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No tolerance for tumors

Dying cells can suppress the immune system. In this way, they prevent immune cells from mounting an undesired defense response against the body's own tissues and organs. In cancer treatment, however, this immunological tolerance has negative effects because it suppresses the fight against the tumor. Immunologists at the German Cancer Research Center (DKFZ) in Heidelberg are now the first to find a cause for this tolerance. In dying cells, special intracellular proteins called annexins are transported to the cell surface, thereby preventing an immune response.

Billions of cells die every day in the human body. This happens according to a strictly controlled process called apoptosis. During apoptosis, dying cells actively suppress the immune system in order to prevent immune cells from targeting the body's own proteins that are being emitted in the process. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg have now discovered how this happens. A team led by Professor Dr. Peter Krammer, head of the Division of Immunogenetics at the DKFZ, has now shown for the first time that apoptotic cells present specific members of a family of proteins – called annexins – on their surface, consequently inhibiting immune cells.

"Annexins are a poorly studied group of proteins," Krammer explains. "They normally reside in the cell interior. In dying cells, however, annexins are transported to the surface." This process enables annexins to make contact with specific cells of the immune system called dendritic cells.

Dendritic cells patrol the body by searching for unusual or foreign structures that originate, for example, from viruses or bacteria. They ingest entire pathogens or parts of pathogens, and sound an alarm to activate other immune cells. In addition, dendritic cells eliminate cells of the body that are dying by apoptosis. "Apoptotic cells actively attract dendritic phagocytic cells and are engulfed by them," Krammer explains. "The annexins then inhibit the activity of the phagocytes and cause the immune system to tolerate the components of the apoptotic cells." The dendritic cells subsequently migrate to the closest lymph nodes, where they present the proteins they have taken up from dying cells to other immune cells. As a result, the immune system does not launch any further response and the immune cells learn to tolerate the apoptotic cells and their proteins. This process keeps cells that may direct themselves against the body's own structures in check and, thus, prevents autoimmune reactions.

However, the immune system's tolerance to apoptotic cells can have negative effects in the context of the fight against cancer. Dying tumor cells also present annexins on their surface and are therefore capable of suppressing the anti-tumor immune response, thus promoting cancer growth. Hence, the scientists at DKFZ's Immunogenetics Division have found a new immune system checkpoint whereby the tumor can stifle the immune response directed against it. In this case, the tumor utilizes the dendritic cells' ability to cause tolerance in other immune cells. Scientists hope that knowledge of this mechanism will aid in developing targeted therapeutic agents that suppress or mask annexins, with the ultimate goal of supporting immunotherapies and conventional cancer therapies. This might also be a promising approach in the management of autoimmune diseases, where immune cells turn against the body's own tissue.

“By analyzing several thousand antibodies, we were able to detect the expression of annexins on the surface of dying cells,” reports Dr. Heiko Weyd, one of the co-authors of the immunotolerance study. “Next, we plan to further investigate whether it will be possible to use the annexin checkpoint system for treating autoimmune diseases and cancer in humans.”

Björn Linke, Lucie Abeler-Dörner, Veronika Jahndel, Alexandra Kurz, Andrea Mahr, Sandra Pfrang, Linda Linke, Peter H. Krammer, and Heiko Weyd: The Tolerogenic Function of Annexins on Apoptotic Cells Is Mediated by the Annexin Core Domain. The Journal of Immunology 2015, DOI: 10.4049/jimmunol.1401299

A picture for this press release is available for download at:
www.dkfz.de/de/presse/pressemitteilungen/2015/bilder/Fresszellen.jpg
Source: Heiko Weyd/DKFZ
Caption: Phagocytic cells in contact with apoptotic cells dyed blue.

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