

Title: Cross Kingdom analysis of data within the GeneLab repository identifies a potential conserved response of life to the stress associated with spaceflight

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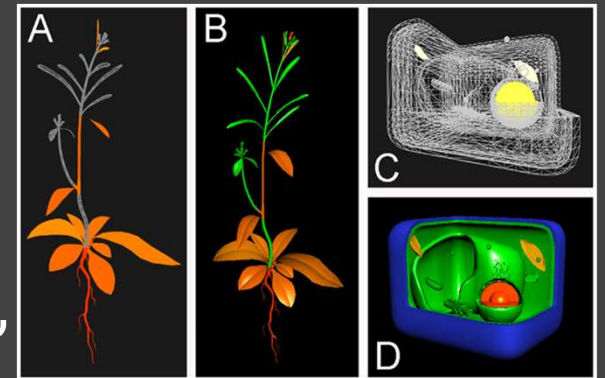
Abstract

It is important to determine the health risks and potential survival for astronauts associated with long-term space missions. This entails not only understanding the impact the space environment will have on humans, but also how it will affect other organisms needed for humans to survive in space such as plants. In addition, it has been reported in the literature that hundreds of genes seem to be conserved and/or transferred between different organisms from bacteria, archaea, fungi, microorganisms, and plants to animals. Since space travel involves humans in a closed environment over a long period of time, we hypothesize that potential conserved biological factors will occur between the different organisms in that environment possibly due to transfer of genes. Determining the conserved factors that are commonly being regulated in space can shed insight into possible universal master regulators and also determine the symbiotic relationship between the organisms in space. Utilizing NASA's GeneLab Data Repository (a rapidly expanding, curated clustering of spaceflight-related 'omics-level datasets for all organisms), we were able to uncover a novel pathway and factors that were commonly shared between humans, mice, plants, *C. Elegans*, and *Drosophila*. Through ChIP-Seq enrichment analysis techniques utilizing various GeneLab datasets from each species that were flown in space, we found the following factors to be conserved across all species: oxidative stress, DNA damage (through GABPA/NRFs and NFY), SIX5, GTF2B and glutamine synthetase. Such commonalities would likely reflect the effects of factors such as microgravity and the increased radiation exposure inherent in spaceflight on basic physical processes shared by all biological systems at the cellular level. Differences between organismal responses revealed by GeneLab's data should also help understand the unique reactions to life in space that arise from the very different lifestyles of microbes, animals and plants.

