Microbial Cell Factories

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Oral Presentation

The Effects of Expressing Anti-Apoptotic Genes On Mammalian Cell Survival, Physiology, and Protein Production

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Mammalian cell culture is used for the production of proteins for numerous therapeutics, diagnostics, vaccines, and the generation of cells used in biomedical devices. During cell culture, the cells are exposed to numerous external and internal insults such as nutrient depletion, toxin accumulation, viral infections, and external shear stress. These events can sometimes cause the cells to trigger a biochemical cascade called apoptosis or programmed cell death in which the cells actively participate in their own demise. The programmed cell death (PCD) cascade decreases the number of viable cells in a bioreactor and leads to the premature termination of cell culture runs. Cell death may also lower productivity since bioreactor resources must be utilized to replace dead or dying cells. As a result, methodologies that limit the activation of this cascade are desirable and represent one of the most significant applications of metabolic engineering in cell culture. In this way, it may be possible to extend mammalian cell lifetimes and function for multiple biotechnology and bioengineering applications. The engineering of production cell lines to express anti-apoptotic genes may have numerous potential process benefits, including enhanced cell survival, increased protein expression and improved product quality. A number of natural anti-apoptosis genes have been identified in both eucaryotes and viruses and these anti-apoptosis proteins are being used to block or limit the cell death cascade. Unfortunately, these anti-apoptosis proteins can be degraded in culture or otherwise eliminated. In order to increase their activity, some of the anti-apoptosis proteins can be modified to limit degradation in cell systems. In addition, apoptosis pathways include feedback and feedforward loops that lead to amplification of the apoptotic response. Strategies that block cell death at multiple points along the cascade may limit the amplification of these apoptotic signals. As a result, the expression of multiple anti-apoptosis genes has been explored in order to extend cell survival and improve protein production. More recently, the role of bioprocess environments is being examined by investigating survival of cells engineered to include anti-apoptosis genes in different bioreactors with various operating conditions. The use of different bioreactors allows cell culture engineers to examine the relationship between anti-apoptosis engineering and cell physiology and productivity for mammalian cell systems.