Immune cells cast nets to save us from harm

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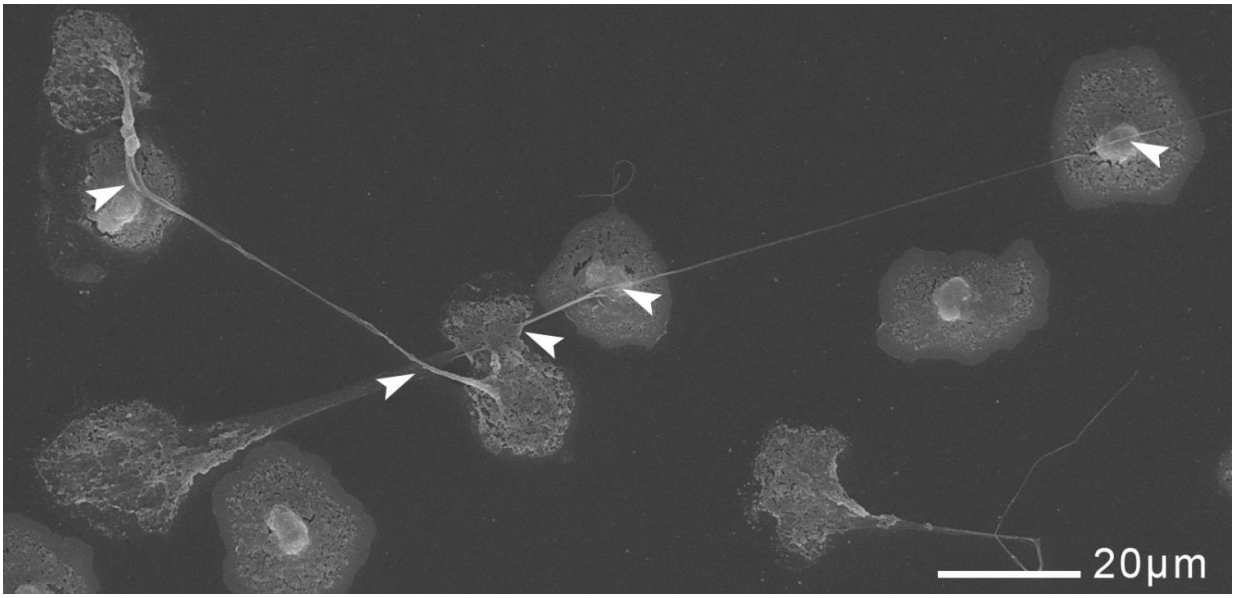


Scanning electron microscopic image of neutrophils in NET-formation. Credit: Dr Astrid Obermayer

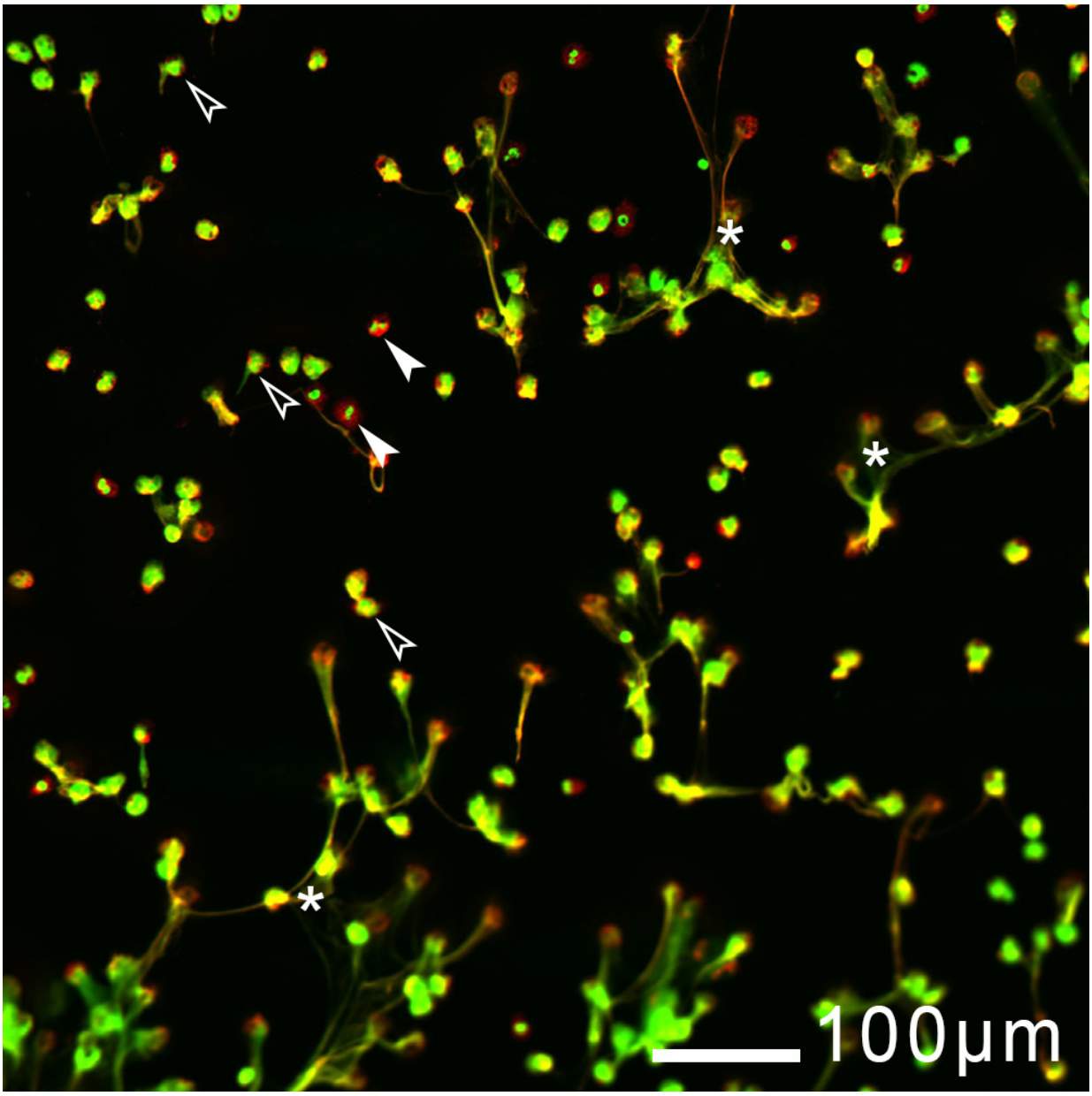
Our immune cells can undergo a spectacular form of cell death, using their own DNA to make nets that kill infectious microbes. Now for the first time, advanced microscopy techniques have allowed scientists to visualise details of how immune cells behave during this extraordinary process.

