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Article proposes important mucin link between microbial infections and many cancers

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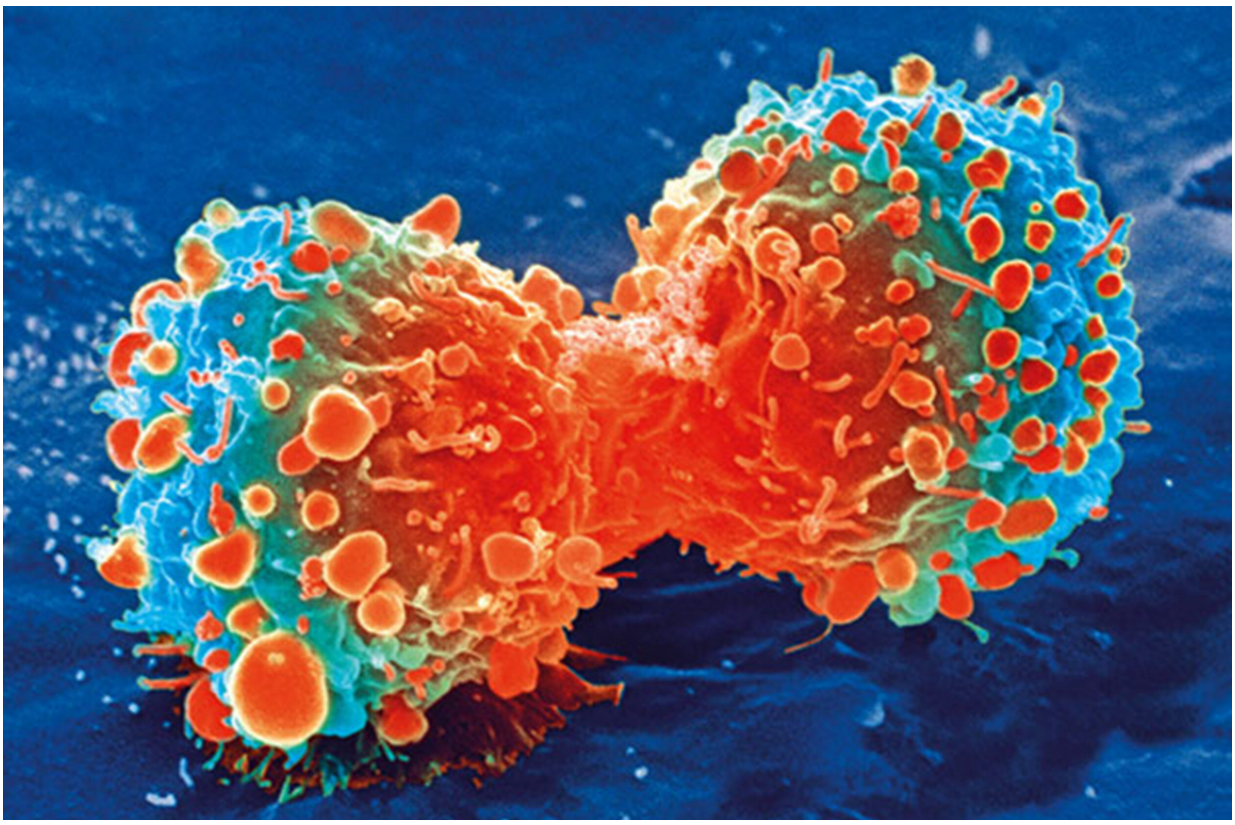

Cancer cell during cell division. Credit: National Institutes of Health

It is generally known that viruses, with their cell-invading capabilities, can be responsible for a number of different cancers. What is less

broadly discussed are the cancer-causing capabilities of bacteria, or the processes by which they may cause malignancy.

In a review article appearing in the November 18 issue of *Trends in Molecular Medicine*, University of North Carolina at Charlotte, cancer biologists Pinku Mukherjee and Mukulika Bose discuss a mechanism that, they suggest, may implicate bacterial infections in a wide variety of cancers—a cause that science has yet to fully understood.

The article, "Microbe—MUC1 Crosstalk in Cancer-Associated Infections," makes the case for the likely implication of microbial (especially bacterial) interactions with the glycoprotein known as MUC1 in cancers involving epithelial cells, including cancers of the colon, lungs, stomach, liver and pancreas.

