QUANTIFICATION OF GENOMIC DNA REPAIR CAPABILITIES IN CHO AND IDENTIFICATION OF GENES IMPACTING GENOMIC STABILITY

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Genomic instability in CHO cells poses a challenge for biopharmaceutical production because it is associated with decline of productivity, product quality, and culture viability. Chromosome rearrangements are particularly problematic since these can decrease or eliminate transgene expression. These are caused by DNA double-strand breaks (DSBs) that are not adequately repaired by the cell, presumably due to deficiencies in DNA repair genes. In this study we have conducted a genome-wide bioinformatic analysis of single-nucleotide variants (SNVs) in DNA-repair genes in the CHO genome. We implement a reporter system in CHO cells that facilitates the quantification of the cell's capability to repair DSBs in genomic DNA. This provides a DNA stability assessment that is superior to previous assays since these would merely read out the capability to repair artificial plasmids. By utilizing this genomic DSB repair assay, we can quantify DNA stability in standard CHO cells, various DNA repair-deficient CHO mutants, as well as in primary Chinese hamster cells. Finally, we explore how by targeting defective candidate genes from our bioinformatic analysis, this assay can be used to engineer CHO cell lines with increased genomic stability.