Microbial Cell Factories

Poster Presentation

Effects of overexpression of X-box binding protein 1 on recombinant protein production in mammalian cells

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Background

X-box binding protein 1 (XBP-1), a key regulator for the cellular secretory pathway, is essential for the differentiation of plasma cells and the unfolded protein response. In the XBP-1 knock-out B primary cells, a profound depression in synthesis and secretion of immunoglobulin M was observed, clearly demonstrating the importance of XBP-1 in protein secretion. There are two protein isoforms of XBP-1, XBP-1S and XBP-1U. The spliced form of XBP-1, XBP-1S, functions as a transcription activator and upregulates many genes associated with protein secretion and biosynthesis of endoplasmic reticula (ER), whereas the unspliced XBP-1U is transcriptionally inactive. Since the production of some recombinant proteins is widely believed to be limited by the secretory capacity of the host cell, we reason that an increase in protein productivity may be achieved by overexpressing XBP-1S in cells. However, XBP-1S is only synthesized when UPR is initiated. To constitutively express XBP-1S in cells, but not XBP-1U, we generated a specific expression plasmid which contains the spliced XBP-1S cDNA. Effects of overexpression of XBP-1S on the productivity of human erythropoietin (hEPO) in CHO-K1 cells were examined.

Results

We hypothesized that protein secretion may become a determinative factor when the production of recombinant proteins exceeds the secretory capacity of host cells. To simulate the saturated condition, CHO-K1 cells were transiently transfected with a hEPO expression vector. 2- to 3-fold increase in hEPO titre was observed when XBP-1S was ectopically expressed in the hEPO-saturated cells. Our findings suggest that the putative saturation of secretory capacity can be alleviated and protein production can be further enhanced by overexpression of XBP-1S.

Conclusion

XBP-1S could be an ideal gene target to improve productivity of recombinant proteins by modulating cellular secretory pathways.