Important regulator of immune system decoded

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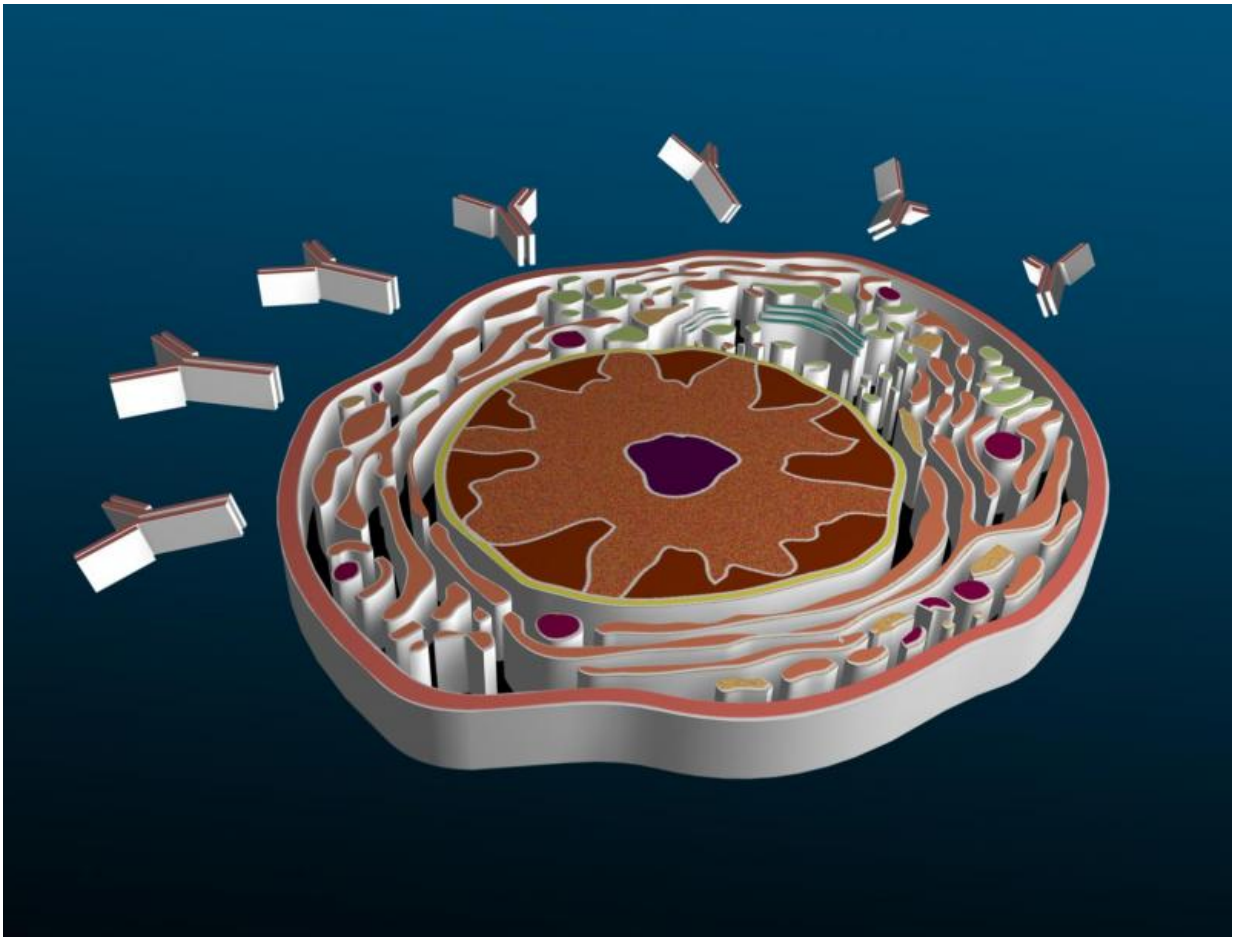

Schematic diagram of a plasma cell

Our environment teems with microorganisms and viruses that are

potentially harmful. The reason why we survive their daily attacks is the ability of the immune system to neutralize these invaders in numerous ways. Plasma cells are key players in this process. They fight infections and establish long-lasting protection against pathogens.

