153 years after discovery of the immune system's dendritic cells, scientists uncover a new subset

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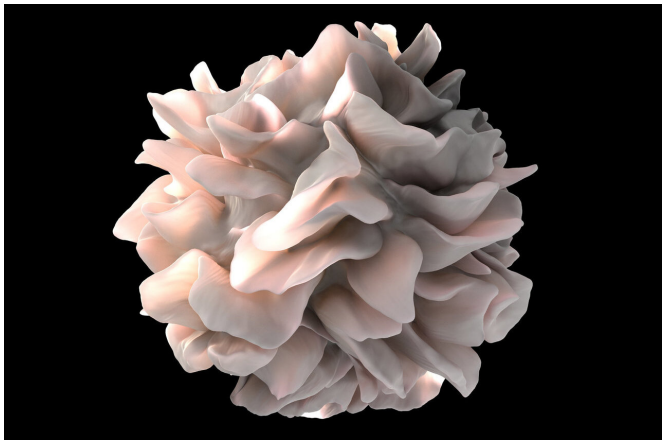

Artistic rendering of the surface of a human dendritic cell illustrating sheet-like processes that fold back onto the membrane surface. Credit: National Institutes of Health (NIH)

When pathogens invade or tumor cells emerge, the immune system is alerted by danger signals that summon a key battalion of first responders, the unsung heroes of the immune system—a population of starfish-shaped sentinels called dendritic cells.

Without them, coordination of the immune response would be slower and less-well organized. Yet even in the face of such an indispensable role, it has taken until now to discover how a sub-population of these cells doesn't perish after completing their primary job in the immune system.

Dendritic cells were discovered in 1868, and at that time were misunderstood and wrongly categorized as members of the nervous system. But immunologists now know there are different types of these cells, even though they all look alike and have roughly the same job as sentinels in the immune system –on patrol 24/7, hunting down infiltrating causes of infection and disease. What separates one group from another, scientists in Germany have just found, is their response to certain signaling molecules and how long they survive in tissues and the blood.

First off, the shape is no accident of nature. It allows these cells to perform their primary role, which involves obtaining microscopic samples—antigens—from an infiltrator slated for destruction. Dendritic cells engulf snippets of the invader and literally present those antigens to key warriors of the immune system.

These highly mobile cells travel to sites where disease-killing immune cells reside to present their samples, introducing T cells, for example, to the enemy that awaits. Formally, the activity of presenting the sample to T cells is called antigen presentation. For all the work involved with alerting the body to danger, a major group of dendritic cells is programmed to die after a job well done.

Now, in a groundbreaking series of studies, a large team of researchers from throughout Germany has discovered why a unique population of dendritic cells doesn't die after antigen presentation. The sub-population continues to stimulate parts of the immune system to aid the fight against invasive viruses, bacteria or potentially deadly tumor cells.

The finding is likely to be viewed as welcome news in a world beset by a pandemic virus and a slew of worrisome variants. All have stoked concerns about the longevity of immunity triggered by COVID-19 vaccines. Another major role of dendritic cells, as it turns out, is marshaling immune forces in response to vaccination.

To understand the importance of the new research, it's first necessary to detour away from the new

finding to delve instead into a primer on the two divisions of the human immune system: the innate and the adaptive.

Also, to fully grasp the research, it's important for another quick lesson: Dendritic cells 101. The new finding, scientists say, promises to change how the cells are defined going forward.

The innate immune system is composed of the big eaters, the so-called professional phagocytes that devour as much of an invading enemy as possible, chewing them into harmless trash. This part of the immune system also releases a tsunami of cytokines and other inflammatory molecules. Adaptive immunity is anchored by the big daddies of the immune response, mainly the various populations of B and T cells.

Dendritic cells, or DCs as they're also known, are the antigen-presenting population, which simply means they engulf a sample of an invader and race to present it to disease-fighting warriors of the adaptive immune system. But dendritic cells have a greater role: They actually activate the adaptive immune response. As a member of the adaptive immune system, dendritic cells serve as a bridge between the innate and adaptive systems.

Signaling activity initiated by the innate immune system's inflammatory molecules stimulates a swift response by dendritic cells, which are already on patrol—on the hunt for invasive trouble.

Despite the chore of activating key players of the adaptive immune system, namely T cells—and, somewhat indirectly, triggering antibody-producing B cells—armies of DCs are inescapably doomed to death. Once their primary jobs of antigen presentation and stimulating the adaptive response are done, the cells are subject to programmed cell death, apoptosis, which leads to their demise. Simply put, nature ensured that armies of dendritic cells perish once their primary roles are complete. Fresh recruits replace the old cells in a renewal process that begins in the bone marrow.

