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The road to terminal B-cell differentiation

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Keywords

B cell development, plasma cells, RAG-2 complementation system, terminal differentiation, transcription factor, XBP-1 (X-box-binding protein-1)

Context

Unlike early B cell development and activation, little is known about the factors that lead to the terminal differentiation of mature B lymphocytes to plasma cells. The authors previously found very high levels of X-box-binding protein-1 (XBP-1) transcripts in myeloma cell lines. In this study they sought to analyze the role of XBP-1 in the generation of plasma cells. Analysis is complicated by the fact that XBP-1-deficient mice die *in utero*, so the work was done using chimeric mice.

Significant findings

The authors found high levels of XBP-1 transcripts in plasma cells of rheumatoid synovium, and in purified B cells committed to plasma cell differentiation. B-cell lines transfected with XBP-1 possessed the surface phenotype of plasma cells. Lymphocytes deficient in XBP-1 failed to produce immunoglobulins in response to activating signals; this was reversed by transducing XBP-1 into the deficient B cells. The XBP-1-/- B cells had the same activation and proliferation profile as control B cells and showed evidence of class switching. Germinal centers formed normally after immunization but there was an absence of plasma cells and a dramatic decrease in immunoglobulin secretion. Interestingly the authors found an increase in the expression of c-Myc, which is usually downregulated as B cells exit the cell cycle. The authors conclude that XBP-1 is specifically required for progression of mature B cells to the plasma B-cell stage.

Comments

These data indicate that XBP-1 acts later than other transcription factors essential for germinal-center formation (e.g. Bcl-3, Bcl-6, nuclear factor-?B/p52 and interferon regulatory factor-4); however, the genes targeted by XBP-1 remain unknown. The increase in the expression of c-Myc in stimulated XBP-1-deficient B cells suggests a mechanism by which the transcription factor exerts its effects, but the authors note that XBP-1 does not directly repress the c-*myc* promoter. XBP-1 is not specific to B cells and plays a role in the development of other immune cell types as well as other organ tissues, most notably the liver. The effects of mosaicism in nonlymphoid tissues of chimeric mice *in vivo* is difficult to know. The identification of this critical factor in B cell terminal differentiation is a promising start to unraveling the mechanisms of plasma cell generation.

Methods

RAG-2 complementation system, *in situ* hybridization, northern blot, FACS analysis, Southern blotting, ELISA, RT-PCR, retroviral transduction, immunization

Additional information

The RAG-2 complementation system is more fully described in this article:

Chen J, Lansford R, Stewart V, Young F, Alt FW: **RAG-2-deficient blastocyst complementation: an assay of gene function in lymphocyte development**

Proc Natl Acad Sci USA 1993, **90**:4528-4532 (PubMed abstract).

References

1. Reimold AM, Iwakoshi NN, Manis J, Vallabhajoshyula P, Szomolanyi-Tsuda E, Gravallese EM, Friend D, Grusby MJ, Alt F, Glimcher L: Plasma cell differentiation requires the transcription factor XBP-1. Nature. 2001, 412: 300-307.