Plasma cells are white blood cells that develop from B-cells. They are the effector cells of the humoral immune response. Their main function is to produce antibodies that patrol the body in large numbers to neutralize harmful invaders. A functional plasma cell produces up to 10,000 antibodies per second to release them into the blood stream. This outstanding achievement can be visualized with a powerful microscope, as active plasma cells are packed with antibody-producing vesicles, constituting the so-called endoplasmic reticulum that is essential for antibody assembly and secretion.

B-cells need to be activated by antigens (foreign substances) in order to develop into plasma cells. They first form plasmablasts that migrate to the bone marrow where they survive for many years or even decades. The long-lasting protection provided by active vaccines is based on this immunological memory of plasma cells.

A Central Role for Blimp1

Scientist have known about the functions of plasma cells for quite a while. However, details of how the differentiation and function of these cells are regulated were still unknown. Now an important key to understanding the function of plasma cells has been discovered by a team headed by Meinrad Busslinger, Senior Scientist and Deputy Director at the Research Institute of Molecular Pathology (IMP) in Vienna, Austria. In a five-year project, the team succeeded in deciphering the role of the protein Blimp1 as a central regulator of plasma cell development and function. In its current issue, the science journal *Nature Immunology* publishes the results of the team in Vienna

as well as the work of Australian colleagues that complements the Viennese results.

In detailed studies, scientists at the IMP identified all genes that are involved in the development of plasma cells in mice. First author Martina Minnich, whose PhD-thesis provided the groundwork for the publication, explains the results: "We found that more than 50 percent of these genes are regulated by Blimp1. Therefore, this factor must be of vital importance for plasma cells. Furthermore, we were able to show for the first time that Blimp1 not only switches genes off but can also switch other genes on. This is an important discovery for the understanding of plasma cell development."

"Most of the essential functions of plasma cells are controlled by the factor Blimp1", Meinrad Busslinger summarizes the results. "It regulates their mobility and migration to the bone marrow. Blimp1 is also responsible for the enormous increase in size of the endoplasmic reticulum and the strong up-regulation of antibody production in plasma cells. Humoral immunity would not be possible without Blimp1."

No Antibodies without Blimp1

Even though Blimp1 is necessary for the development of plasma cells, mature plasma cells can survive without this factor. However, when Blimp1 is switched off, they become non-functional as they no longer produce antibodies. This unexpected finding is the result of work carried out at the Walter and Eliza Hall Institute (WEHI) in Melbourne, Australia. The study, which is published back-to-back with the Austrian paper, was led by Stephen Nutt, Head of the Division of Molecular Immunology at WEHI. The picture that emerges from the Australian study perfectly complements the results obtained at the IMP.

Insight into the manifold functions of Blimp1 is not only important for

our understanding of the immune system but may also be relevant for human medicine. Mutations in the Blimp1 gene can block the further differentiation of B-cells, which contributes to the formation of malign B cell tumors known as lymphomas. Moreover, quiescent plasma cells can sometimes switch to uncontrolled cell growth and thus turn into plasma cell tumors or multiple myelomas.

Another aspect of the immune system that is highly relevant for medicine is the broad spectrum of autoimmune diseases. Conditions like systemic lupus erythematosus (SLE) are an example for the serious damage to organs and tissue caused by misguided immune responses which generate plasma cells producing auto-reactive antibodies that turn against the body's own tissue.

Meinrad Busslinger: "The published results have yielded profound insight into the function of plasma cells. They also raise new interesting questions which we will address in forthcoming projects."

More information: Martina Minnich et al. Multifunctional role of the transcription factor Blimp-1 in coordinating plasma cell differentiation, *Nature Immunology* (2016). DOI: 10.1038/ni.3349

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