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Glycoengineering for improvement of mammalian glycoprotein production

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In recent decades, the biopharmaceutical industry has established a name in the market with the introduction of therapeutic antibody production using mammalian cell expression systems. The industry has adapted glycoengineering and cell engineering for improving glycosylation profiles for the enhanced production of therapeutic antibodies. Since 2017, the market value for biologics has increased to US$121 billion and is expected to reach US$310 billion by 2023. A major portion of this market consists of recombinant proteins that are produced by mammalian cell expression with post-translational modifications in their glycosylation states. Studies suggest that improved glycosylation profiles can enhance the recombinant properties, such as increased stability and half-life in blood circulation and also decrease immunogenicity. The most commonly used cell line in the expression system is the Chinese hamster ovary cells (CHO). They are used for 70% of the biotherapeutic productions, exclusively monoclonal antibodies (mAbs). CHO cells are being extensively used for glycoprotein production as they have advantages, such as a substantial production rate, suitable for large-scale production on suspensions as well as in chemically-defined and serum-free cultures. These recombinant glycoproteins have human-like glycan sequences that have a higher advantage of being compatible and bioactive with human hosts. The refractory nature of the CHO cells reduces any biosafety risk related to commercial production; this lack of susceptibility defines the fact that many viral genes are not expressed in these CHO cells.

Various gene amplification systems have been devised and used in CHO cells, thereby enhancing higher titre yield, good specificity, and productivity. In 2015, more than 13% of new biologics approved were recombinant proteins produced by CHO cells. Although being advantageous, the CHO cells are incapable of producing some types of human glycosylation, such as α-2,6-sialylation and α-1,3/4-fucosylation but they can produce glycans that do not occur in human cells, such as N-glycolylneuraminic acid (Neu5Gc) and galactose- α-1,3-galactose (α-gal) although present in low levels (less than 0.2% or 2%). CHO cells show a limited ability for gamma-carboxylate recombinant proteins such as clotting factors though they have been achieved by metabolic engineering techniques. A study showed that the co-expression of furin was not shown to allow the production of fully cleaved or activated von Willebrand factor at an industrial scale, thus stating that proteins being produced for proteolytic activities may not always be activated or cleaved when produced by these CHO cells. Over the years, many cell engineering tools, such as clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) and recombinase-mediated cassette exchange (RMCE) technologies have been used to increase titres by optimising selection markers, gene expression, cell growth, and proliferation or protein folding and secretion. Besides, glycoengineering strategies have also been devised to reduce fucosylation or increase sialylation. Furthermore, these techniques will bring a valuable contribution to the advancement of research and development in biotechnology.

Keywords: Glycoproteins, Cell engineering, Glycoengineering, Biotherapeutics, Chinese hamster ovary cells

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