Chemical Inhibition of Autophagy - DTU Orbit (08/11/2017)

Chemical Inhibition of Autophagy: Examining its Potential to Increase the Specific Productivity of Recombinant CHO Cell Lines

Chinese hamster ovary (CHO) cells activate and undergo apoptosis and autophagy for various environmental stresses. Unlike apoptosis, studies on increasing the production of therapeutic proteins in CHO cells by targeting the autophagy pathway are limited. In order to identify the effects of chemical autophagy inhibitors on the specific productivity (q_p), nine chemical inhibitors that had been reported to target three different phases of autophagy (metformin, dorsomorphin, resveratrol, and SP600125 against initiation and nucleation; 3-MA, wortmannin, and LY294002 against elongation, and chloroquine and bafilomycin A1 against autophagosome fusion) were used to treat three recombinant CHO (rCHO) cell lines: the Fc-fusion protein-producing DG44 (DG44-Fc) and DUKX-B11 (DUKX-Fc) and antibody-producing DG44 (DG44-Ab) cell lines. Among the nine chemical inhibitors tested, 3-MA, dorsomorphin, and SP600125 significantly increased the qp of DG44-Fc and DUKX-Fc. In contrast, for DG44-Ab, only 3-MA significantly increased the qp. The autophagy-inhibiting activity of the nine chemical inhibitors on the rCHO cell lines was evaluated through Western blot analysis and flow cytometry. Unexpectedly, some chemical inhibitors did not exhibit any apparent inhibition activity on autophagy. The chemical inhibitors that enhanced the q_p, 3-MA, dorsomorphin, and SP600125, exhibited instead an increased autophagic flux. Taken all together, the chemical inhibition of autophagy was not effective in increasing the q_p in rCHO cell lines and the positive effect of 3-MA, dorsomorphin, and SP600125 on the qp was not due to the inhibition of autophagy.

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