

Researcher calls for new framework to study drivers of inflammatory response

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Anyone who has ever twisted an ankle is familiar with swelling, redness, heat, and pain—some of the telltale signs of inflammation. While uncomfortable, it's a biological necessity that protects the body from damage after a disturbance. But according Ruslan Medzhitov, Ph.D.,

Sterling Professor of Immunobiology, this understanding of inflammation is narrow and largely incomplete.

Now, the entire field of [inflammation](#) biology is transforming as immunobiologists realize that the phenomenon is much more pervasive than originally thought. Aging, obesity, and many chronic diseases, for example, are associated with inflammation. However, scientists still understand relatively little of what drives the [inflammatory response](#). Medzhitov calls for developing a new framework in his article published November 26 in *Science*.

"It's now well recognized that practically every human disease has an inflammatory component," he says. "We need to take a step back and study inflammation as an integral part of physiology, not just in the context of infections or injury."

Historically, scientists have viewed inflammation as a specialized pathological response that is only activated in response to perturbation, or disturbance of the body's normal condition. As a result, Medzhitov explains, there is a disconnect between inflammation biology and the rest of physiology. The inspiration for his latest publication stemmed from the growing realization over the past decade that there are many instances in which inflammation plays an important role even in the absence of infection or injury. The current paradigm for inflammation, says Medzhitov, fails to encompass all scenarios in which this process is present, and new research is needed to illuminate the gaps in knowledge.

"I'm primarily interested in building a conceptual framework that is broader than the classical view of inflammation, which is correct but not complete," he says.

Medzhitov calls for a new understanding of inflammation as a fundamental part of the design of an organism. Rather than simply a

defense mechanism against tissue perturbation, inflammation, he says, is a response that's engaged whenever something is "off" in the body. The process of maintaining a normal state is called homeostasis, and inflammation occurs when there is deviation from this normal state. "There are many different ways that the body's normal state can be lost," says Medzhitov. "Therefore, there are many different types of inflammation associated with it."

One of Medzhitov's research interests is understanding the different kinds of inflammation. There are three types of problems, he says, that can cause inflammation—loss of [structure](#), function, and regulation.

Each type of problem can induce an inflammatory response, but the types of responses vary. If a system experiences a problem with regulation, its function and structure may remain intact. On the other hand, if the system experiences loss of structure, all three categories are affected. In other words, a biological system can be thought of like a smartphone, says Medzhitov. If the phone experiences loss of regulation, such as the user not being able to control the volume or brightness, it is still possible for the phone to remain intact and function. However, if the phone breaks and loses its structure, it also loses its function and regulation, including one's ability to change the volume or brightness.

The three forms exhibit an important relationship, in which structure provides function and function enables regulation. Loss of structure involves tissue injury, while loss of function can be triggered by loss of structure or by allergens, environmental toxins, or parasites. Finally, deviation from homeostasis causes loss of regulation. Homeostatic deviation may be a result of loss of structure or function, or it might occur when a biological system experiences other threats such as starvation, dehydration, or hypothermia.

"All three types of problems that are fundamentally possible for any

system lead to inflammation, but the type of inflammation that has been traditionally studied has to do with the most overt type of problem, which is loss of structure," he says. "But I think there are also inflammatory responses associated with loss of function and regulation." In addition, he writes in the article, inflammatory responses to one form of perturbation may clash with responses to one of the others.

This reasoning, he continues, would explain why inflammation occurs in instances of obesity or aging in the absence of infection. He calls for more research investigating the role of inflammation in maintaining the structural, functional, and regulatory integrity of biological systems.

Inflammation drives, or at least perpetuates, nearly every human disease. And COVID-19, says Medzhitov, is an important reminder that inflammation can have fatal implications—most COVID deaths have been due to inflammation caused by the viral infection.

"Our understanding of biology would be incomplete without learning how it is associated with inflammation," says Medzhitov.

More information: Ruslan Medzhitov, The spectrum of inflammatory responses, *Science* (2021). [DOI: 10.1126/science.abi5200](https://doi.org/10.1126/science.abi5200)

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