ENGINEERING CHINESE HAMSTER OVARY CELLS FOR ENHANCED PROTEIN SECRETION

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Chinese hamster ovary (CHO) cells have become the leading production platform for protein-based therapeutics. Whilst their streamlined bioprocessing applications and capacity to perform human-like glycosylation have contributed to their popularity, CHO cells exhibit intrinsic limitations to synthesize, process and secrete large amount of these biological medicines. These limitations often lead to the occurrence of intracellular bottlenecks that impair cell productivities and yield low titers, particularly for molecules that are more challenging to produce[1]. This work aimed to engineer the CHO cell machinery to enhance their biosynthetic capacities and create new cell factories capable of making the medicines of tomorrow.

We based our cell engineering approach on the transcriptional reprogramming of plasma cells (PCs), which are capable of secreting thousands of antibody molecules per second. This project created a new CHO cell host (based on CHO-K1) that overexpressed both BLIMP1 and XBP1s (or CHOBX), two of the main transcription factors driving highly secretory phenotype of PCs. We used the CHOBX cells (and the corresponding CHOK1 control) as an expression platform for producing a recombinant IgG1 and an EPO-Fc fusion protein. Recombinant derived cell lines were characterized in terms of process performance (growth, r-protein production), physiological changes (protein synthesis/secretion rates, organelle content, and metabolism) and expression of recombinant targets (gene/protein expression).

Our CHOBX cells showed a radical change in both culture performance and physiology compared to the controls. Our engineered cell lines decreased cell growth and arrested cell cycle in G1/G0 phase, and in parallel, significantly increased r-protein production and cell-specific productivities. This improvement in culture performance resulted from an increase in overall protein synthesis and secretion rates, as well as an expansion of the endoplasmic reticulum (ER) that facilitated secretion of the r-protein more effectively[2]. Although we did not observed changes in gene/protein expression of the r-proteins (i.e., IgG1 or EPO-Fc), the expression levels of BLIMP1 correlated to the product titres observed in the engineered cell lines. A comprehensive metabolome and transcriptome analyses revealed that CHOBX cells presented an oxidative metabolism (shift in lactate from production to consumption and increased amino acid consumption) and gene upregulation of a series of proteins involved in the secretory pathways. These results indicated that the use of PCs as a model of ‘professional’ secretory cells offered important insights to modify CHO cells for enhanced productivity performance.

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