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Inflammation in the gums can increase susceptibility to other forms of inflammation, such as arthritis, through changes to immune cell precursors in the bone marrow, according to new research led by Penn scientists and collaborators. Credit: Katie Vicari

# Innate immune memory underlies inflammatory comorbidities: study

By Anette Breindl (/authors/2-anette-breindl)
May 2, 2022

Researchers at the University of Pennsylvania have gained new insight into how different inflammatory conditions reinforce each other via trained innate immunity.

Their work, which appeared in the April 27, 2022, advance online issue of *Cell* (https://doi.org/10.1016/j.cell.2022.03.043), "may pave the way to treat inflammatory comorbidities in a holistic manner," senior author George Hajishengallis told *BioWorld*.

Hajishengallis is a professor of basic & translational science at the University of Pennsylvania's School of Dental Medicine.

The work began, he said with "a question we had about a paradox" in trained innate immunity. The idea that there is such a thing as trained innate immunity at all is relatively recent.

"As an immunologist, I was trained there is no memory in the innate immune system -- the textbooks on my shelf say this," Hajishengallis recounted. Immune memory was thought to be exclusive to the B and T cells of the adaptive immune system.

But although the innate immune system remembers differently than the adaptive immune system, "out of sight, out of mind" does not apply there, either.

"Whereas the adaptive immune memory is exquisitely specific, the innate memory is nonspecific," Hajishengallis said. That is, memory B and T cells respond to very specific antigens. Also, adaptive immune system memory, "is due to permanent genetic changes," either recombination or somatic hypermutation.

Innate immune memory, on the other hand, is a more general state of high alert that is brought about by epigenetic changes.

It is not permanent, but in earlier work, Hajishengallis and his colleagues had shown that it can persist for a time – certainly for months and possibly for years.

Which is where the paradox comes in.

"Memory persisted for months, but the monocytes that carried it lived for only a few days," Hajishengallis said. "This is when we hypothesized that the precursors in the bone marrow are the ones that can store changes."

**One, two**

In the work now published in *Cell*, Hajishengallis, co-corresponding author Triantafyllos Chavakis of the Technical University of Dresden, and their colleagues tested this hypothesis by inducing periodontal disease in mice, letting the animals recover, transplanting their bone marrow to another group of animals after recovery was complete, and then inducing inflammatory arthritis in the transplanted animals.

The team showed that inducing periodontitis led to increased production of myeloid cells in the bone marrow, and that those myeloid cells were more sensitive to proinflammatory signals. When the periodontitis resolved, myelopoiesis went back to normal.

But if the normal-seeming bone marrow was transplanted into healthy mice, the animals were more susceptible to arthritis.

Hajishengallis stressed that looking at the myeloid cell transcription yielded "almost nothing... the changes [were] only at epigenetic level. That data showed us that there is genuine memory. These cells were normal except for their memory, which was imprinted epigenetically."

Having one inflammatory disease, he said, is "not going to precipitate a second disease, but if you have the propensity... it's another risk factor."

The team demonstrated that the risk increase of developing an additional disease cut both ways. "Each condition increased susceptibility to the other condition," Hajishengallis said.

"There have been a lot of mechanisms proposed" for the increased risk of a second inflammation-driven condition following a first one, he said, and those mechanisms could all play a part. But "this is the first mechanism that has explained the reciprocal nature of the risk... the only mechanism that is bidirectional."

IL-1beta signaling was required for the maladaptive training, and Hajishengallis "would hope that in light of these findings, there may be more clinical trials trying to block IL-1beta, or the IL-1beta receptor," to see whether it can reduce the risk of inflammatory comorbidities, he said.

There is already one trial that may have succeeded in part due to its effects on innate immune memory.

In the Cantos trial, treatment with the IL-1beta- targeting antibody Ilaris (canakinumab; Novartis) strongly reduced the risk of heart attacks and strokes. The trial was seen as a confirmation that inflammation can independently cause cardiovascular disease, but "I feel that probably part of the success was due to mitigating the effects of maladaptive immune training," he said.

His own team, meanwhile, is testing how general this risk is across inflammatory diseases.

"We expect that this is a general mechanism," he said. "But in science we don't believe, we have to do."