Untangling the mechanism of 3-methyladenine in enhancing the specific productivity: Transcriptome analysis of recombinant Chinese hamster ovary cells treated with 3-methyladenine - DTU Orbit (16/12/2018)

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3-Methyladenine (3-MA) is a chemical additive that enhances the specific productivity ($q_p$) in recombinant Chinese hamster ovary (rCHO) cell lines. Different from its widely known function of inhibiting autophagy, 3-MA has instead shown to increase autophagic flux in various rCHO cell lines. Thus, the mechanism by which 3-MA enhances the $q_p$ requires investigation. To evaluate the effect of 3-MA on transcriptome dynamics in rCHO cells, RNA-seq was performed with Fc-fusion protein–producing rCHO cells treated with 3-MA. By analyzing genes that were differentially expressed following the addition of 3-MA during culture, the role of 3-MA in the biological processes of rCHO cells was identified. One pathway markedly influenced by the addition of 3-MA was the unfolded protein response (UPR). Having a close relationship with autophagy, the UPR reestablishes protein-folding homeostasis under endoplasmic reticulum (ER) stress. The addition of 3-MA increased the expression of key regulators of the UPR, such as $Atf4$, $Ddit3$, and $Creb3l3$, further supporting the idea that the enhancement of ER capacity acts as a key in increasing the $q_p$. Consequently, the downstream effectors of UPR, which include autophagy-promoting genes, were upregulated as well. Hence, the role of 3-MA in increasing UPR pathway could have made a salient contribution to the increased autophagic flux in rCHO cells. Taken together, transcriptome analysis improved the understanding of the role of 3-MA in gene expression dynamics in rCHO cells and its mechanism in enhancing the $q_p$.

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