Bacteria commonly found in the body contribute to stomach cancer, finds study

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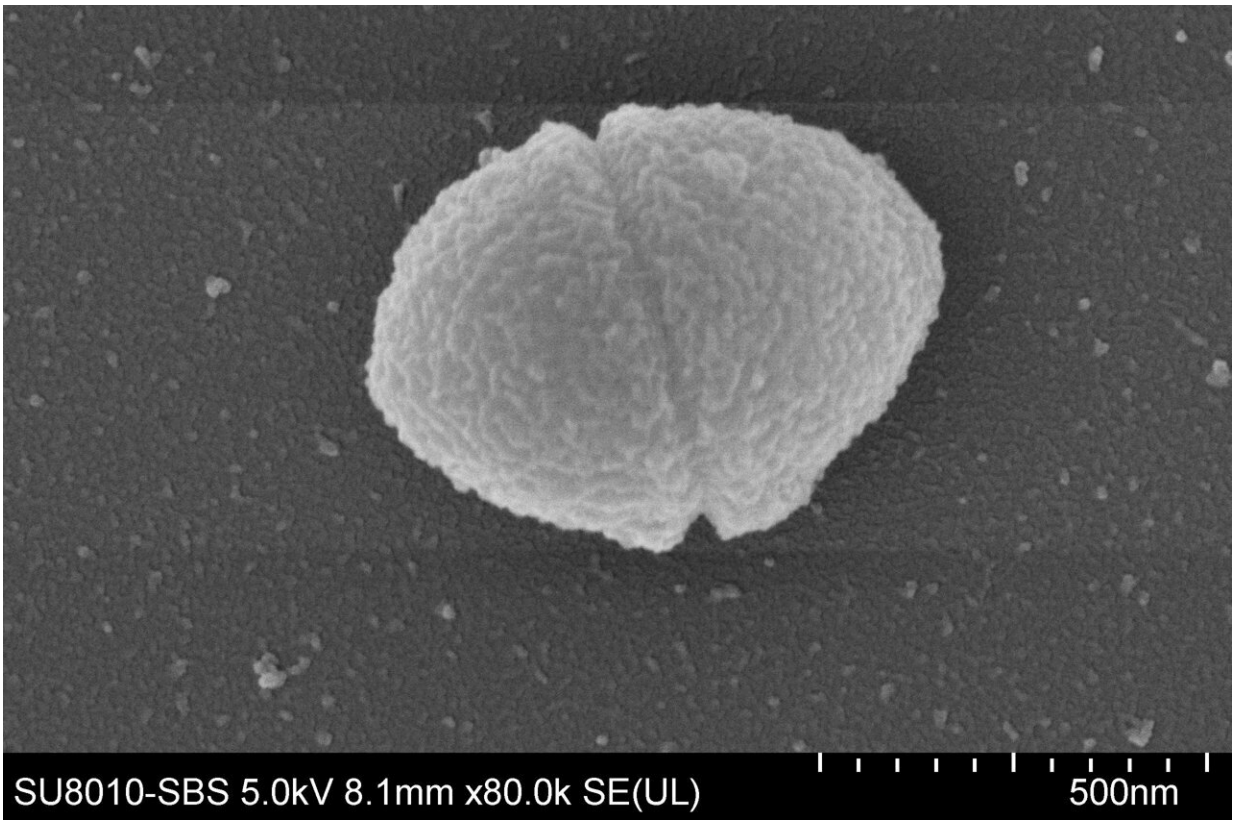


Scanning electron microscope photo of Streptococcus anginosus. Credit: CUHK

A new study has discovered that a type of bacteria commonly found in the body, which usually does not pose problems for healthy people, plays a significant role in causing stomach cancer, the fifth most common cancer in the world. The findings are published in the journal *Cell*.

Streptococcus anginosus bacteria exist alongside other germs in the mouth, throat, intestines and vagina. Occasionally, they may cause mild infections like sore throats and skin infections. For patients with underlying health conditions or compromised immune systems, the bacteria can lead to more serious infections, such as those that damage the heart and brain.

However, research co-led by Nanyang Technological University, Singapore (NTU Singapore) and the Chinese University of Hong Kong (CUHK) showed that S. anginosus is involved in stomach infections in mice that cause cell damage and changes known to encourage gastric cancer. This includes gastric inflammation, in which the stomach lining is irritated. The condition damages gastric lining cells and causes some of them to gradually transform into cancer cells.

