Pathogenic microorganisms overcome the host's innate and adaptive immune system and cause local or systemic infections, potentially leading to organ failure, sepsis, or even death. Some microorganisms can also directly or indirectly alter the differentiation and proliferation of host cells, promoting the development of tumors. A large number of oncogenic viruses have been identified and estimated to account for ~15% of human cancers. They do so by encoding oncoproteins or through their intrinsic ability to manipulate the genomic stability of the host cell by integrating their own genetic elements. Also bacterial infections have been linked to carcinogenesis, although the underlying molecular mechanisms are less well understood. The best-studied example is Helicobacter pylori, which has been classified as a class I carcinogen by the World Health Organization due to its ability to promote stomach cancer after chronic infection, which causes tissue inflammation and atrophy of the gastric mucosa. In a recent issue of Cell Host & Microbe, the Neefjes laboratory explores the association between Salmonella enterica subsp. enterica sv. Typhi (S. Typhi)—which is the causative agent of human typhoid fever—and gallbladder carcinoma [1].

The deadly bite of *Salmonella* Typhi

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*C. jejuni* and *Salmonella* typhi (S. Typhi) infections such as Typhoid fever are often asymptomatic in their early stages. However, once the bacteria become established in the host, they initiate a chronic infection that can persist for years. This chronic infection is characterized by the establishment of a symbiotic relationship between the bacteria and the host, which is essential for the survival and replication of the bacteria. The bacteria use this relationship to evade the immune system and establish a chronic infection, which can lead to the development of cancer.

In the attempt to not only stop the spread of this pathogen, but also prevent the development of GBC, a disease with poor clinical outcome at present. However, a number of questions remain to be addressed. For example, the authors assume that the *Salmonella* mediated carcinogenesis is secondary to enhanced epithelial c-Myc expression. However, *Salmonella* has been shown to induce c-Myc expression [6,7] and thus might provide both signals. This might also explain why epidemiological studies associate only chronic infection with the emergence of gallbladder cancer, despite the fact that short-term exposure was sufficient to transform c-Myc high epithelial cells [2]. A related question is how the deficiency of the examined *Salmonella* effector molecules...
alters the overall bacteria–host cell interaction. The results presented by Scanu and colleagues suggest a major influence on bacterial invasion, intracellular survival, and proliferation, and thus, indirect downstream effects might contribute to the observed phenotype. For example, Salmonella translocates a second set of effector proteins encoded by the so-called Salmonella pathogenicity island (SPI) 2 once it reaches the intracellular vacuole. Individual SPI2 effectors, such as SpiC, have also been shown to stimulate MAPK and might thus contribute to GBC development [8]. Finally, the precise molecular mechanisms that promote carcinogenesis downstream of Akt and MAPK activation remain unclear. Constitutive MAPK signaling has been linked to epigenetic changes involving histone phosphorylation, which might explain the lasting carcinogenic effects of short-term bacterial exposure [9]. Consistently, the epigenetic modulator histone deacetylase 9 (HDAC9) was found to be up-regulated upon bacterial contact. Marked epigenetic differences have been noted between gallbladder tissues from patients from the US and Chile, countries of low and high incidence of S. Typhi infection, respectively [10].

The authors discuss the presence of similar epidemiological associations between cancer and other pathogenic bacteria, such as Chlamydia spp. and Mycobacterium tuberculosis, calling for detailed studies of the possible bacterial contribution to carcinogenesis. In addition, commensal bacteria might exert similar responses and should be examined for their potential to support the development of tumors, particularly within the gastrointestinal tract. Ongoing studies on the composition of the enteric microbiota in patients with malignancies might give a first hint on potential additional bacterial actors in this deadly play.

References