

New immunoregulation and biomarker

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Clinicians at LMU have elucidated a mechanism involved in determining the lifespan of antibody-producing cells, and identified a promising new biomarker for monitoring autoimmune diseases like multiple sclerosis and lupus erythematosus.

The so-called humoral immune response is mediated by [plasma cells](#) and plays a central role in combating infections. Plasma cells secrete antibodies – a class of proteins that specifically recognize infectious pathogens and facilitate their destruction. Individual plasma cells make only a single species of antibody that normally recognizes a single structure. Nevertheless, antibodies with certain specificities may erroneously attack the tissues of their host, causing [autoimmune diseases](#) such as multiple sclerosis (MS) or [lupus erythematosus](#) (SLE). "Balanced

regulation of the production and activity of plasma cells is therefore vital," says Professor Edgar Meinel (LMU Medical Center). Long-term antibody-mediated immunity is provided by so-called long-lived plasma cells, and Meinel and his research team have now identified a novel mechanism involved in regulating the lifespan of these antibody producing cells. This involves the shedding of a particular cell-surface receptor, named BCMA, which is known to bind factors that promote plasma-cell survival. The released segment that is cut off the receptor can be detected in the circulation, and the LMU group has shown that it provides a useful biomarker for monitoring the severity of autoimmune conditions. The new findings appear in the online journal "*Nature Communications*".

Protease γ -secretase truncates receptor

Plasma cells develop from progenitors called B-cells that carry specific membrane-bound receptors which recognize foreign proteins termed antigens. When a B cell encounters its cognate antigen, it differentiates into a clone of plasma cells that secrete the antigen-binding protein in soluble form as antibody. How long an antibody-producing plasma cell survives in the body depends largely on the survival receptor BCMA.

When the BCMA binds its ligands, the survival factors BAFF and APRIL, a genetic program is activated which effectively extends the lifespan of the plasma cell. "However, the lifetime of plasma cells cannot be prolonged indefinitely. Otherwise the organism would become swamped with antibodies, increasing the risk of an autoimmune reaction," Meinel explains. "We have now shown, in cooperation with colleagues in Munich, Berlin and Stockholm, that the membrane-bound enzyme γ -secretase acts as a brake on immune reactions by fragmenting BCMA."

As a so-called transmembrane receptor, BCMA extends through the cell

membrane and projects into the extracellular medium. Gamma-secretase removes the exposed portion by cutting the protein inside of the plasma membrane. That this enzyme cleaves the receptor directly was a surprise: "Up to now, it was only known to be involved in the degradation of membrane proteins that had already been cleaved by other enzymes. "BCMA is the first natural substrate of gamma-secretase to be identified that is directly cleaved by the enzyme," says Meinel, "and probably reflects the fact that the extracellular segment of the receptor is unusually short."

Informative immunological indicator

The cleaved fragment is stable, and can be detected in body fluids as soluble BCMA (sBCMA). Analysis of clinical samples from patients with multiple sclerosis or lupus erythematosus has indicated that the molecule could provide a useful biomarker for autoimmune disease. Lupus is a systemic condition which affects the whole organism. In lupus patients, levels of sBCMA in the blood were found to be abnormally high – and were correlated with the severity of the disease. Multiple sclerosis is an organ-specific disease, which targets the central nervous system. "Correspondingly, in MS patients sBCMA levels were increased specifically in the cerebrospinal fluid, which bathes the brain and the spinal cord," says Meinel. "So, sBCMA is an indicator of the intensity of ongoing immune reactions. sBCMA is therefore well suited to serve as an informative clinical parameter for the assessment of the therapeutic effects of different treatment regimes on plasma cells."

These findings could facilitate the development of optimized and personalized modes of therapy. Both B cells and the BCMA/BAFF/APRIL system constitute promising targets for the treatment of lupus and [multiple sclerosis](#), as blocking their activity could inhibit the production of the autoimmune antibodies. In the case of lupus, an agent directed against BAFF has already been approved for

clinical use. Unfortunately, for unknown reasons, it is effective in only a subset of patients. Further clinical studies on agents that target BAFF, APRIL and their receptors are currently underway. In future, sBCMA could be used to measure and optimize the impact not only of these new therapies but also of already proven treatments, since it enables one to monitor the levels of plasma cells.

More information: " γ -secretase directly sheds the survival receptor BCMA from plasma cells" *Nature Communications* 6, Article number: 7333 [DOI: 10.1038/ncomms8333](https://doi.org/10.1038/ncomms8333)

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