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Bioinformatics and Genetic Modification Methodologies for Generating Recombinant Biopharmaceutical Membrane Proteins in Phytoplankton

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DESCRIPTION

In recent years, there has been a noticeable surge in interest in using microalgae as cell factories to generate biopharmaceutical glycoproteins. Microalgae frequently create biopharmaceutical glycoproteins by post-translational protein N-glycosylation. The N-glycosylation process influences the physicochemical characteristics of biopharmaceutical glycoproteins such as folding, stability, and molecular recognition. As a result, detailed study of the processes and routes of N-glycosylation in microalgae is required to better understand the activity and function of biopharmaceutical glycoproteins. Using sophisticated bioinformatics approaches, researchers examined entire genome databases of several microalgae for the presence and evolutionary connection of suspected Golgi Glycosyltransferases (GTs) and Glycosidases (GSs). The findings revealed that the existence and number of GTs, GSs, and mature N-glycan structures differed depending on the organism. GTs and GSs might have complicated evolutionary links and various activities in different creatures since they have complex phylogenetic trees and conserved motif designs. The microalgal and human N-glycosylation processes were quite different, suggesting that more work will be required to create humanized therapeutic glycoproteins in microalgae. As a result, genetic engineering techniques for five distinct microalgae were presented to remodel N-glycosylation into human-compatible N-glycans. Overall, the bioinformatics analysis and proposed genetic engineering in microalgae are critical for manufacturing functional pharmaceutical proteins with humanized N-glycosylation in the future. Biopharmaceuticals are a class of biological macromolecules synthesised in living cells (bio-factories). Antibodies, enzymes, growth factors, and vaccinations are examples of biopharmaceuticals. At least 60% of the 200 biopharmaceuticals in use today are recombinant proteins. Monoclonal antibodies are being employed in the treatment of cancer, autoimmune illnesses, and inflammatory diseases, whereas plant-derived taliglucerase alfa enzymes are used in the treatment of Gaucher's disease. Understanding biopharmaceutical manufacturing utilising bio-factories is becoming increasingly crucial, with worldwide value anticipated at US$ 140 billion. There are various constraints to commercialising biopharmaceuticals utilising standard expression

techniques. Bacteria (*Escherichia coli*), yeast (e.g., *Saccharomyces cerevisiae* and *Pichia pastoris*), and mammalian cells (Chinese Hamster Ovary (CHO) cells) have historically been used to manufacture biopharmaceuticals. Lacing the complex Post-Translational Modifications (PTMs) in *E. coli* results in the expression of recombinant proteins that form inactive inclusion bodies in the cytoplasm. Although glycoengineered P. pastoris has been extensively developed for the production of monoclonal antibodies, the majority of them were antibody fragments with low yields and poor quality. CHO cells presently dominate biopharmaceutical production, accounting for more than 50% of the industry. Despite their ability to undergo sophisticated glycosylation, CHO cell lines have a high manufacturing cost and are prone to viral and prion contamination. According to reports, recombinant proteins for medicinal usage cost billions of dollars per kilogramme, but industrial proteins cost merely tens of dollars per kilogramme. Because traditional expression methods have limitations, attempts have been made to find, describe, and design alternative, safe, and efficient expression systems for the biosynthesis of functional recombinant proteins.

Alternative expression systems have arisen in microalgae such as *Chlamydomonas reinhardtii*, *Phaeodactylum tricornutum*, *Dunaliella salina*, *Chlorella sp.*, and *Nannochloropsis oculata*. Unlike the heterotrophic systems outlined above, autotrophic photosynthetic microalgae can use sunlight and CO_2 to synthesise carbon-based molecules, making them appealing for biopharmaceutical manufacturing. Microalgae cultivation is a low-cost (approximately $30/gramme fresh algae), safe, and scalable method of manufacturing large quantities of biopharmaceuticals. There have been 29 recombinant biopharmaceutical proteins successfully produced in microalgal chloroplasts to far. Seventeen distinct recombinant proteins were expressed in the nucleus of seven different microalgae, including *Chlorella vulgaris* and *Chlorella sorokiniana*, *Chlorella ellipsoidea*, *Phaeodactylum tricornutum*, and *Nannochloropsis oculata*. These pharmaceutical proteins' function and bioactivity are mostly dependent on appropriate and proper Post-Translational Modifications (PTMs). These expression systems, with their particular protein modification machinery, will, nonetheless, produce medicinal proteins including PTMs. As a result, the most major barrier to manufacturing functioning biopharmaceuticals in non-human systems is obtaining appropriate and proper PTMs for the recombinant proteins. N-glycosylation is a crucial PTM because it affects the biological activity, stability, and half-life of recombinant glycoproteins. As a result, more than half of all biopharmaceutical proteins are N-glycosylated recombinant proteins.

N-glycosylation occurs in eukaryotes *via* the Endoplasmic Reticulum (ER) - Golgi apparatus route. The whole N-glycosylation mechanism in the ER is relatively conserved in most eukaryotes; however, the maturation process in the Golgi apparatus, which is mediated by several glycosyltransferases and glucosidases, is organism-specific. The presence of inappropriate N-glycan structures (e.g., fucose and/or xylose modified N-glycans) may have negative impacts on human health, such as reduced immune response. Understanding the N-glycosylation route in the Golgi apparatus is therefore essential for designing microalgae to produce functional recombinant proteins with humanized glycosylation patterns. Bioinformatics approaches were utilised in this work to examine and compare N-glycosylation routes in the Golgi apparatus and main mature N-glycan structures of different microalgae; the results give a critical overview of protein N-glycosylation processes in distinct microalgal expression systems. The human and microalgal N-glycosylation processes were examined with the objective of establishing genetic engineering methodologies for manufacturing human-compatible N-glycans utilising microalgal expressed systems. As a result, this research lays the groundwork for future microalgae engineering to manufacture functional pharmaceutical glycoproteins.