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Analysis of molecular mechanisms associated to the adaptation of NS0 myeloma cell line to protein-free medium

de la Luz K.Rashida

Center of Molecular Immunology, Cuba

The NS0 mouse myeloma cell line has become one of the most popular systems for large-scale heterologous protein expression. For reasons of regulatory compliance, cost, batch consistency, downstream processing, and material availability, industrial applications of NS0 has moved towards serum or protein-free medium platforms [Barnes and Sato, 1980]. For serum- or protein-free cultivation, the cell culture medium is often supplemented with lipids (derived from plant or synthetic sources) in addition to other protein supplements. NS0 cells are naturally cholesterol-dependent; not only is their growth greatly facilitated by lipid supplementation, but is also dependent on provision of cholesterol. Different mechanisms underlying a cholesterol-dependent phenotype could include the absence (or mutation) of a gene or a segment of gene along the cholesterol biosynthesis pathway. There could be changes in the expression level of some proteins of the pathway due to gene regulation or other control mechanisms. In addition to the specific gene expression alterations along the cholesterol and lipid metabolism pathways, cholesterol dependence could also be the result of insufficient precursor supply [Spens and Haggstrom, 2005].The molecular mechanisms of host and recombinant NS0 cell lines that could be related to the adaptation to protein-free medium are studied in this work. A quantitative study of proteins with differential expression levels in four conditions (host NS0 cell line adapted and non-adapted to protein-free medium, and a monoclonal antibody (Mab) transfectoma producer NS0 adapted and non-adapted to the same protein-free medium) is reported. The study is based on the use of the combination of two-dimensional electrophoresis and mass spectrometry, and a novel quantitative proteomic approach, isobaric tagging for relative and absolute quantification (iTRAQ). The metabolic study of these cell lines cultured in different nutrient conditions is also reported. Taking into account the proteomic results and metabolic analysis, a possible mechanism related to the adaptation of NS0 cell line to protein-free medium is proposed.