients. "We assumed that tumourmicroenvironment-induced endothelial cell heterogeneity or plasticity might be involved in the differential responses to treatment," says author Elisabeth Naschberger.

To test their theory, the authors isolated pure TECs from CRC samples with or without a T helper 1(T_H1) tumour microenvironment, which is associated with IFNγ activation and improved prognosis. High guanylate-binding protein 1 (GBP1) expression, previously shown to closely associate with a T_H1 microenvironment, was used to differentiate tumour samples. Isolated TECs from tumours expressing high ($n = 8$) and low ($n = 8$) levels of GBP1 were then cultured and their transcriptomes assessed.



SPARCL1 expression in vessel endothelial cells of colon tissue (SPARCL1, green; αSMA, blue; CD31, red). Image courtesy of E. Naschberger and M. Stürzl.

A large number of genes were found to be differentially expressed between the two tumour subtypes; the most upregulated gene in high-GBP1 TECs was *SPARCL1*, which encodes a secreted matricellular glycoprotein. In patient tissue, SPARCL1 was predominantly expressed by endothelial cells in healthy and CRC tumour samples, with lower expression in mural cells and no expression in CRC tumour cells. *SPARCL1* mRNA levels were reduced in CRC tumours, and low *SPARCL1* expression was associated with low-GBP1, non-T_H1 tumours. Notably, addition of the T_H1-associated cytokines IFNγ and IL-2 to cultured TECs increased SPARCL1 expression, whereas the T_H2-associated cytokine IL-4 reduced SPARCL1 expression, indicating that the tumour microenvironment can regulate SPARCL1 levels.

An analysis of confluent and subconfluent cultured endothelial cells revealed that *SPARCL1* is a marker of endothelial cell quiescence. Moreover, high levels of SPARCL1 were associated with mature, non-angiogenically active vessels in patient CRC samples. When *SPARCL1* was overexpressed in primary endothelial cells in 3D culture, sprout formation and proliferation was reduced. Proliferation, migration and sprouting of endothelial cells was also inhibited by recombinant SPARCL1 added to culture media.

"In ongoing work we are investigating the structure–function relation of SPARCL1 and putative cellular receptors in order to determine the minimally active motif and the underlying mechanisms of SPARCL1s anti-angiogenic and antitumorigenic functions," concludes author Michael Stürzl.

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