Microbial Cell Factories

Oral Presentation

The making and breaking of an efficient antibody factory

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from The 4th Recombinant Protein Production Meeting: a comparative view on host physiology
Barcelona, Spain. 21–23 September 2006

Published: 10 October 2006

Microbial Cell Factories 2006, **5**(Suppl 1):S5 doi:10.1186/1475-2859-5-S1-S5

Upon encounter with antigen, long-lived B lymphocytes differentiate into short-lived plasma cells, the terminal effectors of the humoral immune response. Plasma cells are specialized in immunoglobulin (Ig) secretion, each of them being capable of releasing thousands of molecules per second. We have performed proteomics analyses to unravel mechanistically the massive *de novo* ER biogenesis during terminal plasma cell differentiation, with emphasis on how cells adapt ER quality control to exuberant Ig production and secretion. These studies revealed that waves of functionally related proteins are produced to increase the capacity of the antibody factory, and led to the identification of novel ER chaperones. As to the mechanisms that lead to plasma cell death, we show that in the late phases of plasmacytic differentiation, when antibody production becomes maximal, proteasomal activity unexpectedly decreases. The excessive load for the reduced proteolytic capacity correlates with accumulation of polyubiquitinated proteins, stabilization of endogenous proteasomal substrates (including Xbp1s, Ik-Bα and Bax), onset of apoptosis, and sensitization to proteasome inhibitors. A developmental program seems therefore to link plasma cell death to protein production, explaining the peculiar sensitivity of normal and malignant plasma cells to proteasome inhibitors.