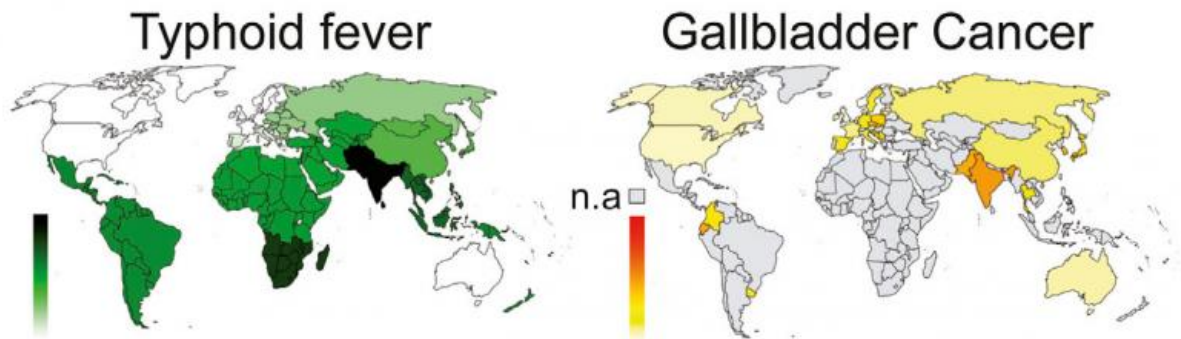


Controlling typhoid bacterium key to prevent gallbladder cancer in India and Pakistan

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Salmonella Typhi infection is associated with gallbladder carcinoma (GBC), a frequent tumor in India and rare in the Western world. Credit: Scanu et al./Cell Host & Microbe 2015

Controlling bacterial infections responsible for typhoid fever could dramatically reduce the risk of gallbladder cancer in India and Pakistan, according to a study published by Cell Press May 28th in *Cell Host & Microbe*. The findings establish for the first time the causal link between bacterial infection and gallbladder cancer, explaining why this type of cancer is rare in the West but common in India and Pakistan, where typhoid fever is endemic. Public policy changes inspired by this research could have an immediate impact on preventing a type of cancer that currently has a very poor prognosis.

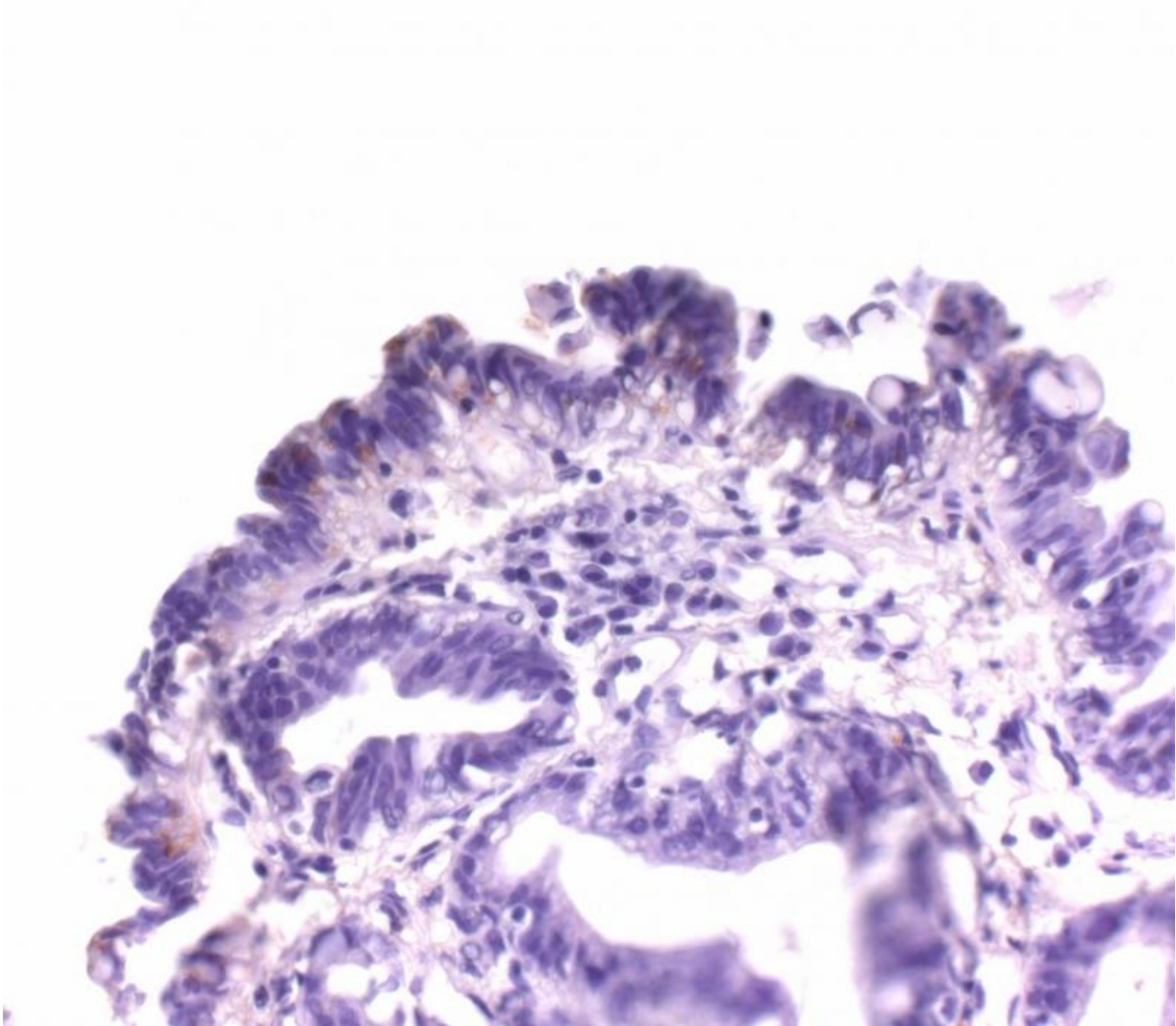
"While viruses are among the established causal factors for particular cancers, bacteria are largely ignored as direct contributors," says senior study author Jacques Neefjes of the Netherlands Cancer Institute.

