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Adaptation of CHO metabolism to long term phosphate limitation

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Phosphate is an important component of abundant intracellular molecules like RNA, is a critical component of energy metabolism and is involved in substrate phosphorylation in cellular metabolism and signaling. Inorganic phosphate (P_i) is transported through specialized transporter proteins and limitation in the availability of phosphate in the growth medium limits cell growth. P_i concentrations have been reported to regulate the rates of aerobic glycolysis and oxygen uptake. Thus it is expected that cellular metabolism will adapt to long term phosphate restriction. Since complete phosphate deprivation will result in lack of growth, such an adaptation needs to be carried out under conditions where P_i concentration are kept at restricted levels while still allowing some cell growth.

We have evolved CHO cells under phosphate limited conditions over several weeks using in-situ slow-release of P_i. As a control, cells were also passaged in parallel in the absence of phosphate limitation. Surprisingly, adaptation to phosphate limitation resulted in selection of cells able to reach higher peak cell densities in batch culture. This increase in growth potential is accompanied by changes in energy metabolism reminiscent of the Warburg effect. Cells selected under phosphate limitation also have an altered ability to tolerate deprivation of glucose and glutamine in the medium. Adaptation of cells to long term glucose limitation does not result in similar changes in metabolism indicating these changes are specific to adaptation to phosphate limitation, and not a generic stress response.