The two sides of inflammation—the cure and the curse
29 December 2020, by Delthia Ricks

One of the many wonders—and mysteries—of human biology is the complex response of the innate immune system, which is known for its swiftness in annihilating invading pathogens and capacity to mount an explosive inflammatory response.

The body's ability to rapidly sense and react to infiltrating microbes is essential in the all-out warfare required to stop the progression of an infectious disease and initiate the stabilizing processes that restore homeostasis. Inflammation, however, is like an unruly and burly bouncer at a nightclub who's great when simply doing the job of ridding the place of bad guys—but terrifying as a turncoat who keeps slugging everything in sight.

Nature designed the inflammatory response as a powerful form of protection, dilating blood vessels, raising the temperature and attracting a flood of immune cells into infected or injured tissue. Yet, sometimes inflammation doesn't switch off. Instead of playing a beneficial role, persistent inflammation becomes an ongoing, unrestrained burden capable of seriously damaging the skin, gnarling the joints or raising the risk of cancer.

Chronic inflammation can occur in the aftermath of bacterial or viral infections. Indeed, some of the malingering problems associated with COVID-19 among those coping with "long COVID" (conditions that emerge after the infection has cleared) have been linked to chronic inflammation. Aside from COVID-19, persistent inflammation is associated with myriad medical disorders, which has led to a wide range of studies over the years. Teams of scientists worldwide have been tackling a critical question: What sets off the complex cascade of molecular events that results in chronic inflammation?

In Seattle, Leah Rommereim and colleagues have found that small increases in the abundance of a single protein that senses pathogens can, in turn, cause a disproportionately large inflammatory response in cells. That protein, NOD1, is an intracellular molecule that stimulates proinflammatory and antimicrobial responses when it's activated by complexes present in some pathogens. Although inflammation is beneficial for clearing infections, prolonged inflammation can be a curse.

"Persistent inflammation is believed to instigate oncogenesis in many ways, including triggering the transformation process itself and providing a suitable milieu for the proliferation of transformed cells," Rommereim and colleagues wrote in the journal Science Signaling, referring to normal cells that were transformed into cancerous ones.

Along with her team, Rommereim, a research scientist at the Seattle startup known as SEngine Precision Medicine, provided a detailed look into the functions of NOD1 and its star role as a proinflammatory protein.

"NOD1 is a ubiquitously expressed intracellular innate sensor of microbial infection that senses meso-diaminopimelic acid, a component of bacterial peptidoglycan," Rommereim, lead author
Peptidoglycan is a thick structural polymer in Gram negative and positive bacteria. The polymer provides exceptional rigidity to the cell wall, particularly in Gram positive bacteria. Some of those microbes can contain up to 40 layers of peptidoglycan.

"NOD1 activity is also intimately linked to gastric cancer," Rommereim and her team wrote. "In some studies, genetic variants in NOD1 are associated with gastric cancer risk and NOD1 expression is increased in gastric tumors."

The bacterium she zeroed in on as part of the research is Helicobacter pylori, which causes a chronic infection of the digestive tract. H. pylori is intimately associated with gastric cancer. NOD1 detects the presence of H. pylori and is central in the initiation of the inflammatory response, the war to rid the body of the bacteria. H. pylori also causes gastric ulcers, and while treatable with antibiotics, half the world's population is believed to be colonized by the bacteria, especially people living in developing countries.

H. pylori is a Gram negative pathogen, a spiral-shaped colonizer of the human gastrointestinal tract, which for years has been the subject of research, including studies that led to a Nobel Prize. Long before the Rommereim investigation on the role of NOD1 was launched, H. pylori was already linked to inflammatory conditions including gastritis, gum disease and cancer. Most patients who are infected are asymptomatic, and are unaware that they've been colonized by the bacteria.

H. pylori was once known as Campylobacter pylori, and its corkscrew shape, according to prevailing scientific wisdom, is believed to be an evolutionary adaptation that allows it to pierce the thick mucus lining of the stomach, which it colonizes. Beyond the stomach, it is found in the esophagus, colon, rectum and a host of other sites.

The bacterial presence triggers the innate immune system, the segment that is present at birth and continues fighting infections throughout life. (Another part, the adaptive immune system, which includes B cells and T cells, develops over time starting before one year of age. B and T cells are noted for their capacity to form memories of previous infections and to respond faster when those infections are encountered in the future). But it is the inflammatory response triggered by the innate immune system that captured the investigatory attention of Rommereim and her collaborators because of its link to cancer.

On the other hand, when NOD1 was increased 1.5-fold, that in turn, stimulated NOD1-mediated transcriptional responses. Both types of increases in NOD1 resulted in a disproportionately potent escalation of inflammatory genes and oncogenes. These data may explain why certain genetic variants in NOD1 and reduced miR-15b/16 are associated with a higher risk of developing gastric cancer.

Gastric cancer isn't the only major malady associated with H. pylori and inflammation. A growing body of evidence strongly suggests the bacteria are associated with idiopathic thrombocytopenic purpura, atherosclerosis, periodontitis, anemia, Guillain-Barre syndrome and several autoimmune skin disorders, including rosacea and psoriasis.

Still other studies have linked H. Pylori and the inflammation it causes to brain disorders via the gut/brain axis. Two devastating disorders include Parkinson's and Alzheimer's diseases.

"We provide evidence that a prolonged small increase in expression of NOD1, a ubiquitously expressed cytosolic sensor of bacterial infection resulted in a large impact on cellular transcription state including both inflammatory and especially oncogene expression," Rommereim said.

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