CRISPR/Cas9 screen for functional MYC binding sites reveals MYC-dependent vulnerabilities in K562 cells

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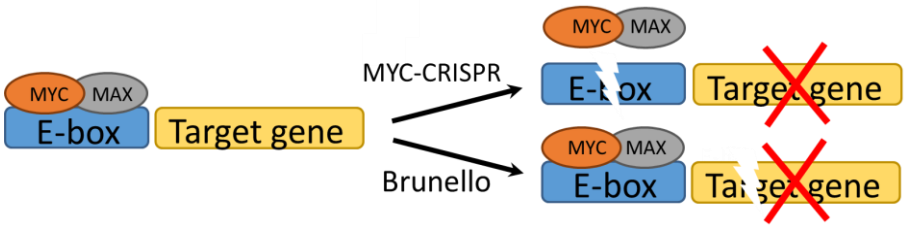
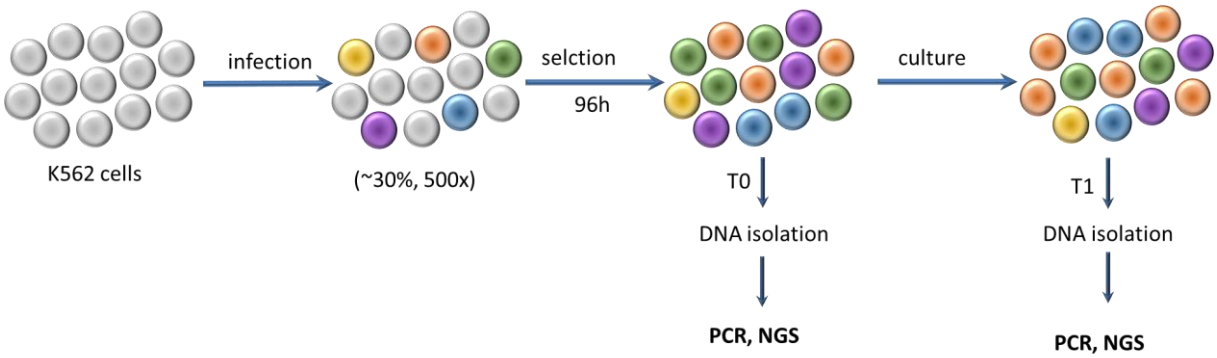
MYC is an oncogene with a well-documented essential role in the pathogenesis and maintenance of several types of cancer. As a transcription factor, MYC binds to specific E-box sequences in the genome to regulate expression of adjacent genes. It is known that MYC can regulate around 15% of genes associated with apoptosis, proliferation, metabolism, ribosomes and mitochondria biosynthesis and others. However, there is no universal set of MYC targets, as many of them are cell type- and developmental stage-specific. To date a comprehensive analysis of direct MYC targets with essential roles in different types of cancer is missing. Here we used CRISPR/Cas9 to destroy E-box sequences and perform a genome-wide screen to identify functional MYC binding sites and corresponding target genes essential for growth of MYC-addicted cancer cells.



Based on publicly available MYC-ChIP-Seq data in different cancer types we designed a MYC-CRISPR sgRNA library. We performed this analysis in chronic myelogenous leukemia (CML) cells, which is an example of MYC-dependent tumor. We conducted a high-throughput screen in K562 cells with the MYC-CRISPR library to disrupt E-boxes and in parallel with the Brunello library to knock down protein-coding genes.



As a result, we identified 152 E-boxes essential for growth of K562 cells, for 45% of them we found adjacent genes significantly depleted in Brunello library as well. Moreover, 25% of these genes were well-known MYC targets. Gene ontology analysis revealed that the genes localized near essential E-boxes were involved in processes crucial to cancer cell growth such as RNA and DNA biosynthesis, ribosome biogenesis, cell migration, translation and metabolism. Moreover, we have proven efficient E-box disruption which affects adjacent genes expression and decreased K562 cells growth. Our results provide novel insights into MYC dependency in CML.