Drs. Lukas Hatscher and Diana Dudziak of the Laboratory of Dendritic Cell Biology at University Hospital Erlangen, a division of Friedrich-Alexander University, led the team that uncovered a long-lasting subset of dendritic cells. They've identified them as human type 2 conventional dendritic cells.

Hatscher, Dudziak and their collaborators analyzed this dendritic population, obtaining them from a variety of sites—the blood, spleen and thymus. The organ-derived DCs used in the research were acquired from donated organs. Scientists compared their activity to human type 1 conventional dentritic cells. They found that longevity distinguished the type 2 population from the doomed type 1s.

Hiding in Plain Sight

The big surprise in the research was discovering that this elusive group of DCs had been hiding all along in plain sight. The challenge for the German team was elucidating why type 2 DCs stay active even though type 1s are programmed to die.

"Instead, these cells entered a 'hyperactive' state that enhanced the stimulation of certain T helper cell subsets," Hatscher and Dudziak wrote in the journal *Science Signaling*, describing the dendritic cell population they discovered. "The findings suggest that conventional dendritic cells type 2 could be critical to the efficacy of vaccines and immunotherapies as well as for therapeutically controlling inflammation."

The German team confirmed that type 2 DCs augment immune system activity by responding to inflammasome signaling. Chemically, inflammasomes are complex polymers and part of the innate immune system. Inflammasome signaling induces cytokines. The DC response to inflammasomes also occurs in vaccine immunity and the body's ability to repel infections, Hatscher and Dudziak found.

Type 1 dendritic cells tend to undergo regulated cell death after inflammasomes activate. But the investigators found that automatic death wasn't inevitable for type 2 DCs, which did not succumb after inflammasome activation. Type 2 DCs not only survived, but continued their role as a bridge between the innate and adaptive immune systems. The researchers suggest that these cells may be prime targets for approaches to treat inflammatory

diseases or to boost the effects of vaccines and adjuvants.

"When conventional type 2 dendritic cells were stimulated with ligands that weakly activated the inflammasome, the DCs did not enter [programmed cell death], but instead secreted interleukin-12 family of cytokines [IL-12] and interleukin-1? [IL-1?]. These cytokines induced prominent T helper type 1 cells and T helper 17 responses," the scientists wrote.

The discovery of how some dendritic cells survive and others are programmed to die was made by a large team of immunobiologists who represented more than a dozen leading research centers throughout Germany. Investigators described the signaling pathway that alerts these cells, and defined the biological role of dendritic sub-population. Scientists proved in their research that nuances of difference separate type 2 conventional dendritic cells differed from type 1s. "We found that the conventional type 2 dendritic cell subset is the major human DC subset," the researchers concluded.

Dendritic cells, in general, act as sentinels by conducting surveillance in tissues. For instance, they can detect infection in the body by pinpointing "danger signals" linked with invading pathogenic agents. Dendritic cells regardless of type zero in on PAMPS—pathogen-associated molecular patterns—which are derived from microorganisms. One of the most notorious PAMPs is a potentially deadly bacterial component known as lipopolysaccharide, or LPS, which is found on the outer cell wall of gram-negative bacteria. Dendritics obtain antigens from the deadly invasive source—and the launch of the adaptive immune system assault on the infiltrator begins.

While the findings by Hatscher, Dudziak and their colleagues may prompt scientists worldwide to take stock of a broader role for these immune system constituents, it's now clear that Germany has been in the vanguard of dendritic cell research for 153 years.

German pathologist Paul Langerhans, while still a medical student, was the first to describe DCs in skin cells. Although he mistakenly defined them as nerve cells, he is credited with bringing attention to bear on this hardworking cell population. (Langerhans is also famous for research involving the pancreas. An insulin-secreting cluster of cells in the pancreas is named after him: the islets of Langerhans).

Hatscher and Dudziak, meanwhile, report that their 21st-century discovery not only enhances overall knowledge about the immune system, but paves the way for using this new knowledge in the fight against disease processes. "These findings not only define the human conventional type 2 dendritic cell subpopulation as a prime target for the treatment of inflammasome-dependent inflammatory diseases, but may also inform new approaches for adjuvant and vaccine development."

More information: Lukas Hatscher et al. Select hyperactivating NLRP3 ligands enhance the TH1- and TH17-inducing potential of human type 2 conventional dendritic cells, *Science Signaling* (2021) DOI: 10.1126/scisignal.abe1757