Studying 'inflamm-aging': Monocytes, cytokines, and susceptibility to pneumonia

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The chronic state of low-level inflammation seen in many elderly individuals (sometimes called "inflamm-aging"), is associated with diseases such as cardiovascular disease and dementia, as well as susceptibility to infections, especially pneumonia. A study published on January 14th in *PLOS Pathogens* reveals a crucial role of monocytes in the immune system changes that occur with age, and may help explain why older people are more susceptible to pneumonia.

Acute inflammation is part of a healthy immune response to infection or tissue injury. Chronic inflammation—ongoing heightened activity of the immune system—on the other hand, has been linked to many diseases, including asthma, diabetes, and heart disease. In the aging immune system, healthy responses are weaker, and chronic inflammation is common.

Dawn Bowdish, from McMaster University in Hamilton, Canada, and colleagues, are interested in how the immune system ages. In this study, they focus on monocytes, immune cells that are central to the process of inflammation. Monocytes multiply and mature in the bone marrow and circulate in the blood stream. They are recruited to sites of injury or infection and there turn into macrophages (literally "large eaters") that ingest pathogens, infected cells, or cellular debris. Monocytes are also potent producers of pro-inflammatory cytokines, small molecules that promote an inflammatory immune response.

Comparing younger and older mice, the researchers found that the latter have higher numbers of monocytes both in the bone marrow and in the blood. They also saw higher levels of TNF and IL-6, two pro-inflammatory cytokines, in blood from older mice and blood from older human donors. Studying mouse monocytes in more detail, the researchers found that the increase in TNF levels that occurs with age causes premature release of immature monocytes from the bone marrow into the blood stream. When stimulated with bacterial products, these immature monocytes themselves produce more inflammatory cytokines, thus further increasing levels in the blood.

The researchers then infected younger and older mice with the bacteria Streptococcus pneumoniae, which causes so-called pneumococcal pneumonia. They found that, although the older mice had higher numbers of monocytes in the blood and at the sites of infection, their monocytes were not able to clear the bacteria and successfully fight the infection. However, when the researchers used drugs or mouse mutations that reduced the number of monocytes or removed TNF, they were able to restore antibacterial immunity in aged mice.

The researchers conclude that "monocytes both contribute to age-associated inflammation and are impaired by chronic exposure to the inflammatory cytokine TNF, which ultimately impairs their anti-pneumococcal function." They go on to suggest that "lowering levels of TNF may be an effective strategy in improving host defense against S. pneumoniae in older adults", and that, "although it may be counterintuitive to limit inflammatory responses during a bacterial infection, [some existing] clinical observations and our animal model indicate that anti-bacterial strategies need to be tailored to the age of the host".

More information: Puchta A, Naidoo A, Verschoor CP, Loukov D, Thevaranjan N, Mandur TS, et al. (2016) TNF Drives Monocyte Dysfunction with Age and Results in Impaired Anti-pneumococcal Immunity. *PLoS Pathog* 12(1): e1005368. DOI: 10.1371/journal.ppat.1005368

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