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Editorial

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Omics-Based CHO Cell Engineering – Entrance into Post-Genomic Era

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Chinese hamster ovary cells (CHO) cells have been the most commonly used mammalian host for the production of therapeutic proteins since the first therapeutic protein from recombinant mammalian cells, tissue plasminogen activator (tPA, Genentech, USA) synthesized in CHO cells, was approved for clinical use in 1987. Despite the availability of various mammalian cell lines (such as BHK, HEK-293, HeLa, NS0, and PerC6), nearly 70% of all recombinant protein therapeutics produced today are made in CHO cells [1]. CHO cells have become the mammalian equivalent to *E. coli* in research and biotechnology today because they are a safe host with a non-replicable property for human pathogenic viruses, offer easy adaptability in a suspension culture, offer functionality with gene amplification systems for constructing high-producing cells, and have a glycosylation pattern similar to those of naive human origin. Recent achievements in CHO cell culturing at levels of more than 10 g/L titer are mainly associated with progression in the development of serum-free media as well as the optimization of feeding strategies [2]. Nevertheless, to meet the ever-escalating levels of demand in today's market, the establishment of high-producing CHO cells with enhanced growth properties in bioreactors under rigorous optimization schemes is of upmost importance. Thus, CHO cell engineering is one of the most promising prospects for the efficient production of therapeutic proteins in a CHO cell culture.

Various cell engineering strategies have been developed to improve the characteristics of CHO cells with regard to cell growth and the production of foreign proteins by increasing the time integral of viable cell concentration (IVCC) and/or enhancing specific protein productivity (q) [3]. IVCC enhancement can be achieved by prolonging the longevity of the culture, increasing the specific growth rate (μ), and improving the maximum viable cell density. Successfully engineered CHO cells can induce cell proliferation at the initial stage and reduce cell death at the end of the culturing process. The introduction of key components related to the regulation of the cell cycle, folding, transport, and secretion into cells can enhance the q of CHO cells, thus increasing protein production. In this strategy, a potential key regulator known as 'direct' cell engineering has been discovered from basic research. However, the result of 'direct' cell engineering is highly clone-specific due to the increased heterogeneity caused by the gene amplification system. It also shows different responses to various environments of CHO cells. Therefore, a strategy to identify the key regulators in individual clones differentially expressed by omics-based approaches can draw the attraction in CHO cell engineering.

Until recently, various tools for omics, such as transcriptomics, proteomics, and metabolomics, have been used widely throughout the process of the development of CHO cell culture including clone selection, cell engineering, culture media, protein purification and characterization [4]. The results of comparative transcriptome analysis based on DNA microarrays and proteomics using two-dimensional gel electrophoresis (2-DE) combined with mass spectrometric analysis (MS) have been successfully applied to CHO cell engineering [3]. The main feature of proteomics in CHO cells is the application of two-dimensional differential in-gel electrophoresis (2D-DIGE) to the CHO cell proteome to overcome the gel-to-gel variation encountered in conventional 2-DE [5,6]. Currently, the combination of the transcriptomic result and proteome changes is generalized to consider post-transcriptional changes [7,8].

One recent area of strong interest in omics-based CHO cell engineering involves the use of metabolomics to chase metabolites related to cell growth and/or protein production. The advantages of qualitative analyses in transcriptomics and proteomics are the easy amplification of samples for DNA/RNA and the availability of specific probe for protein, whereas the analysis of metabolites is limited because they cannot be amplified due to lack of common probes for metabolites. Due to the importance of metabolites as a final product, several reports dealing with metabolomics in CHO cell culture were published recently to identify critical regulators or to chase metabolite flux [9-11]. A report by Chong et al. [10] showed a typical application of metabolomics-based CHO cell engineering using malate dehydrogenase II selected as a key protein. Their study focused on malate accumulation and its introduction to improve cell growth in IVCC. With these advances in metabolomics analysis, applications to identify cellular targets for CHO cell engineering will develop rapidly in the coming years.

Another attractive topic is microRNA (miRNA), short non-coding RNA that regulates global gene expression post-transcriptionally, in CHO cell engineering. Owing to its advantageous features such as multi-target regulation, a simple introduction process, and a reduced metabolic burden, the use of miRNA will increase in omics-based CHO cell engineering [12]. A report by Barron et al. [13] demonstrated in detail, how to find specific miRNA candidates to regulate cell metabolism and use them as targets in CHO cell engineering. Despite the beneficial effects of omics tools in CHO cell engineering, a lack of genomic information pertaining to CHO cells limits their application. Hence, a recent report dealing with the CHO-K1 genomic sequence can lead to a giant step forward for the current sequence-based technology in CHO cell engineering [14]. This finding and a better understanding of the miRNA information in CHO cells through the use of a computational identification method based on the recently published sequence is a good example [15]. Updated public repositories, such as the Chinese hamster genome database (http://www.chogenome.org/) and the CHO gene coexpression database (http://www.cgcdb.org/) will expedite the study of miRNA in CHO cell engineering [16,17].

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