ENGINEERING OF CHINESE HAMSTER OVARY CELL LIPID METABOLISM RESULTS IN AN EXPANDED ER AND ENHANCED RECOMBINANT BIOTHERAPEUTIC PROTEIN PRODUCTION

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Chinese hamster ovary (CHO) cells are routinely employed for the production of recombinant biotherapeutics such as monoclonal antibodies (mAbs) as they are able to generate efficacious, multi-domain proteins with human-like post-translational modifications. However, the emergence of new, novel format biotherapeutic molecules present new challenges for existing CHO hosts and such proteins are often considered difficult-to-express (DTE). Existing CHO expression systems must therefore be developed and updated to align with arising challenges involved in generation and secretion of mAb and non-mAb products in order to improve productivity and product quality attributes. Recombinant protein production is reliant on a number of cellular processes that are highly dependent on lipid biosynthesis and manipulation but, despite this, cell engineering of lipid metabolism to improve the performance of mammalian expression cell lines has not been investigated. Here we show that a global transcriptional activator of lipid biosynthesis, sterol regulatory binding factor 1 (SREBF1), and an enzyme which catalyses the conversion of saturated fatty acids to monounsaturated fatty acids, stearoyl CoA desaturase (SCD1), can be overexpressed in CHO cells to enhance cellular processes involved in production of recombinant biotherapeutics. The amount of overexpression of these lipid metabolism modifying (LMM) genes is related to the phenotypes observed and, by tuning the overexpression levels of SREBF1 and SCD1, we were able to modify the cellular lipid profile, alter cellular structure and expand the endoplasmic reticulum (ER) of an existing CHO expression host. Ultimately, direct engineering of lipid metabolism machinery through overexpression of these LMM genes resulted in improved productivity of a range of different biotherapeutic products evaluated. Transient and stable expression of a number of model secretory biopharmaceuticals was enhanced between 1.5-9 fold in either SREBF1 or SCD1 engineered CHO host cells as assessed under batch and fed-batch culture.

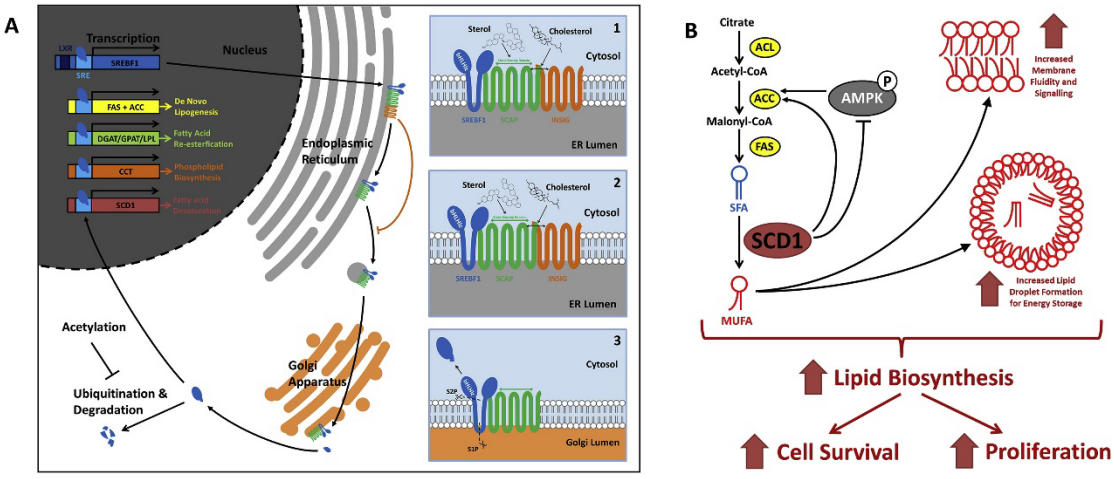

Figure 1: Schematics illustrating the function of selected genes involved in lipid biosynthesis in eukaryotic cells.