DEFINING THE ESSENTIAL DOWNSTREAM TARGETS OF THE *MYC* PROTO-ONCOGENE

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The transcription factor *Myc* is a central hub in the growth regulatory network and one of the most frequently deregulated genes in cancer. Genomic studies revealed that *Myc* affects about 15% of all human genes, whereby many of its target genes are implicated in growth-related processes. Excess *Myc* activity promotes tumorigenesis, while experimental reduction of *Myc* levels prolongs the lifespan of flies and mice. Reduction of *Myc* activity also impairs malignant growth in mouse models of common cancers, thus qualifying *Myc* as a prime target for the development of anticancer therapeutics. However, transcription factors like *Myc* are difficult drug targets because Protein-DNA interactions do not rely on enzymatic activity that could be abolished by competitive-binding of small molecule inhibitors. Identification of critical *Myc* targets that are more amenable for drug development could be an alternative strategy for the development of highly specific drugs for the treatment of cancer and age-related diseases, but due to the immense number of *Myc*-regulated genes it has yet been impossible to make significant progress in this area. However, the game seems to change as the recent invention of sophisticated genome-editing tools now enables us to address this problem in a systematic manner.

To reduce the pool of target genes to a manageable size, we used a combination of different genomic methods to identify conserved target genes that are regulated by *Myc* irrespective of species or cell type. This analysis revealed 126 *Myc* targets that are responsive to *Myc* depletion and bound by *Myc* in both human and fly cells. To evaluate the requirement of these targets for cellular growth and organimal lifespan in the fly model *(Drosophila melanogaster)*, we use CrispR/*Cas9*-mediated genome editing to mutate the *Myc* binding sites in the regulatory regions of the target genes. Cutting the regulatory nodes instead of targeting the gene itself allows to directly address the requirement of specific regulatory relationships without affecting basal expression levels that might be important for viability or other cellular processes. Because of the fast generation time and easy maintenance, the fly model allows time- and cost-effective *in vivo* screening of a large number of *Myc* target genes in time. The suitability of the shortlisted target genes for drug development will then be validated in more complex animal models and/or human cell or organ culture models of common cancers.

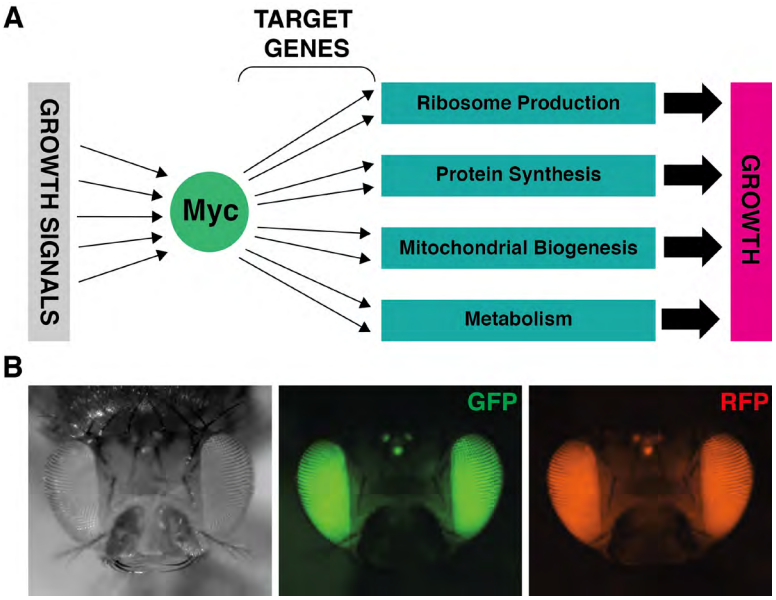

Figure: A) Schematic representation of the Myc*-regulated network. The* Myc *proto-oncogene integrates various growth signals and modulates the expression of a plethora of target genes involved in growth-related processes. B) Micrographs of a gene-edited fly that expresses* Cas9 *(marked by GFP), and also carries a RFP-based marker that has been integrated into the regulatory region of the* pitchoune *gene, a well known* Myc *target whose function is only poorly understood.*

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