479g Comprehending the Molecular Portraits of Hyper-Producers in Bioprocessing

Gargi Seth, Robin J. Philp, Mugdha Gadgil, Miranda Yap, and Wei-Shou Hu

Critical to the success of bioprocesses is the development of a superior producing cell line. The phenotype of hyper-production is manifestation of a set of complex traits. Little is known about the physiological mechanism or the genetic alteration that confers the high productivity. Understanding the genetic basis of the hyper-production phenotype will greatly enhance our capability to harness the full synthetic potential of biological systems. We employed DNA microarrays to identify gene expression signature associated with high recombinant protein production in mammalian cells. RNA samples of cells from different populations of varying productivity were used for microarray hybridizations. Furthermore, we employed a multiplexed protein quantification strategy for relative measurement of proteins in the high and low producer cells to complement the transcript profiles. The enhanced capability of heterologous protein production likely involves multiple physiological traits, including enhanced energy metabolism and increased machinery for protein secretion. Furthermore, multiple routes may exist to attain a given trait. Adding to the complexity of the analysis is the heterogeneity that exists both between and within cell populations. Statistical analysis was performed taking into consideration such intra-population heterogeneity. Sliding scale of stringency was applied to obtain sets of genes differentially expressed between high and low producing cell populations. Weighting factors were assigned to rank the genes for further exploration. Potential sets of target genes for cell engineering were refined with the aid of physiological insight. From this study, a systematic approach for identifying gene sets that may confer the complex trait of high productivity has evolved. Further application of this strategy may lead to greatly enhanced bioprocess efficiency.