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THE DIFFERENTIAL POLARIZABILITY OF CHO CELLS CAN BE USED TO MONITOR CHANGES IN METABOLISM

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The continuous monitoring of cell growth and viability is an integral part of biopharmaceutical production. Measurements of changes in the polarizability of individual cells can identify early emerging sub-populations of apoptotic cells in a dielectrophoretic (DEP) cytometer designed at the University of Manitoba. In this instrument the trajectory of individual cells was tracked as they passed through a bank of electrodes (sensitivity: 0.1 μm; rate: 5 cells per second) designed to differentially perturb the cells according to their polarizability. This perturbation was recorded as a force index (FI), which was related to the electrical displacement of the cells. Using this principle we were able to show the changing profile of Mab-secreting CHO cells from samples taken from a bioreactor during the later stages of culture. These sub-populations could be correlated with the fluorescent markers of apoptosis analyzed in a flow cytometer with fluorescent detection (Guava). The DEP cytometer can be compared to capacitance measurements of a cell population in a bioreactor using commercially available sterilizable probes (e.g. Aber). However, these probes measure an average change in the population as opposed to the analysis of single cells, which allows greater insight into the metabolic changes of sub-populations. Cytometric analysis of single cells enables low density sub-populations to be identified that might otherwise be masked by the overall response of the whole cell population. We have extended our analysis of cultures to the induction of apoptosis by alternative means such as nutrient starvation or the addition of the anti-metabolites, oligomycin, and staurosporine. In each case, discrete cell sub-populations were identified as cells passed through the various stages of apoptosis. These sub-population could be correlated with alternative measurements by fluorescent markers, a cell population-based capacitance probe and trypan blue exclusion. In the batch and the starvation culture the early changes in the measured FI of cells correlated with the Annexin V fluorescent assay, which was associated with early phase apoptosis. For the oligomycin and staurosporine cultures changes in the FI could be correlated to modifications in the mitochondrial metabolism linked with early apoptosis for both inducers. Overall our results showed that the DEP cytometer offers a sensitive method of monitoring the metabolic state of CHO cells during a bioreactor run or following treatment with a metabolic inhibitor using single cell analysis.