Suppression of apoptosis in perfusion culture of Myeloma NS0 cells enhances cell growth but reduces antibody productivity

Abstract

A spin filter perfusion systems was used to achieve a high cell density culture for two NS0 cell lines in 2 litres bioreactors. One cell line is transfected with the bcl-2 gene (NS0 Bcl-2) encodes the 'anti-apoptotic' human Bcl-2 protein and the other cell line (NS0 Control) with a blank vector. The runs started as batch cultures for two days and were perfused with fresh medium at 0.5 volumes per day (day-1) for 4 days, increasing gradually to 2 day-1 at day 7. The increase of the viable cell density of Bcl-2 cell line was far greater than the control cell line, although they were perfused with the same amount of medium. At the end of the period of each perfusion rate, the viable cell densities of Bcl-2 culture were 30%, 120%, 160% and 220% higher than its control cell line corresponding values. Overall, there was a roughly 9 fold increase in viable cell density from the inoculum for the control culture, but almost a 30 fold increase for the Bcl-2 culture. The mode of cell death in the control culture was initially predominantly by necrosis (viability higher than 80%), but apoptotic cell death became more significant after day 8 of the culture. Cell death in the Bcl-2 culture was almost entirely by necrosis, although it remained at a very low level (less than 5%) to the termination time. The cell cycle distributions for both cell lines were very much similar indicating they have a similar doubling time and G1 to S progression rate. Interestingly, the Bcl-2 cultures exhibited reduced antibody specific production rate with increasing viable cell number and time. The volumetric production rate was, however, similar in both cultures. Bcl-2 as an anti-death protein allowed cells to survive and thus divide to higher cell densities without the need for additional nutrients. Most of the cellular energy in a producer cell line is used for biomass production rather than for antibody production, as was the case with the control cell line. © 2004 Kluwer Academic Publishers.

Keyword: Apoptosis; bcl-2; Bioreactor; Monoclonal antibodies; NS0 myeloma cells; Perfusion culture