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TUMOUR SUPPRESSORS

Sorting it out

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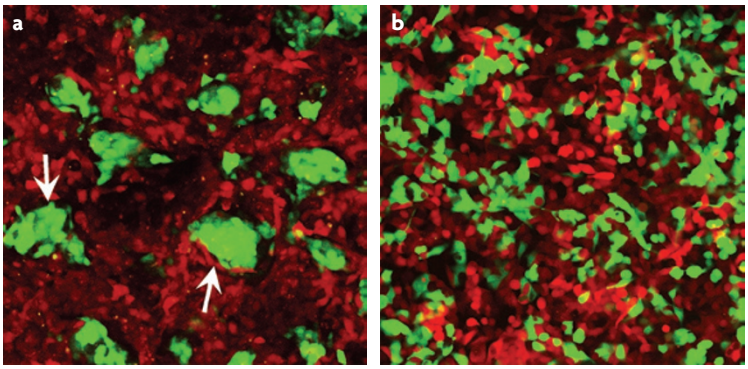
The tumour suppressors EPHB2, EPHB3 and EPHB4 are usually silenced in the intestine around the adenoma–carcinoma transition, but little is known about how EphB signals prevent cancer progression. Eduard Batlle and colleagues have now shown that EphB compartmentalizes colorectal cancer cells to restrict the spread of tumour cells into ephrin-B1-positive areas of the intestine.

The authors first infected EphB and ephrin-B1-negative colorectal cancer cell lines with lentiviruses bearing green fluorescent protein (GFP) and *EPHB3* cDNA, or with lentiviruses bearing red fluorescent protein (RFP) and ephrin B1. When these cell populations were co-cultured, the EphB and ephrin B1 cultures did not intermingle (see figure part a); if EphB–GFP cells were co-cultured with RFP-labelled control cells, or ephrin B1–RFP cells were co-cultured with GFP-labelled control cells, the two populations were completely mixed (see figure part b). They also noticed that addition of ephrin B1 to EphB-expressing colorectal cancer cells spread over a laminin-coated surface caused the cells to cluster, become more epithelial like, and redistribute E cadherin from the cytoplasm to the basolateral membranes. If E cadherin levels were knocked down using short hairpin RNA, EPHB3 activation levels did not change, but the cells no longer clustered. Therefore, EphB signalling promotes E cadherin adhesion, so restricting the capacity of malignant cells to expand into adjacent ephrin-B1-positive regions.

So, how does this mechanism function in the intestine? Adenomas (which are EphB positive) in the small intestine of $Apc^{Min/+}$ mice appear completely enclosed by normal epithelium (which is ephrin-B1 positive), mirroring the compartmentalization of tumour cells seen in the cell-line work. The authors created $Apc^{Min/+}$ mice with ephrin B1 conditionally knocked out in the intestinal epithelium ($Efnb1^{Int-KO}$). These mice had cell-positioning defects; for example, Paneth cells were no longer restricted to the crypt base, but there were no changes in the numbers of different cell types present in the crypts. The $Apc^{Min/+}$ mice lacking ephrin B1 developed fewer polyps in the small intestine than $Apc^{Min/+}$ mice, and the adenomas that formed had a very different morphology — 70% were classified as villous-like, compared with 20% in the $Apc^{Min/+}$ mice. In addition, these tumours were often not enclosed by normal mucosa and invaded the ephrin-$B1^+$ territory. Lack of compartmentalized growth led to accelerated tumorigenesis in the colon and rectum — the tumour load in $Efnb1^{Int-KO}$;$Apc^{Min/+}$ mice was at least double that seen in $Apc^{Min/+}$ mice — and the tumour growth patterns were more disorganized.

Batlle and colleagues conclude that tumour cell compartmentalization in epithelial tissues, which limits tumour progression, is defined by EphB–ephrin interactions.

Ezzie Hutchinson



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ORIGINAL RESEARCH PAPER Cortina, C. *et al.* EphB–ephrin-B interactions suppress colorectal cancer progression by compartmentalizing tumour cells. *Nature Genet.* 30 September 2007 (doi/10.1038/ng.2007.11)