"Accepting that bacterial infections can directly contribute to cancer formation makes these tumors in principle preventable. If Salmonella Typhi infections are cured immediately with antibiotics and chronic infections are prevented, or if vaccination programs to eradicate S. Typhi work, we would expect a major reduction in the incidence of a tumor that represents the third most common gastrointestinal tumor in India and Pakistan."

Gallbladder cancer is hard to diagnose in its early stages because there are no signs or symptoms. By the time the cancer is detected, it is often too late to save patients' lives. Because the prognosis of [gallbladder cancer](#) is so poor, Neefjes, Tiziana Scanu of the Netherlands Cancer Institute, and Gopal Nath of Banaras Hindu University set out to gain insight into how to combat this tumor by identifying causal factors underlying its unique global distribution. The researchers quickly zeroed in on S. Typhi because this typhoid-causing bacterium is endemic in India and has been associated with gallbladder cancer in epidemiological studies. Moreover, proteins that Salmonella injects into host cells activate cancer-related signaling pathways called AKT and MAPK, which support not only [bacterial infection](#) and survival, but also the growth and proliferation of cancer cells.

To explore the role of S. Typhi in cancer in the new study, Neefjes and Scanu compared tumor samples from Indian and Dutch patients with gallbladder cancer. While both groups showed signs of AKT and MAPK activation and an inactive, mutant TP53 cancer gene, only Indian patients showed strong evidence of S. Typhi infection and over-activating mutations in a cancer gene called c-Myc. To mimic the features of the tumor samples from India, the researchers transplanted Salmonella-infected cells with mutations affecting TP53 and c-Myc

