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COLORECTAL CANCER

On the origin of colonic tumours—outside the niche

The pathogenetic mechanisms underpinning tumour formation in hereditary mixed polyposis syndrome (HMPS) have been revealed. Using a mouse model of HMPS, the researchers have shown that aberrant epithelial *GREM1* expression disrupts the strict gradients of morphogens in the intestine that dictate the pattern of tissue development, thus altering cell fate and leading to the initiation of colonic tumorigenesis from cells outside the stem cell niche.

Previous work had identified *GREM1* as a key genetic determinant of HMPS. "This mouse model was designed to replicate the change in tissue compartmental expression seen in patients with HMPS to be able to assess the dynamic changes that occur during polyp and cancer development," explains author Simon Leedham.

By examining polyp samples from individuals with HMPS, Leedham and colleagues confirmed epithelial expression of *GREM1*, which encodes Gremlin1, a mesenchymal bone morphogenetic protein (BMP) antagonist, and found that these polyps had mixed dysplastic and nondysplatic areas. Further histopathological analysis revealed that ectopic crypt foci contained actively proliferating cells and developed orthogonally to the crypt axis, with some dysplastic cells emerging from these ectopic crypt foci.

The researchers then switched to their mouse model, so-called *Vil1-Grem1* mice that express *Grem1* under the control of an intestinal-epithelium-specific *Vil1* promoter, and found similar features to humans. Crucially, in 3-month-old *Vil1-Grem1* mice, *Grem1*-expressing ectopic crypts developed orthogonally to the axis of the villi. These crypts budded off, becoming actively proliferating lesions within the villus that eventually developed dysplastic features and, by 7 months, had progressed to panintestinal polyposis with mixed serrated, adenomatous and cystic characteristics just as with human HMPS. Early lesions developed outside of the basal stem cell niche in the intestinal crypt, either on the luminal surface in the colon or within the ectopic crypts.

Further work using these transgenic mice indicated that *Grem1* expression disrupts the coupling of cell fate to position along the intestinal vertical axis, and *Grem1* and Wnt signalling act in a synergistic manner during the initiation and progression of intestinal polyps. Finally, aberrant epithelial *GREM1* expression was confirmed in human traditional serrated adenomas, which the authors consider as a sporadic equivalent of HMPS polyps.

"The research demonstrates that the crypt base columnar stem cell is not the sole cell of origin in all types of cancer and questions the intestinal unidirectional tissue organisational heirarchy," notes Leedham. He adds that they are exploring the role of GREM1 signalling in sporadic tumorigenesis and looking for methods to restore the balance of BMP signalling.

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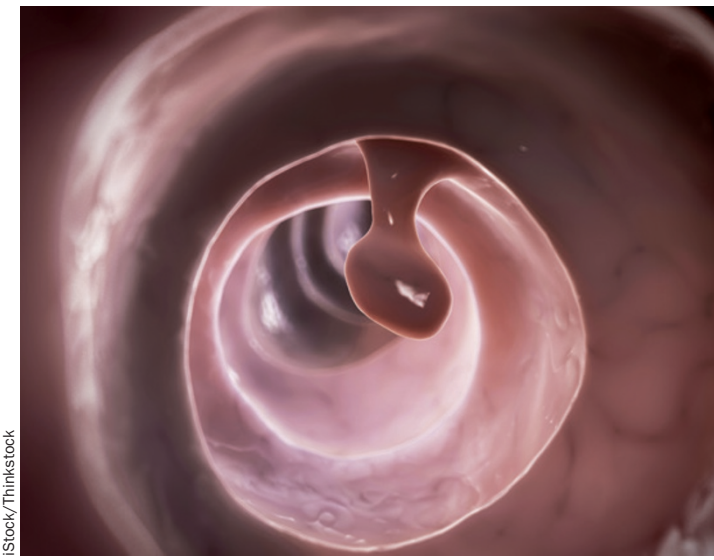

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