

 BACTERIAL PATHOGENESIS

# *E. coli* claims the driving seat for cancer

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In recent years, mounting evidence has implicated the microbiota in various inflammatory diseases, but whether or not these commensal bacteria have an active role in the development of cancer has been unclear. Now, Arthur *et al.* provide evidence that inflammation alters the intestinal microbiota by favouring the proliferation of genotoxic commensals, and that the *Escherichia coli* genotoxin, colibactin, promotes colorectal cancer (CRC).

To learn more about the link between the microbiota, inflammation and carcinogenesis, the authors began by comparing the intestinal microbial composition of interleukin-10-deficient (*Il10*<sup>-/-</sup>) mice (which are susceptible to colitis) with that of wild-type mice, in the presence and absence of the colon-specific carcinogen azoxymethane (AOM). They found that in *Il10*<sup>-/-</sup> mice the microbiota was

less diverse but the prevalence of commensal *E. coli* was ~100-fold higher than in wild-type mice. Importantly, the observed shift in microbial composition was independent of AOM treatment, indicating that inflammation (and not cancer) was the cause of the modified microbiota in *Il10*<sup>-/-</sup> mice.

To examine the impact of *E. coli* on CRC development, AOM-treated germ-free *Il10*<sup>-/-</sup> mice were colonized with either *E. coli* str. NC101 (a mouse commensal strain) or *Enterococcus faecalis* (a human commensal species). Histological analysis revealed that, despite both mouse groups having similar levels of colitis, *E. faecalis*-colonized mice rarely showed signs of tumorigenesis, whereas 80% of mice colonized with *E. coli* developed invasive tumours. This effect was independent of any differences in the levels of cytokines or infiltrating immunological cells, implicating an *E. coli*-specific factor as the tumour-promoting agent.

The polyketide synthase (*pks*) pathogenicity island, encoding the DNA-damaging toxin colibactin, was detected in the genome of *E. coli* str. NC101 and was also found in almost 70% of intestinal *E. coli* strains from human patients with CRC, making this island a potential candidate for the tumour-promoting agent. To test this hypothesis *in vivo*, the authors examined the ability of an *E. coli* str. NC101

mutant lacking *pks* (NC101Δ*pks*) to cause tumorigenesis in AOM-treated *Il10*<sup>-/-</sup> mice. Like the wild-type strain, NC101Δ*pks* induced chronic inflammation, but for the mutant this occurred in the absence of invasive tumours, indicating that colibactin is a requirement for progression to cancer. In addition, the NC101Δ*pks* mutant induced less DNA damage in mouse colonocytes than the wild-type strain.

Together, these data demonstrate the complex interplay between inflammation and the microbiota in driving CRC, and provide further support for the ‘pathobiont’ model, which posits that chronic inflammatory disease triggers the pathogenic potential of resident commensals. This study suggests that inflammation-induced changes in the gut microbiota can have a direct influence on the development of CRC. It also identifies *pks*-containing *E. coli* as a new risk factor for CRC, although the authors note that additional studies using other models will be needed to confirm this link.

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**ORIGINAL RESEARCH PAPER** Arthur, J. C. *et al.* Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 16 Aug 2012 (doi:10.1126/science.1224820)  
**FURTHER READING** Chow, J. & Mazmanian, S. K. A pathobiont of the microbiota balances host colonization and intestinal inflammation. *Cell Host Microbe* 7, 265–276 (2010)

