Improving recombinant bone morphogenetic protein-4 (BMP-4) production by autoregulatory feedback loop removal using BMP receptor-knockout CHO cell lines - DTU Orbit (25/02/2019)

**Improving recombinant bone morphogenetic protein-4 (BMP-4) production by autoregulatory feedback loop removal using BMP receptor-knockout CHO cell lines**

A Chinese hamster ovary (CHO) cell line producing recombinant human bone morphogenetic protein-4 (rhBMP-4) (CHO-BMP-4), which expresses essential components of BMP signal transduction, underwent autocrine BMP-4 signaling. RNA-seq analysis on CHO host cells (DG44) treated with rhBMP-4 (20µg/mL) suggested that rhBMP-4 induced signaling in CHO cells could be a critical factor in limiting rhBMP-4 production and should be removed to improve rhBMP-4 production in recombinant CHO (rCHO) cells. The inhibition of autocrine BMP signaling in CHO-BMP-4 cells by the addition of LDN-193189, a chemical inhibitor of BMP receptor type I, significantly increased the mRNA expression levels of rhBMP-4. To establish BMP signaling-free host cells, a BMP receptor, the BMPRIA or BMPRII gene in DG44 cells, was knocked out using CRISPR/Cas9 gene-editing technology. Using three different knockout (KO) host cell lines as well as a DG44 wild-type (wt) cell line, rCHO cell clones producing rhBMP-4 were generated by a stepwise selection with increasing methotrexate concentrations. KO-derived clones showed a significantly higher maximum rhBMP-4 concentration than wt-derived clones in both batch and fed-batch cultures. Unlike wt-derived clones, KO-derived cell clones were able to produce higher amounts of hBMP-4 transcripts and proteins in the stationary phase of growth and did not experience growth inhibition induced by rhBMP-4. The mean maximum rhBMP-4 concentration of KO host-derived clones was approximately 2.4-fold higher than that of wt-derived clones (P <0.05). Taken together, the disruption of BMP signaling in CHO cells by knocking out the BMP receptor significantly improved rhBMP-4 production.

**General information**

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