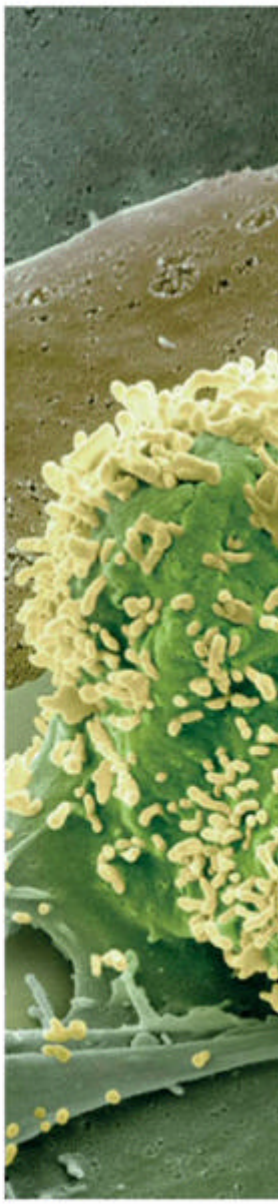
Time to enlist life-saving, gutsy allies

A surprising new front is opening up in the war on cancer. We just need to get a few trillion foot soldiers on side, says **Christian Jobin**



There are subtle links between cancer cells (tinted green) and gut microbes (orange)

THE human body is occupied by trillions of microorganisms, acquired at birth and maintained throughout our lifetime. Though we are mostly oblivious to this microbiome, it forms an intimate and essential part of our being. It is involved in many vital biological processes such as nutrition, the immune system and even mental health. Now evidence is mounting that the microbiome plays a role in cancer too.

In the past five years a comprehensive catalogue of the microorganisms living on and in the different surfaces and cavities of our bodies has been created – a sort of "getting to know your neighbours". This has revealed that the microbiome is a diverse community of more than 1500 species, with the vast majority residing in the intestine. We are just beginning to discover how these microbes influence the development and treatment of cancer.

The first evidence that "friendly" gut bacteria might have a darker side comes from studies in rodents, which developed fewer tumours when their microbiome had been wiped out, indicating the tumour-promoting potential of gut microbes.

In humans, the strongest evidence of the potential role of the microbiome in cancer comes from studies on colorectal cancer (CRC) – the third commonest form of cancer in the US and that country's second leading cause of cancer deaths. Recent research on people with CRC showed that their intestinal microbial communities become unbalanced. For example, compared with healthy people, the stools of people with CRC contain less of the bacterial groups *Lachnospiraceae* and *Roseburia* but an increased abundance of others such as *Enterococcus* and *Streptococcus*.

Why does it matter which types of microorganisms are present in the gastrointestinal tract? Not only does the microbiome play a key role in our immune system, but it also produces 10 per cent of our energy and ferments dietary carbohydrates into a range of metabolites such as the short-chain fatty acids acetate, propionate and butyrate.

These compounds serve as energy sources and also perform various key immunological and anti-carcinogenic functions in the body. Butyrate, for example, is a major energy source for the cells lining the intestine and also helps counteract inflammation and cancer development in the colon. Consequently, it is likely that an alteration of the microbiome's composition would have repercussions on the health of its host.

How might a "dysbiotic" microbiome play a role in cancer? *Roseburia* microbes, for instance, produce high quantities of butyrate, so fewer of these organisms in the intestines could result in smaller amounts of protective butyrate. Studies in mice showed that low levels of colonic butyrate could foster the development of CRC.

These are interesting findings, but it is not yet known whether a dysbiotic microbiome is a cause of CRC, or arises as a result of it. Nevertheless, these studies suggest a new way of identifying people at risk of developing CRC, through identifying markers of this distinctive microbiota. Potential microbial candidates have already been identified and tested using animal models. For example, samples of strains of *E. coli* and *Fusobacterium nucleatum* obtained from individuals with CRC were found to promote tumour development when introduced in mice.

It is important to stress that the microbes associated with CRC are not infectious pathogens, but rather indigenous residents of the intestine whose numbers and activities have been altered. This "enemy within" concept contrasts sharply with the infection paradigm, in which infectious microorganisms enter the body and cause harm. The environmental conditions under which our native microorganisms fluctuate in their numbers or change their niche in the body is unclear. But once we find out more about this process,

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this knowledge could be used to manipulate microbial levels, to enhance protective functions and alleviate harmful ones.

How else could gut microbes play a role in cancer? Recent evidence indicates that bacteria may produce noxious agents – gases, toxins, radical oxygen species – that can cause instabilities in the host's genetic material. For instance, the bacterium *E. coli* is found in abundance in the intestinal mucosa of people with CRC, compared with people without CRC. Interestingly, genomic analysis of these CRC-associated *E. coli* revealed the presence of a cluster of genes responsible for producing a substance called colibactin. This natural product triggers DNA breakage and genomic instability in different cells, including cells lining the intestine. In this case, the activity of the *E. coli* is directly compromising the integrity of the host DNA, which probably contributes to the development of tumours.

Other intestinal bacteria, such as *F. nucleatum*, appear to promote cancer through the action of molecules it produces, which bind to the cells lining the intestine, triggering these cells to proliferate out of control.

All this research is indicating that microbes could not only be used as a predictor of CRC onset, but also be manipulated as part of cancer therapy. This field of "bacteriotherapy" is still young, but it might one day be possible to screen individuals at risk of developing CRC for particular biomarkers of a dysbiotic microbiome, and then nudge their unbalanced microbiota back towards a healthier composition. This kind of therapy has been used with great success for recurrent cases of *Clostridium difficile* infection.

What about cancer treatment? Does our microbiome also affect how we react to chemotherapy? Two key studies published

"The interplay of cancer and our microbiome is still a frontier area"

in *Science* in 2013 showed that it does, and highlighted the important role that gut bacteria play in shaping the body's immune response to cancer. One study, by a team of researchers at several laboratories in France, showed that when the intestinal microbiota of mice with cancer were wiped out using antibiotics, this severely compromised the effectiveness of the chemotherapy drug cyclophosphamide. The researchers found that cyclophosphamide causes certain gut microbes to enter the lymph system, where they activate anti-tumour cells. These findings highlight a hitherto unknown risk associated with using antibiotics during chemotherapy treatment.

The other study, led by researchers at the US National Cancer Institute in Maryland, showed that gut bacteria can control the response to cancer therapy by influencing the level of inflammation around the tumour. It found that certain gut microbes enhance the efficacy of anticancer drugs by boosting immune cells' production of a substance called tumour necrosis factor, a messenger molecule which is part of the anticancer immune response.

The interplay of cancer and the microbiome is still a frontier area, but these studies highlight the complex and wide effect of microbes on cancer development and treatment. Once we know more about the microbiome, it may be possible to manipulate it using diet to boost the abundance or activity of microbes with cancer-fighting potential. Alternatively, inhibitors could be designed to target microbial genes implicated in tumour formation, for example to block the enzymes which produce harmful substances such as colibactin.

In the near future I expect that new therapeutic options for cancer will open up, courtesy of our microbiota. ■