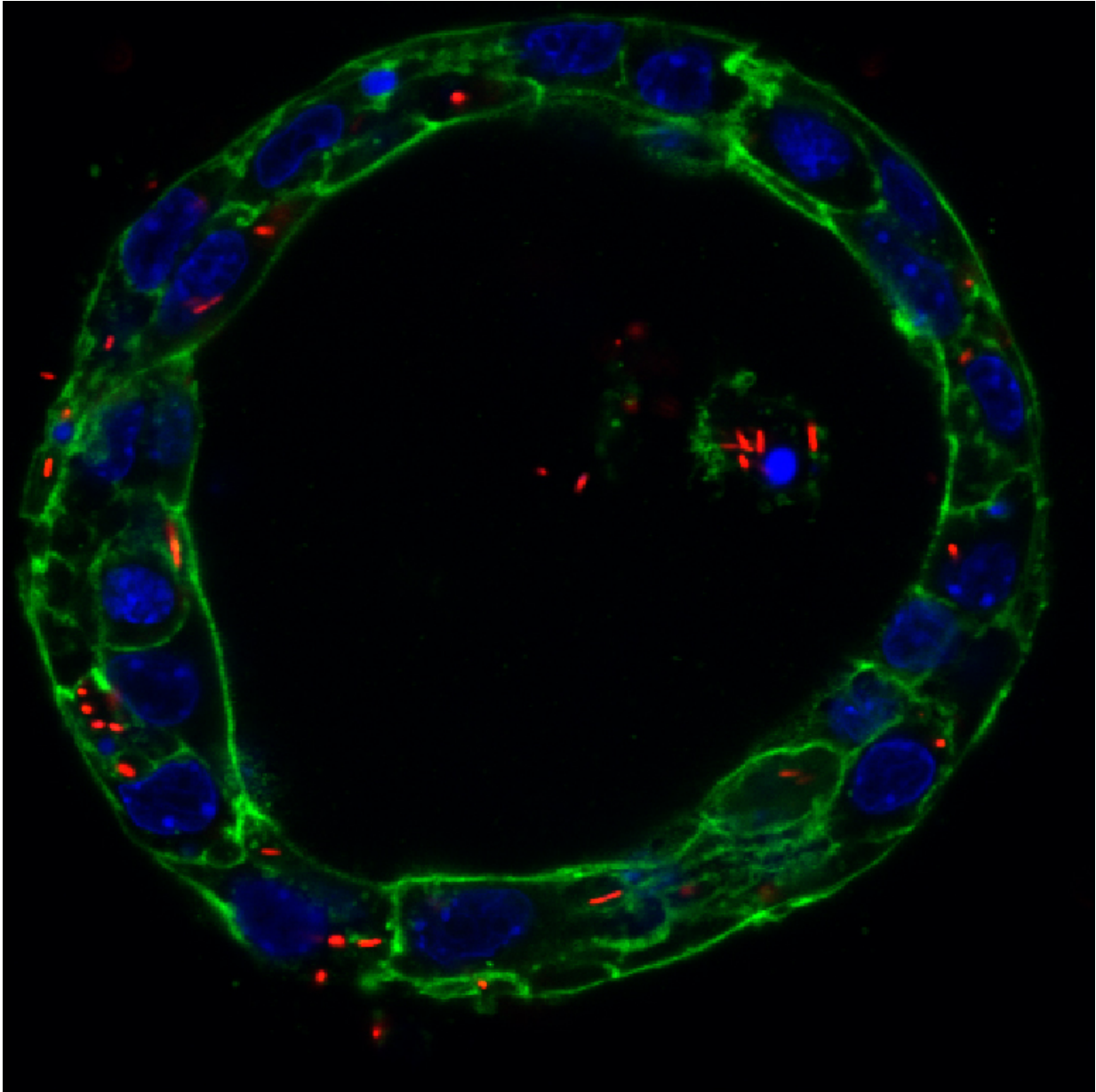
activity into mice. These mice later developed tumors, demonstrating that *Salmonella* causes cancer in genetically at-risk hosts as a result of the collateral damage induced by its normal infection cycle.



Gallbladder carcinoma tissue of a patient from India that still contains traces of *S. Typhi* infection (detected by immunohistochemistry with anti-*Salmonella* LPS antibody [brown]). Credit: Ji-Ying Song.

Additional experiments suggested that Salmonella infection sets genetically predisposed host cells on the cancerous path by secreting proteins that increase AKT and MAPK activity, which remains elevated and perpetuates the cancer trajectory long after the bacteria have disappeared. These same two host signaling pathways are activated by bacterial pathogens implicated in cervical and lung cancer, suggesting that a direct contribution of bacteria to tumor formation could be more common than previously anticipated. "The findings also suggest that the use of antibiotic treatment to control these bacterial infections may come too late for individuals who have already developed cancer," Scanu says. "Instead, the main goal should be prevention through proper treatment with antibiotics, vaccination programs, or better sanitary conditions."

In future studies, the researchers will investigate whether Salmonella contributes to tumors in other tissues, identify other [cancer](#)-causing bacteria, and determine how these pathogens leave an imprint of infection in host cells. But policymakers do not have to wait for answers to these questions before taking action to save countless lives. "Our findings may now be used to urge policymakers to take appropriate measures to eliminate or better control these infections," Neefjes says. "If [typhoid fever](#) is controlled, gallbladder carcinoma in India and Pakistan could be prevented and become as rare as in the Western world."



A slice of a gallbladder organoid infected with Salmonella. The organoids are small mini-organs that are cultured in the lab. The organoid is in green, the nuclei are in blue, and Salmonella is red colored. Credit: Tiziana Scanu.

More information: *Cell Host & Microbe*, Scanu et al. "Salmonella

manipulation of host signaling pathways provokes cellular transformation associated with gallbladder carcinoma"

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