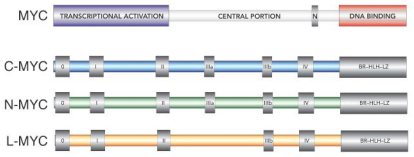
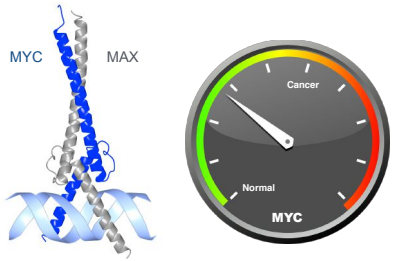
MYC ~ The Emperor of All Oncogenes

THE TANSEY LABORATORY

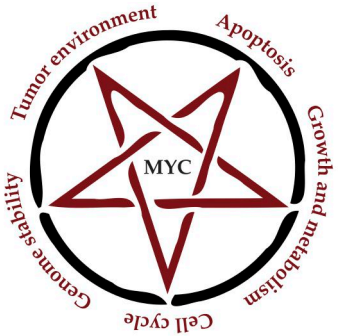
The MYC family



The MYC family of oncoproteins are overexpressed in the majority of cancers and contribute to an estimated 100,000 cancer deaths in the USA every year.

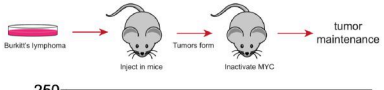


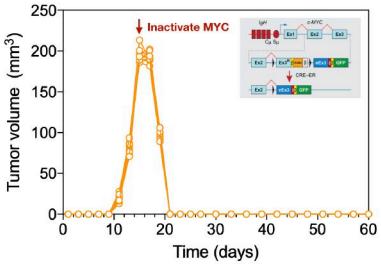
MYC proteins function as transcriptional regulators. They heterodimerize with MAX to bind DNA elements in target genes, and recruit effectors to modulate gene activity. When MYC is overexpressed, its oncogenic properties are unleashed.



MYC proteins control the expression of thousands of genes linked to tumorigenesis. Cells overexpressing MYC are fundamentally reprogramed at all levels to become cancerous. It is likely that cells cannot initiate or maintain the malignant state without the involvement of MYC.

The challenge





MYC proteins are highly validated anti-cancer targets. In preclinical mouse models, like the one we established (above), inactivating MYC in the context of a pre-formed cancer promotes rapid tumor regression.

But MYC is widely considered to be undruggable. It has no small "pockets" suitable for pharmacological inhibition. MAX would be the best way to target MYC, but that has proved impossible. So one of the best anti-cancer targets remains untargeted…

Did you know?

That a Bulgarian chicken featured prominently in the discovery of MYC oncogenes?

That a PubMed search for "MYC" will recover ~38,000 papers?

That, on average, six new MYC publications appear each day?

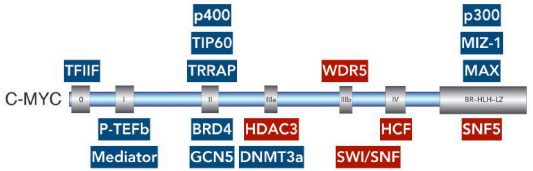
That MYC is one of the four famous Yamanaka factors?

That c-MYC uses both an ATG and a CTG as start codons?

That you can spell "ethylenediaminetetraacetic acid" from the letters in c-MYC? And still have lots of letters left over?

That normal cells have a few thousand molecules of MYC, but that cancer cells can have up to a million? Above 25,000 is considered oncogenic.

The solution

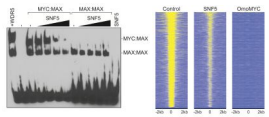


MYC interacts with a lot of things. Some of these interactions regulate MYC itself. Others are used by MYC to do its dirty work. Quite a few of these interactions occur through small conserved sequence motifs known as MYC boxes. If something interacts with a sequence in MYC that is conserved, it must be important.

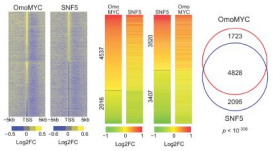
We believe that studying MYC co-factors is the key to understanding MYC and finding ways to thwart its function in cancer. Our goal is to learn as much as we can about the co-factors (highlighted in red) that impact MYC in cancer cells, and use this information to either know if MYC is playing malignant a role in those cells, or to open up a new therapeutic approach.

SWI/SNF

MYC interacts with multiple subunits of the SWI/SNF chromatin remodeling complex. What is the purpose of these interactions?



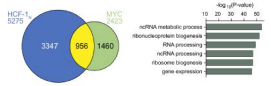
We recently found that SNF5 binds to MYC to inhibit the ability of MYC:MAX dimers to bind DNA. This is important because SNF5 is lost in rhabdoid tumors (RT), which are rare and aggressive pediatric cancers.



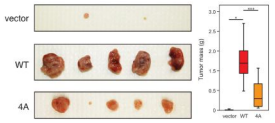
Putting SNF5 back into an RT cell displaces MYC from chromatin and mimics the impact of MYC inhibition. These results show that MYC regulates the tumorigenic transcriptional program in rhabdoid tumor cells.

HCF

MYC interacts with HCF, a scaffold for the assembly of multiple epigenetic regulatory complexes. MYC and HCF colocalize on chromatin, but what does this mean?

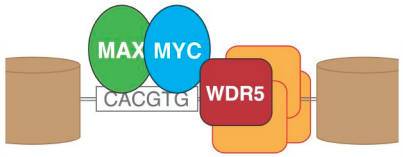


One of the things that makes MYC such a potent oncogene is how it connects increased cell division with increased protein synthesis. HCF appears to be dedicated to helping MYC drive cancer cells to accumulate biomass.

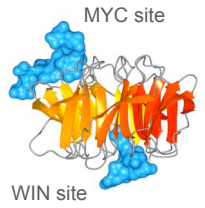


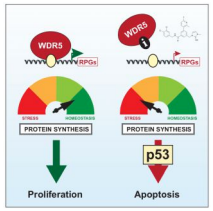
HCF binds to MYC through a four amino acid peptide motif within MYC box IV. Mutations in MYC that disable interaction with HCF decrease MYC-driven tumors in mice. The small interaction surface between MYC and HCF make this an attractive surface for drug discovery initiatives.

WDR5



WDR5 is a co-factor that facilitates the recruitment of MYC to key target genes in the context of chromatin. Mutations in MYC that disable interaction with WDR5 prevent it from binding chromatin and disable its tumorigenic potential in mice. We know precisely how MYC binds to WDR5. Can this interface be targeted for anti-cancer therapies?





We collaborate with the Fesik laboratory to discover and validate small molecule inhibitors against two sites on WDR5: the site that binds MYC and the so-called "WIN" site that's important for survival of multiple cancer types. WIN site inhibitors have a unique mechanism of action.

Our team

Thanks!

NIH National Cancer Institute
Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation
Alex's Lemonade Stand Foundation for Childhood Cancer
NExT NCI Experimental Therapeutics Program
CSHL at the leading edge