Immune system molecule with hidden talents

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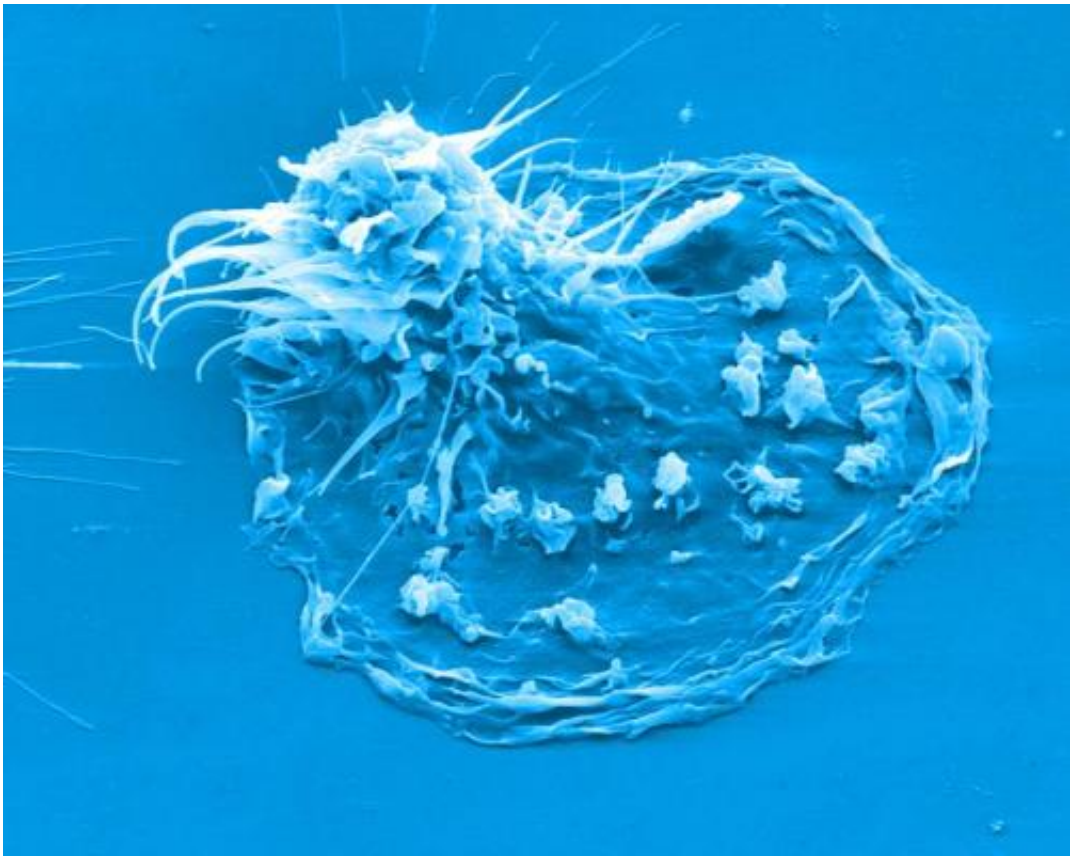

Dendritic cells, shown here in an electron microscopic picture, need antibodies produced by B cells for their maturation. Credit: HZI / Rohde

Dendritic cells, or DCs for short, perform a vital role for the immune system: They engulf pathogens, break them down into their component parts, and then display the pieces on their surface. This in turn signals other immune cells capable of recognizing these pieces to help kick-start

their own default program for fighting off the invaders. In order to do their job, the DCs are dependent upon the support from a class of immune system molecules, which have never before been associated with dendritic cells: antibodies, best known for their role in vaccinations and diagnostics. Now, scientists at the Helmholtz Centre for Infection Research (HZI) and the Hannover Medical School (MHH) were able to show that antibodies are essential for dendritic cell maturation. The researchers' findings have been published in the renowned scientific journal, *Proceedings of the National Academy of Sciences* (*PNAS*).

The human immune system is made up of some half a dozen different cell types that are all working in tandem. Team work is key since each cell type has a single unique job to perform, which is central to its ability to help defend the body against invaders and ward off disease. If one of these players is taken out of commission, the entire system is thrown out of whack.

This is precisely what Dr. Siegfried Weiss, head of HZI Department of Molecular Immunology, and his team of researchers observed when they looked at immunodeficient mice. "Our 'RAG' mice are lacking adaptive, or acquired immunity," explains Weiss. "Basically, what this means is they are missing their antibody-producing B cells, among others."

The dendritic cells belong to a different branch of the immune system - innate immunity, which, although far less pliable, is capable of a fairly rapid response. Which is why these cells should not be affected by a defect in acquired immunity. Still, the scientists noticed that DCs obtained from this particular murine strain were not working properly - their maturation process was faulty and instead of breaking down a pathogen into small pieces, they ended up destroying the pathogen altogether. "The broken down pieces are called antigens. Presenting antigen is the dendritic cells' main job," explains Dr. Natalia Zietara, one of the scientists who worked on this study. "In fact, it is one of the most

important points of intersection between the immune system's innate and acquired branches. If it goes missing, any subsequent immune responses don't ever get triggered," adds her colleague, Dr. Marcin Lyszkiewicz. The cells' normally highly precise interplay comes to a standstill and the acquired immune response becomes largely ineffective at a targeted defense against invading pathogens.

Starting with this observation, the immunologists were interested in identifying the cause behind the defect in the DCs' function. To this end, they initially examined the dendritic cells' surface markers for any potential deviation from the norm - albeit to no avail. Only once they began studying the transcriptome, the sum total of genes that are active in the cells that were being examined, the researchers found what it was they were looking for: The activity of a select few genes, among them those encoding a family of receptors capable of binding antibodies, had been altered. Through a series of subsequent experiments, the researchers were able to show that it was these very molecules, which stimulated dendritic cell maturation.

Antibodies, also called immunoglobulins, are proteins made by B cells. Their normal job is one of neutralizing toxins or viruses and labeling bacteria for destruction by other immune cells. The concept of vaccination is based on artificially prompting the organism to make antibodies, which, at a later stage - specifically, upon contact with the actual pathogen - helps the body ward off disease. Until now, this new role for antibodies was completely unknown. "We had no idea that B cells and dendritic cells use immunoglobulins to communicate with each other. It just goes to show you how complex the immune system really is and how we are a long way from truly grasping the full scope of its complexity," says Dr. Andreas Krueger, head of the Lymphocyte Biology research group at the MHH's Institute of Immunology. In a way, you might say the researchers discovered a 'hidden talent' of antibodies.

Natalia Zietara and Marcin Lyszkiewicz are both named as the study's primary co-authors. They initially kicked off their investigation during the time of their doctoral work in Siegfried Weiss' department at HZI and, upon earning their PhDs, transferred to the MHH where they were able to see the project to its conclusion working in Andreas Krueger's lab. According to Weiss, "this is a prime example of a genuine scientific collaborative." Two other HZI research groups, along with scientists from Freiburg University and the Max Planck Institute of Immunobiology and Epigenetics, were also part of the research project.

More information: Natalia Zietara, Marcin Lyszkiewicz, Jacek Puchalka, Gang Pei, Maximiliano Gabriel Gutierrez, Stefan Lienenklaus, Elias Hobeika, Michael Reth, Vitor A. P. Martins dos Santos, Andreas Krueger, Siegfried Weiss, Immunoglobulins drive terminal maturation of splenic dendritic cells, *Proceedings of the National Academy of Sciences*, 2013.

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