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The engineering of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR-associated proteins (Cas) continues to expand the toolkit available for genome editing, reprogramming gene regulation, genome visualization, and epigenetic studies of living organisms. In this review the emerging design principles on the use of nuclease-deficient CRISPR-based reprogramming of gene expression will be presented. The review will focus on the designs implemented in yeast both at the level of CRISPR proteins and gRNA, but will lend due credits to the seminal studies performed in other species where relevant. In addition to design principles, this review also highlights applications benefitting from the use of CRISPR-mediated transcriptional regulation and discuss the future directions to further expand the toolkit for nuclease-deficient reprogramming of genomes. As such this review should be of general interest for experimentalists to get familiarised with the parameters underlying the power of reprogramming genomic functions by use of nuclease-deficient CRISPR technologies.

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