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Genome-wide RNAi screen for improved functional expression of recombinant proteins from HEK 293 cells

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Genome-scale RNA interference screen identifies key pathways and genes for improving recombinant protein production in mammalian cells

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For the purpose of improving recombinant protein production from mammalian cells, an unbiased, high-throughput whole-genome RNA interference screen was conducted using human embryonic kidney 293 (HEK 293) cells expressing firefly luciferase. 21,585 human genes were individually silenced with three different siRNAs for each gene. 56 genes whose silencing caused the greatest improvement in the luciferase expression were found to be part of several different pathways that are associated with spliceosome formation/mRNA processing, transcription, metabolic process, transport and protein folding. 10 genes whose downregulation significantly enhanced the protein expression were validated by their silencing effect on four different recombinant proteins. Among the validated genes, the gene encoding the ornithine decarboxylase antizyme1- was selected for detailed investigation, since its silencing improved the reporter protein production without affecting cell viability. Silencing this gene caused the increase of the ornithine decarboxylase enzyme and the cellular levels of putrescine and spermidine, and indicated that increased cellular polyamines enhanced luciferase expression without affecting its transcription. The study shows that this gene is a novel target for improving expression of recombinant proteins. The genome-scale screening demonstrated in this work can establish the foundation for targeted design of an efficient mammalian cell platform for different biotechnological applications.