isms that produce them—by activating autoimmune pathways or encouraging tumor cells to metastasize, for example.

Today, it is widely accepted that NETs have both a protective and a pathological impact on the host. In 2012, Mariana Kaplan, now of the National Institutes of Health, and the University of Tennessee’s Marko Radic termed NETs a “double-edged sword of immunity” and suggested that healthy organisms must tightly control their release to minimize negative consequences for the host. The details of NET regulation and function are now a very active area of research.

NET basics
Neutrophils are essential for immune defense and prevention of microbial overgrowth. They are very abundant—around 100 billion are produced in a human’s bone marrow in a single day—and they circulate in the bloodstream to quickly infiltrate tissues if the neutrophils detect a microbial threat. Belonging to a class of white blood cells called granulocytes, they are characterized by a cytoplasm packed with granules containing antimicrobial proteins. Neutrophils can engulf pathogens and then fuse their granules with their phagosomes, which contain the internalized microbes. Alternatively, the cells can fuse their granules with the plasma membrane to release antimicrobials to attack extracellular parasites.

Research on neutrophils is complicated by the fact that they are short-lived cells. For instance, unlike some other human cell types, neutrophils cannot be cultured for more than a few hours, and they are not amenable to gene editing. For this reason, we still lack a detailed mechanistic picture of how exactly NETs are formed. Early reports confirmed the original hypothesis that NETs do not result from passive necrosis of neutrophils. Later studies added complexity by demonstrating that different inflammatory triggers induce various pathways that all lead to the release of NETs, and that NET release doesn’t always result in lysis of the neutrophil.

That said, most pathways of NET formation do kill the immune cell, typically as a result of the production of reactive oxygen species (ROS). Bacterial or fungal pathogens cause neutrophils to activate kinases that induce assembly of an enzyme complex called nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH oxidase then produces large amounts of superoxide—a highly reactive oxygen compound that carries an extra electron—during a process called the neutrophil oxidative burst. ROS resulting from the oxidative burst trigger disintegration of a multiprotein complex to release active NE, a primary component

NET FORMATION
When a neutrophil encounters a pathogen, it can respond in several ways: phagocytosis, degranulation, or by releasing neutrophil extracellular traps (NETs). In NET release, shown here, the enzyme complex NADPH oxidase generates reactive oxide species (ROS), which in turn initiate the disintegration of granules, releasing neutrophil elastase (NE). NE then migrates to the neutrophil’s nucleus, where it cleaves proteins that package the cell’s DNA as chromosomes. The chromatin expands until it fills up the entire cell, which breaks open and extrudes the NET into the extracellular space. There, the webs are thought to trap and kill the triggering pathogens.