Scientists zero in on atomic driver of tumor formation

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Growing evidence suggests that certain types of bacteria are capable of causing colorectal cancers, indicating that a sub-set of these cancers

could be the result of infectious disease.

But understanding how bacteria interact in the human gut—our microbiome—has been challenging because of the complex microbial mixture of "good" and "bad" bacteria.

Over a decade ago, French scientists discovered a pathway in certain strains of *E. coli*, a bacterium normally found in 90% of humans, that is "genotoxic"—toxic to DNA—causing tumor formation and colorectal cancer in mice.

While the "colibactin" pathway is not found in all strains of *E. coli*, colibactin-producing strains are supported as epidemiological risk factors for colorectal cancer in humans.

Until recently, important questions remained about how this pathway actually damages the DNA to cause colorectal cancer, ultimately barring progress towards the development of future treatments.

"We found that certain *E. coli* produce specific molecules that 'cross-link' our DNA, effectively locking it together," said Jason Crawford, Associate Professor of Chemistry and of Microbial Pathogenesis, and co-corresponding author of the findings, published today in *Science*.

Through close collaboration between Crawford's lab at the Yale Chemical Biology Institute and Seth Herzon, Professor of Chemistry, for the first time the scientists were able to crack the identity of the structure of the cross link, establishing how the molecules work—their so called "mode of action"—and how they are made.

"Establishing what is driving colorectal cancer at an atomic resolution expands on previous cellular studies over the past decade, ultimately bringing us closer to strategies to effectively treat and eliminate this risk

factor," said Herzon. The paper was written by co-first authors Mengzhao (Lucy) Xue, graduate student in the Herzon lab, and Chung Sub Kim, a post-doc in the Crawford lab.

More information: Mengzhao Xue et al. Structure elucidation of colibactin and its DNA cross-links, *Science* (2019). DOI: 10.1126/science.aax2685

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