Epithelial cells are cells that are frequently specialized for absorption or secretion purposes, and to form linings or barriers in organs, including the intestines, lungs, stomach, liver and reproductive organs. MUC1 is a "transmembrane" protein—extending outside, through and inside the cell membrane to the cytoplasm—and is present in nearly all glandular epithelial cells. It is one of a group of proteins known as "mucins" for their involvement in protective mucous layers, whose gel-forming features are caused by sugar molecules coating part of the protein's length ("glycosolation"). The sugars, essentially, interact with water molecules, creating a slippery, slimy barrier, protecting cell layers against pathogens and environmental damage.

Mukherjee, Irwin Belk Distinguished Professor of Cancer Research and chair of UNC Charlotte's Department of Biological Sciences, has done considerable past research on the surprisingly negative roles MUC1 can play in a variety of cancers. The association of the protein with cancer is very strong—as the article notes, "the National Cancer Institute ranked MUC1 as the second best target antigen for the development of cancer

vaccines."

Mukherjee also does work on the interaction of cancer and pathogen infections. "Now it is known that about 20% of all malignancies, especially epithelial malignancies, are associated with some sort of infection, viral or bacterial, persistent inflammation being the root cause" she notes.

Mukherjee explains that a lot is now known about viruses and the biological mechanisms involved—the association of HPV with cervical cancer, for example.

"But there is very little known about what causes cancers associated with bacterial infections... not much is known about this. But when there are bacterial infections that have definitely been linked to cancer—like H. pylori with stomach cancer and ulcers—that appears to have to do with the basic persistence of the bacteria," she said.

Persistent infections may be different because of the effects of their long-term attacks on cellular defense mechanisms.

"But if these persistent bacterial infections cause aberrations on the epithelial layers, mucins must be involved because every glandular epithelial cell has mucins and we know that mucins are the first protective layer in any bacterial infection."

Imbedded in the epithelial cell membrane, with its outside end coated with attached sugars and its inside end floating largely naked in the cell's cytoplasm, MUC1 serves a largely protective role, Mukherjee explains. Molecules on the surface of bacterial cells bind to the mucosal layer or to the glycosolated end of MUC1, but the cell is ready for the attack and responds.

"Attachment by the bacteria triggers MUC1 to shed its extracellular domain (the glycosolated section) with the bacteria attached, and the whole thing goes to the mucous layer, where the bacteria is removed," she said. "It thus works as an anti-inflammatory by pushing the attacking bacteria out and engulfing it into the sugary molecule."

However, the process can have side-effect, she explains: "That's mainly how MUC1 works, but what happens sometimes when MUC1 sheds, its remaining outside and cytoplasmic tail (the protein's inner segment) gets activated. A persistent bacterial barrage on a cell activates some cytoplasmic tail and we know that when the cytoplasmic tail is activated it can trigger signaling pathways that cause cancer."

MUC1 can thus play a dual role during infection, either being anti-inflammatory by staving off bacterial attack, or pro-inflammatory, triggering inflammation processes, which, in turn, can cause malignancy.

"The dual role of MUC1 as protective and oncogenic in the presence of microbial infection is, in a nutshell, what this article is about," she said. "There are pieces of research out there that point to this, but we are trying to pull them together."

The article surveys studies on a dozen common infections by bacteria and viruses that are known to involve MUC1 and notes a limited number of examples where the protein is known to play a pro-inflammatory role.

"The field has only looked at these mechanisms in small number of infection-associated cancers, and even fewer where bacteria are involved," she noted. "We hope our hypothesis leads to people looking at this in a more scientific manner."

Mukherjee's hypothesis stresses the central role of MUC1 and mucins in targeting future research. Because of strong connections between the

protein and cancer processes in epithelial cells and the protein's strong involvement in combating microbial infections, it is an obvious, yet understudied connection between infection and cancer.

"The idea is that at some point we are going to have to start studying mucins more seriously," she said. "Rather than only studying mucins in already transformed cancer cells, we need to be studying them before the cells transform and see what is going on. The work being done on the cancer side needs to be connected with the work on the bacterial side, and the role of infection in triggering inflammation."

More information: Mukulika Bose et al. Microbe–MUC1 Crosstalk in Cancer-Associated Infections, *Trends in Molecular Medicine* (2019). DOI: 10.1016/j.molmed.2019.10.003

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