DYNAMIC REGULATION OF MITOCHONDRIAL METABOLISM AS A STRATEGY TO MAXIMIZE MAB PRODUCTION IN INDUSTRIAL CHO CELL CULTURES

Kevin J. Ruiz-Márquez, Vanderbilt University
kevin.j.ruiz-marquez@vanderbilt.edu
Sarah A. Sacco, Vanderbilt University
Lauren Kraft, Janssen Research and Development
Michael J. Betenbaugh, Johns Hopkins University
Jamey D. Young, Vanderbilt University

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A significant increase in the production of monoclonal antibodies (mAbs) may be attributed to the increased use of these drugs to treat diseases such as cancer and asthma. To meet market demand, increasing mAb titers and cell-specific productivity (qP) is necessary to achieve a more cost-effective product and, in turn, decrease production costs. Chinese hamster ovary (CHO) host cells are used to produce about 80% of mAbs approved on the market. Our lab has previously shown that high-producing CHO cell lines exhibit elevated metabolic activity in the mitochondrial TCA cycle. In particular, overexpressing an endogenous regulator that promotes mitochondrial metabolism increased mAb titer and qP but also attenuated cell growth compared to the parental line. This study aims to engineer CHO metabolism to promote mitochondrial respiration and TCA cycle flux specifically during the stationary phase, in order to minimize negative impacts on culture growth during the exponential phase. Here, we hypothesized that overexpressing a mitochondrial regulatory gene at the onset of stationary phase would promote maximal qP while enabling the culture to reach high VCDs during growth phase. According to our previous study, if growth attenuation was caused by constitutive activation of mitochondrial metabolism, inducing transgene overexpression during stationary phase should alleviate it. Our work uses an engineered cumate-inducible transposon system to generate stable cell lines by integrating foreign DNA into the CHO genome. A key objective of this study is to demonstrate the application of host cell engineering to increase the metabolic efficiency of mammalian cell lines used in biomanufacturing.