Mice experiments also revealed that the bacteria spurred the growth of stomach cancer cells, doubling the size and weight of tumors in some cases.

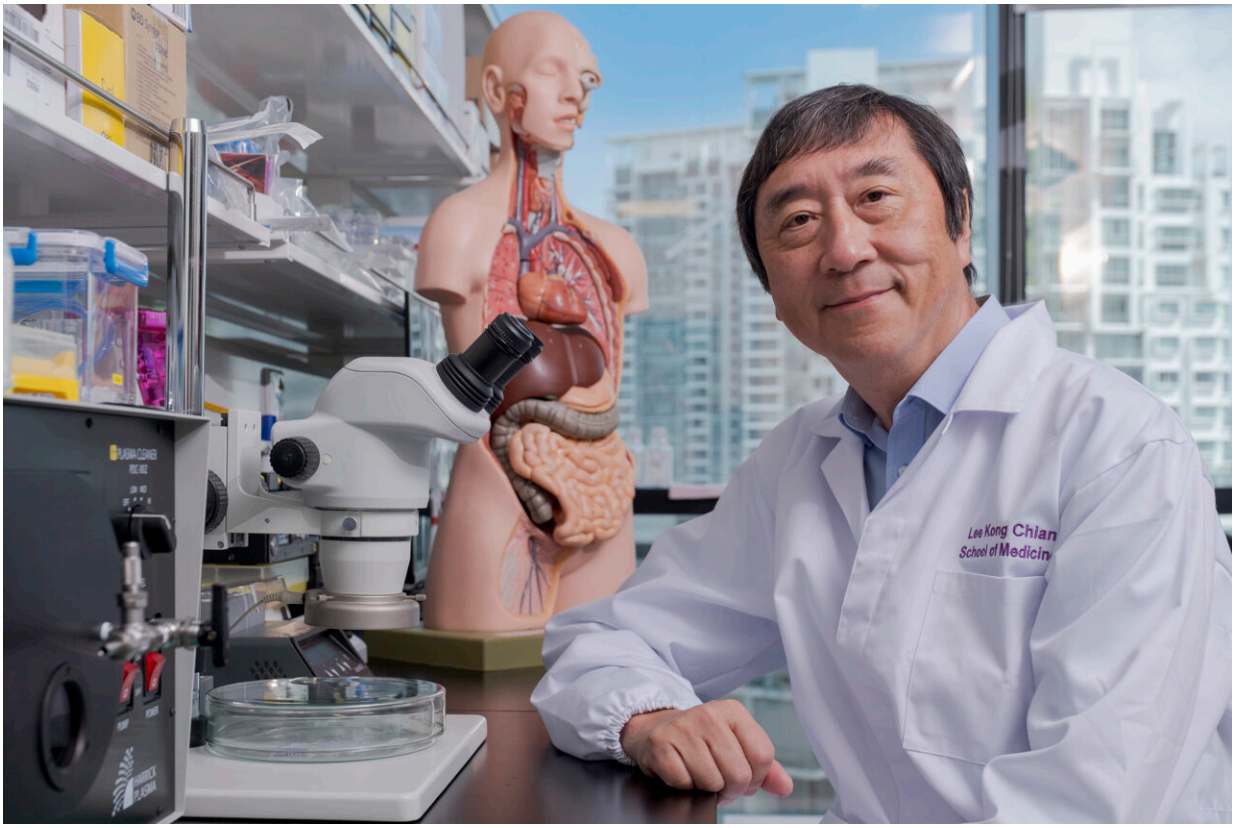
But the researchers also found that disrupting a protein on the bacteria's surface, which they need to interact with stomach lining cells, reduced S. anginosus' ability to contribute to stomach cancer.

The findings add to the number of bacteria species known to cause gastric cancer. Another bacteria species, Helicobacter pylori, is known to cause gastric ulcers in people. These painful sores increase patients' risk

of developing gastric cancer. Whether other bacteria are involved has remained unclear until now.

"Our latest findings in mice shed light on another pathogen that contributes to stomach cancer, and how it does so," said the study's co-lead, Professor Joseph Sung, NTU's Senior Vice President (Health and Life Sciences).