GeneLab Cross Species



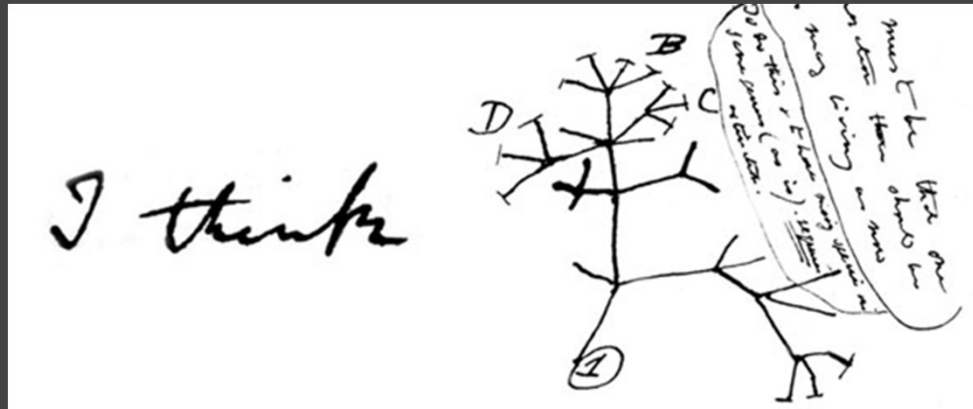
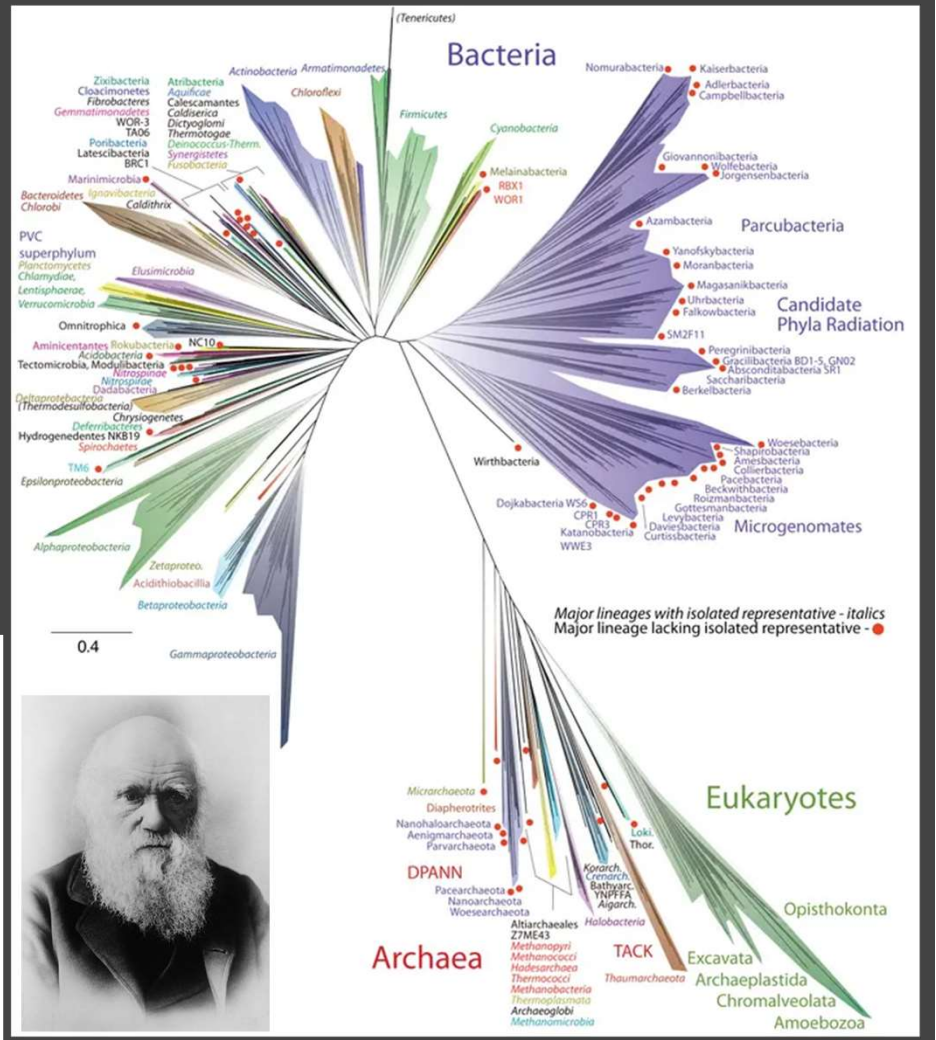
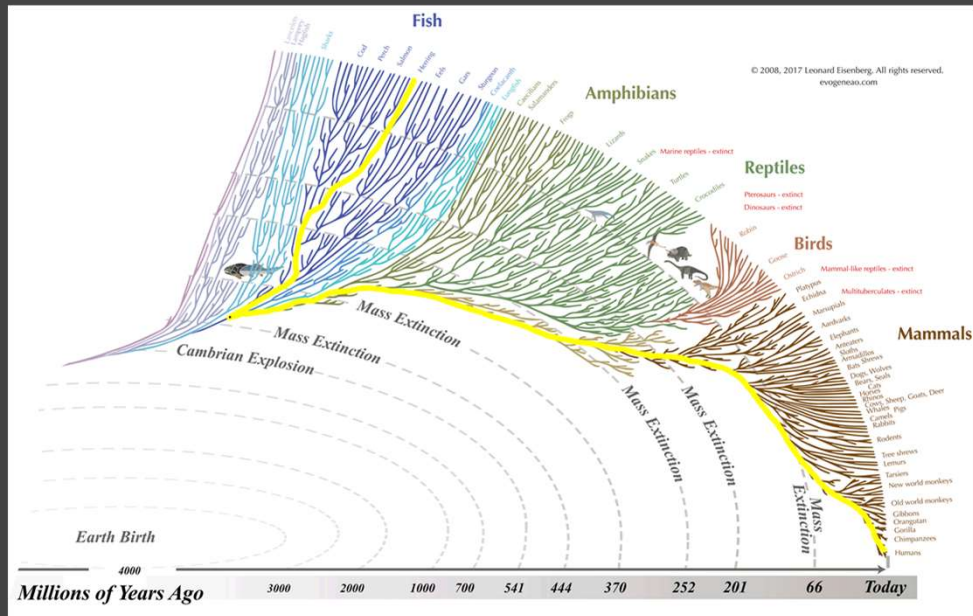
Richard Barker
Neil McKenna,
Eric Weitz,
Joshua Vandenbrink,
Willian da Silveira,
Reinsch, Sigrid S,
Beheshti, Afshin,
Sylvain Costes
Simon Gilroy