"Neutrophils, the most common type of white blood cell, are usually one of the first immune cells at a site of infection and they have a wide

repertoire of possible responses", says lead researcher Dr Astrid Obermayer (University of Salzburg). "These include ingesting microbes (a process called phagocytosis) and sending out signals to recruit other types of immune cell." In 2004, it was discovered that they can also catch microbes using traps made from threads of DNA with anti-microbial proteins attached to them (Neutrophil Extracellular Traps - NETs). This happens when the neutrophils undergo a specialized form of cell death, called NETosis [1][2].

During NETosis, the presence of disease-causing microorganisms stimulates enzymes in the neutrophils to transform and degrade proteins called histones that keep DNA tightly coiled. This causes the nucleus to swell and is followed by the breakdown of the nuclear envelope, releasing DNA into the main part of the cell. Here, bactericidal and digestive enzymes become attached to the decondensed DNA. Eventually the cell membrane ruptures, releasing the NETs into the extracellular space where they destroy microbes directly and act as a barrier to prevent the disease spreading.

"Although NETosis in single cells has been well documented, NETs typically form complex and continuous networks and it was unclear how these interconnected patterns form" says Dr Obermayer. To investigate this, the researchers used a variety of highly-skilled microscopy techniques on neutrophils from mice and humans. These included tagging cells with fluorescent-antibodies that recognize NET-specific proteins and generating high depth-of-field images of the 3D NET structure using a scanning electron microscope (SEM).



Laser scanning microscopic image of neutrophils (arrowhead), net-forming neutrophils (open arrowhead) and NETs (*). Credit: Dr Astrid Obermayer

By treating the cells with a chemical stimulus, the researchers were able to artificially trigger NET formation and capture each stage of the process. They found that neutrophils produce their NETs in a similar

fashion to how a spider weaves its web. First they attach a thread of DNA to an obstacle and then crawl away from it, allowing the DNA to unravel into a long string. The thread later disperses, forming a net-like structure. "Very often, these threads are pulled over or past other neutrophils, and this contact appears to activate NET formation in those cells, leading to a chain reaction" says Dr Obermayer. This explains how a small number of cells can construct such interconnected traps over large areas.

Evolutionarily, extracellular traps are an ancient defense strategy and they are even seen in invertebrates such as crabs or mussels. "NETs are a very fast, broad-spectrum defense mechanism of the innate immune system but they can act as a double-edged sword" says Dr Obermayer. "Because it is non-specific, the enzymes can also act against host tissue". In the future, Dr Obermayer plans to develop a technique for observing NETosis in live cells and to investigate whether NETs form differently depending on the type of infection.

These results will be presented at the 2016 Annual Meeting of the Society for Experimental Biology, in Brighton, on Wednesday July 6, 2016.

More information: References:

[1] Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303: 1532-1535.

[2] Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, et al. Novel cell death program leads to neutrophil extracellular traps. *J Cell Biol*. 2007;176: 231-241

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