"This lays important groundwork for further studies in humans that will help clinicians better treat and prevent gastric cancer driven by bacteria," added Prof Sung, who is also the Dean of NTU's Lee Kong Chian School of Medicine.



Professor Joseph Sung, NTU Singapore's Senior Vice President (Health and Life Sciences) and Dean of the Lee Kong Chian School of Medicine, is the co-lead of

the study which found that Streptococcus anginosus bacteria play a significant role in causing stomach cancer. Credit: NTU Singapore

Professor Yu Jun, the study's other co-lead who is Director of CUHK's State Key Laboratory of Digestive Disease, said that the researchers will next "explore the therapeutic potential of targeting S. anginosus to reduce gastric inflammation and cancer risk."

The S. anginosus study contributes to one of the goals of the NTU 2025 strategic plan to address the needs and challenges of healthy living.

Bacteria-induced abnormalities

H. pylori bacteria are classified as carcinogenic (cancer-causing) to humans. But among people infected with the bacteria, only 1 to 3% develop stomach cancer, which suggests that other factors are involved in its development.

Past research has shown that 20% of patients with chronic gastritis—a known contributor to gastric cancer—are not infected by H. pylori. Chronic gastritis refers to long-term inflammation of the stomach.

Studies have also posited that other bacteria, including S. anginosus, could play a part in stomach tumor development too.

To confirm S. anginosus' role, Prof Sung and collaborating scientists from CUHK ran a series of experiments.

The researchers infected the stomachs of mice with S. anginosus over two weeks and found mild to moderate gastric inflammation. This was similar to what was observed in mice infected with H. pylori over the

same time frame.

When Streptococcus anginosus infection occurred at stomach tumors implanted under mice skin, the bacteria spurred the growth of the gastric cancer cells, doubling the size and weight of tumors in some cases (middle row), compared to tumors without Streptococcus anginosus infection (top row). When a specific surface protein of the bacteria was genetically removed, the bacteria's ability to encourage tumor growth was impaired (bottom row). Credit: CUHK

When S. anginosus infection of the mice was extended—by up to a year—persistent and prolonged inflammation of the stomach, or chronic inflammation, was observed three months after the initial infection. The level of inflammation was also similar to that of rodents infected by H. pylori only.

But when mice were co-infected by both S. anginosus and H. pylori, the level of chronic gastric inflammation recorded after three months was two times greater than infection by either bacteria alone.

As the S. anginosus infection progressed, anomalies that signal cancer development were also observed in the stomach. There was a surge in gastric cell numbers six months after the original infection, stomach acidity rose after nine months, and many cells of the stomach lining transformed into abnormal pre-cancerous cells after 12 months.

The scientists observed another way that S. anginosus infection created an environment conducive to gastric cancer—by disrupting the population of other microorganisms in the stomach. The bacteria increased the number of stomach microbes that typically reside in the mouth while reducing the number of probiotic bacteria important for good gut health, like Lactobacillus.

They demonstrated that S. anginosus was able to drive the growth of gastric tumors. When stomach cancer cells were implanted under the skin of mice or into the rodents' stomach lining, infection by S. anginosus at those sites encouraged the tumors to grow, doubling their size and weight in some cases.

The researchers also discovered that the bacteria needed a specific protein on their surface to physically bind to and invade stomach lining cells to promote gastric cancer development. When this protein was deficient in the bacteria, the germs' ability to bind to stomach lining cells and encourage the growth of gastric cancer implants was impaired.

Prof Sung said, "Our results suggest that long-term S. anginosus infection causes intensive chronic gastritis that is comparable to H. pylori infection. In fact, these two pathogens might act collaboratively to promote gastric inflammation and, eventually, gastric cancer. This could change how we approach prevention and treatment of the disease."

He added that detecting S. anginosus in feces could be useful for assessing whether a patient is at risk of gastric cancer in the future.

Since S. anginosus is commonly found in the mouth, the bacterium could be swallowed through saliva and find its way into the stomach. So, one potential way to guard against stomach cancer from developing could be to practice good oral hygiene, said Prof Sung.

More information: Kaili Fu et al, Streptococcus anginosus promotes gastric inflammation, atrophy, and tumorigenesis in mice, *Cell* (2024). DOI: 10.1016/j.cell.2024.01.004

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