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MANIPULATION AND EXPLOITATION OF MICRORNAs FOR ENHANCED RECOMBINANT PROTEIN PRODUCTION IN CHO CELLS

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MicroRNAs (miRNAs) are regulatory non-coding RNA molecules around 22 nucleotides in length which control gene expression via translational repression of their cognate messenger RNA(s) (mRNAs). Regulating as much as 30% of the genome, miRNAs exhibit a high level of promiscuity as a single miRNA is able to target multiple mRNA targets and a single mRNA transcript can be under the regulation of several miRNAs. Thus, global regulation and control of almost all cellular processes and pathways is heavily dependent on the level and activity of miRNAs. This work has set out to investigate the biology of miRNAs in the industrially relevant Chinese Hamster Ovary (CHO) cell line and to develop the findings from these studies to augment the phenotype(s) of recombinant CHO cell lines. To date, we have shown that genetically engineered miRNA sponges for the 'knockdown' of specific miRNAs can target endogenous miRNA knockdown as determined via subsequent repression of an eGFP reporter. MiRNA spongeshave also been shown to augment the production of recombinant protein upon transfection of different recombinant IgG producing GS-CHOK1SV cell lines. In addition, cellular engineering to enable specific miRNA over-expression hasbeen shown to lead to phenotypic changes beneficial to the cell such as improved cell viability and longevity. By manipulating miRNAs to control gene expression in recombinant cell lines the quality and quantity of recombinant proteins may potentially be enhanced with no further translational burden placed upon the cell. Here we describe the effects of the manipulation (up/down-regulation) of specific miRNAs on industrially relevant host and recombinant CHOK1SV and derivative cell lines, reporting the effects and potential mechanisms by which these effects are elicited.