Long-lived plasma cells require stromal cell-dependent activation of PI3K signaling and APRIL to prevent caspase-dependent cell death

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Abstract

Long-lived plasma cells are maintained in the bone marrow in close contact to mesenchymal stromal cells, constantly secreting antibodies and maintaining life-long humoral immunity. However, plasma cells are not intrinsically long-lived but require constant provision of extrinsic signals for their long-term survival. It has remained elusive how the niche microenvironment and specifically stromal cells support bone marrow plasma cell survival.

To analyze the survival signaling of plasma cells, we mimicked the bone marrow environment of plasma cells *in vitro*, providing them with cell-contact to a bone marrow-derived stromal cell line and recombinant APRIL.

We show that both cell-contact and APRIL are required and sufficient to prevent caspase-mediated cell death of primary *ex vivo* isolated bone marrow plasma cells. Interruption of integrin expression in plasma cells or pharmacological inhibition of either the cell contact-induced PI3K or APRIL-induced NF-κB signaling pathway result in the quantitative depletion of plasma cells. Cell contact-induced PI3K-signaling inactivates FoxO1/3 and prevents activation of caspases 3 and 7. Both cell-contact and APRIL synergistically upregulate the master transcription factor IRF4 and prevent activation of the endoplasmic reticulum stress-induced caspase 12. IRF4 and FoxO1/3 control the expression of the important anti-apoptotic proteins BCL2 and MCL1, respectively. These results demonstrate that the two essential survival factors provided in the bone marrow niche, stromal cells and APRIL, synergize and address multiple pathways to ensure the survival of bone marrow plasma cells and the long-term maintenance of humoral immunity.