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].

See also: T Scanu et al (June 2015)

Chronic carriage of S. Typhi following acute infection has been previously linked to cancer [2]. Although gallbladder carcinoma (GBC) is rare in western countries, there is a high incidence in countries with endemic S. Typhi infections such as South America and parts of Africa and Asia, particularly India and Pakistan [3,4]. Salmonella’s ability to persist within the gallbladder of a significant fraction of patients (2–5%) after systemic infection appears to provide the milieu for its tumor-promoting effect. Initial experimental evidence in mice supports an association between Salmonella infection and GBC, as long-term histopathological follow-up of chronically infected mice revealed pre-malignant lesions with hyperplasia and metaplasia of the gallbladder [5].

Now, Scanu and colleagues provide insights into the molecular mechanisms underlying this association [1].

They start with the intriguing observation that GBC in the Netherlands, which has a very low incidence of S. Typhi infection, differs phenotypically from GBC in India, where the incidence of typhoid fever is very high. Furthermore, the authors detect increased expression of the proto-oncogene c-Myc in Indian tumor tissue and set out to test the effect of Salmonella infection in tumor-prone mice that express enhanced c-Myc levels, the so-called adenomatous polyposis coli (Apc) /min mouse model. Infection of Apc /min SV129Ola mice—which additionally express the lysosomal metal transporter Ntap and survive acute Salmonella infection—with the murine S. Typhi homolog S. Typhimurium induced signs of colon cancer-like anal bleeding. Subsequent histopathological analysis confirmed the presence of colorectal adenocarcinomas in addition to the small intestinal adenomas usually found in Apc /min mice. Of note, colorectal carcinoma was found following infection with wild-type S. Typhimurium but not after infection with an attenuated strain that is unable to translocate effector molecules through the plasma membrane into infected host cells. A similar tumor-promoting effect was confirmed using gallbladder epithelium-derived stem cell organoids or c-Myc-overexpressing mouse embryonic fibroblasts (MEFs). Neither model includes immune cells, indicating that the carcinogenic effect results from the direct interaction between Salmonella and epithelial or fibroblast cells. MEFs were subsequently used to analyze the bacterial effector molecules and cellular signaling pathways involved. As elevated Akt and mitogen-activating protein kinase (MAPK) activities are frequently observed in human cancer tissue, the translocated bacterial effector molecules SopE, SopE2, SopB, and SpIP, which are known to stimulate Akt and MAPK activities, were analyzed. Indeed, bacteria deficient in all four effector molecules or deficient only in SopB, or administration of Akt or MAPK inhibitors, prevented MEF transformation. Strikingly, even short-term infection (terminated by antibiotic treatment) readily promoted long-term transformation of MEFs and induced a defined alteration in the global gene expression pattern. Thus, Salmonella—through its effector molecules SopE, SopE2, SopB, and SpIP—drives activation of Akt and MAPK in gallbladder epithelial cells, rendering existing pre-transformed (i.e. c-Myc high) cells into malignant tumor cells (Fig 1).

The established models now provide unique tools to further unravel the molecular mechanisms of bacteria-induced carcinogenesis. Similar to the clinical management of H. pylori, the results call for the development of strategies to prevent S. Typhi persistence 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

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The mechanisms of Salmonella-induced tumorigenesis

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Salmonella pathogenicity island (SPI) 1 effector proteins and/or Salmonella invasion activate MAPK and Akt signaling. This, in turn, drives the expression of genes such as histone deacetylase (HDAC) 9, which are able to induce epigenetic modifications. In the pre-disposed host, such as one expressing enhanced levels of c-Myc, these changes may lead to tumor formation.

Figure 1. The carcinogenic effect of Salmonella.

Salmonella pathogenicity island (SPI) 1 effector proteins and/or Salmonella invasion activate MAPK and Akt signaling. This, in turn, drives the expression of genes such as histone deacetylase (HDAC) 9, which are able to induce epigenetic modifications. In the pre-disposed host, such as one expressing enhanced levels of c-Myc, these changes may lead to tumor formation.

References