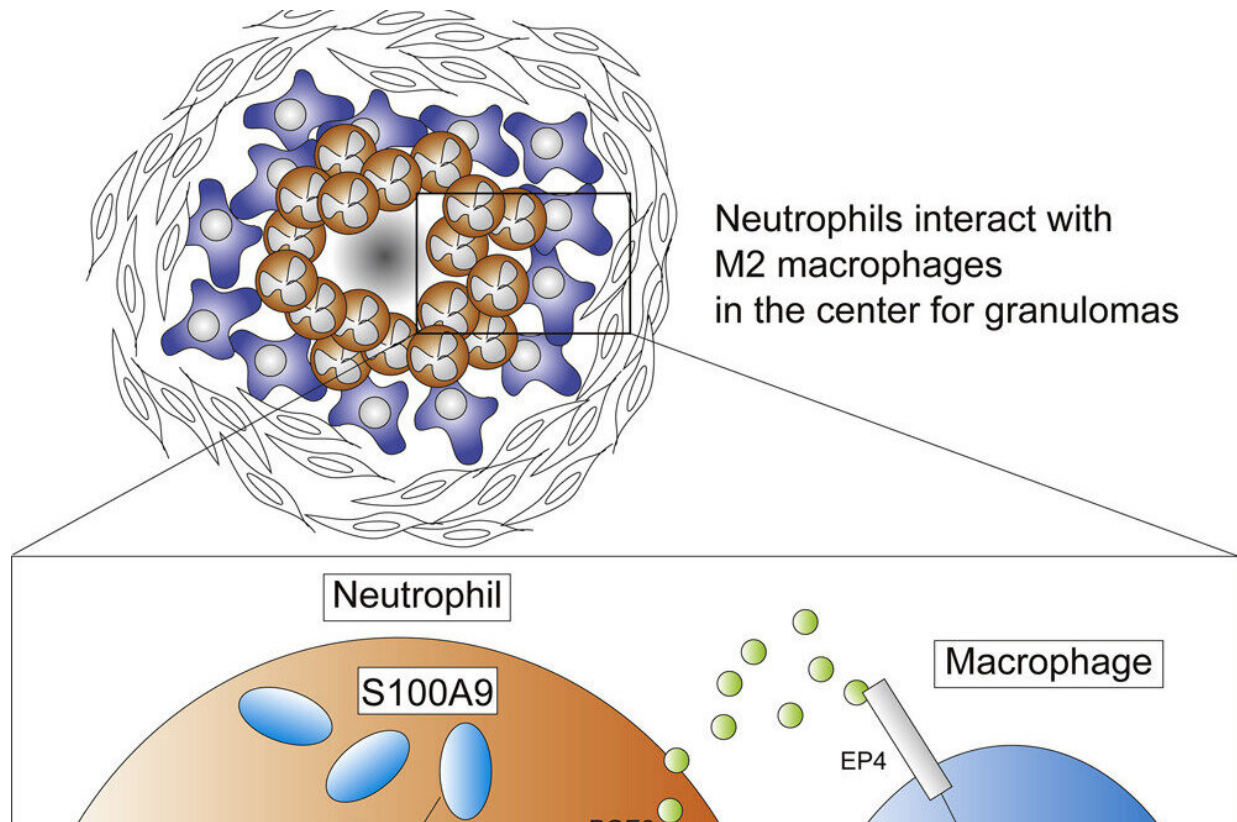


In search of the 'inflammatory Achilles heel'

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Credit: *iScience* (2023). DOI: 10.1016/j.isci.2023.106081

When our bodies become infected, various immune responses are triggered, starting with a release of granulocytes, white blood cells containing special enzymes that make up about half or more of all human white blood cells.

Neutrophils are also granulocytes that fight off invasive bacteria and fungi, often with zero tolerance for such invaders. Sometimes, however, a balanced and less aggressive approach goes even further in providing a cure.

Now, a team of researchers at Kyoto University has determined that neutrophils induce anti-inflammatory—or M2—macrophages deep in the core of these granulocytes. The team's research paper is published in the journal *iScience*.

In previous studies, chronic inflammatory macrophages were found to have the potential to polarize or differentiate into two opposite versions: pro-inflammatory, or M1, and anti-inflammatory (M2) types. These constitute an M1-M2 equilibrium that regulates the severity of inflammation and tissue health—or homeostasis.

This dual nature or polarization describes how M2 can revert to M1 or even M0—the non-inflammatory or steady state—in the deep granuloma zone where a bacteria-permissive [microenvironment](#) is formed. The team has examined the dense globular structures of granulomas in animals, particularly in the lungs.

"Microbes and [cancer cells](#) may manipulate this permissive microenvironment to favor their survival," says the paper's first author, Tatsuaki Mizutani.

Human granuloma-related disorders including tuberculosis are a hallmark of chronic inflammatory diseases. Mizutani posits that the results his team obtained from tuberculosis may also be applied to tumors.

Previous studies have revealed that intercellular interactions within granulomas drive effective inflammatory responses against pathogens or

contaminants, but [chronic inflammation](#)—as in tuberculosis and tumors—persists over prolonged periods of time.

To test how to predict [tumor](#) development, Mizutani's team previously established a lung granuloma model in [guinea pigs](#), which demonstrated the specific accumulation of Neutrophil S100A9—or A9—deep in the cores of granulomas. A9 is expressed in monocytes and macrophages at low levels, but at high levels within neutrophils.

"What is interesting is that both the inflammatory and anti-inflammatory effects of A9 have been reported in A9-deficient mice," notes Mizutani, whose team is now considering whether to make A9's multifunctional nature anti-tumorigenic in the [tumor microenvironment](#).

"Our understanding of how a permissive microenvironment in tumors is formed may be applied to effective cancer drug development," says Mizutani.

More information: Tatsuaki Mizutani et al, Neutrophil S100A9 supports M2 macrophage niche formation in granulomas, *iScience* (2023). [DOI: 10.1016/j.isci.2023.106081](https://doi.org/10.1016/j.isci.2023.106081)

Provided by Kyoto University

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