The Stresses of life on the ISS

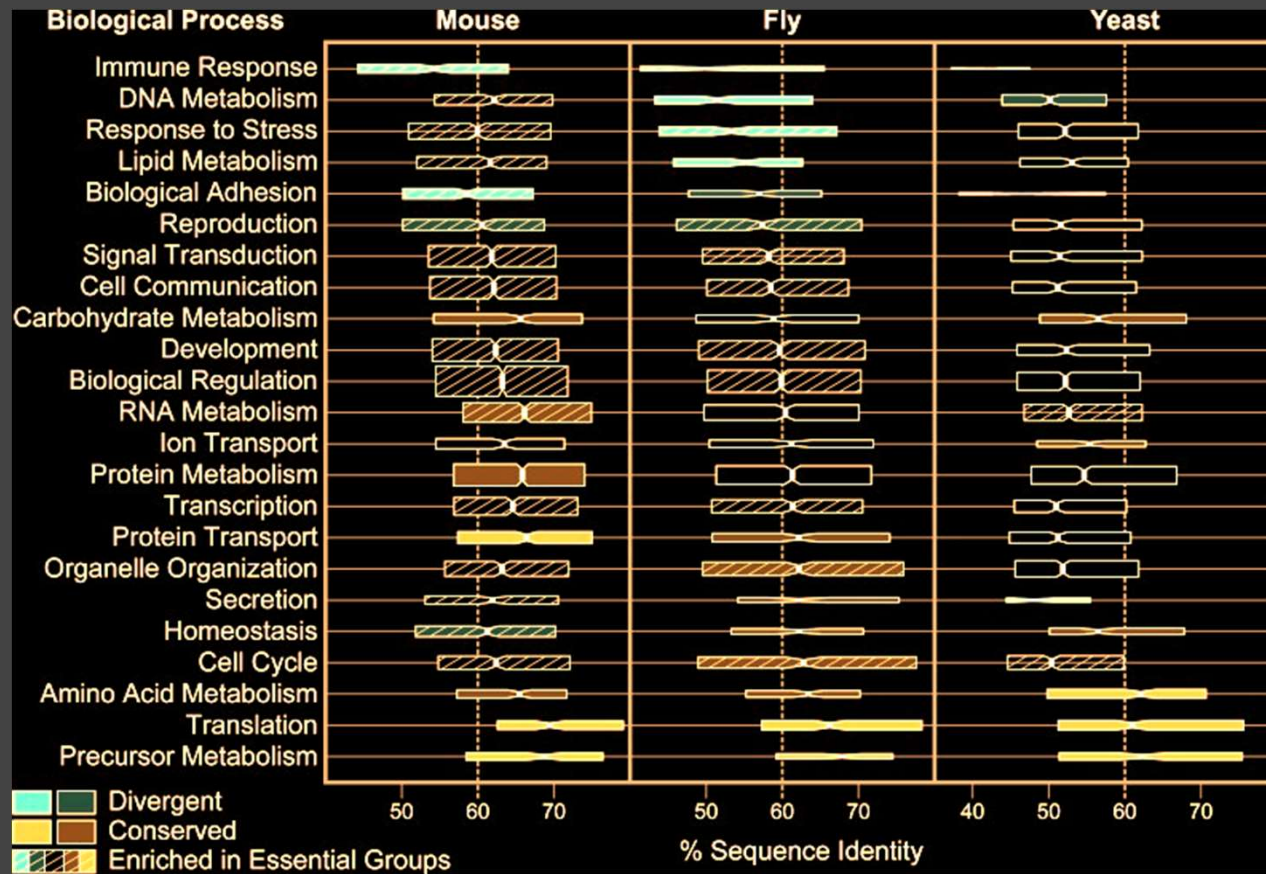
- Increased Ionizing Radiation
- Poor Gas Mixing (Reduced convection reducing oxygen)
- Microgravity
- Hypergravity during launch





OrthoDB

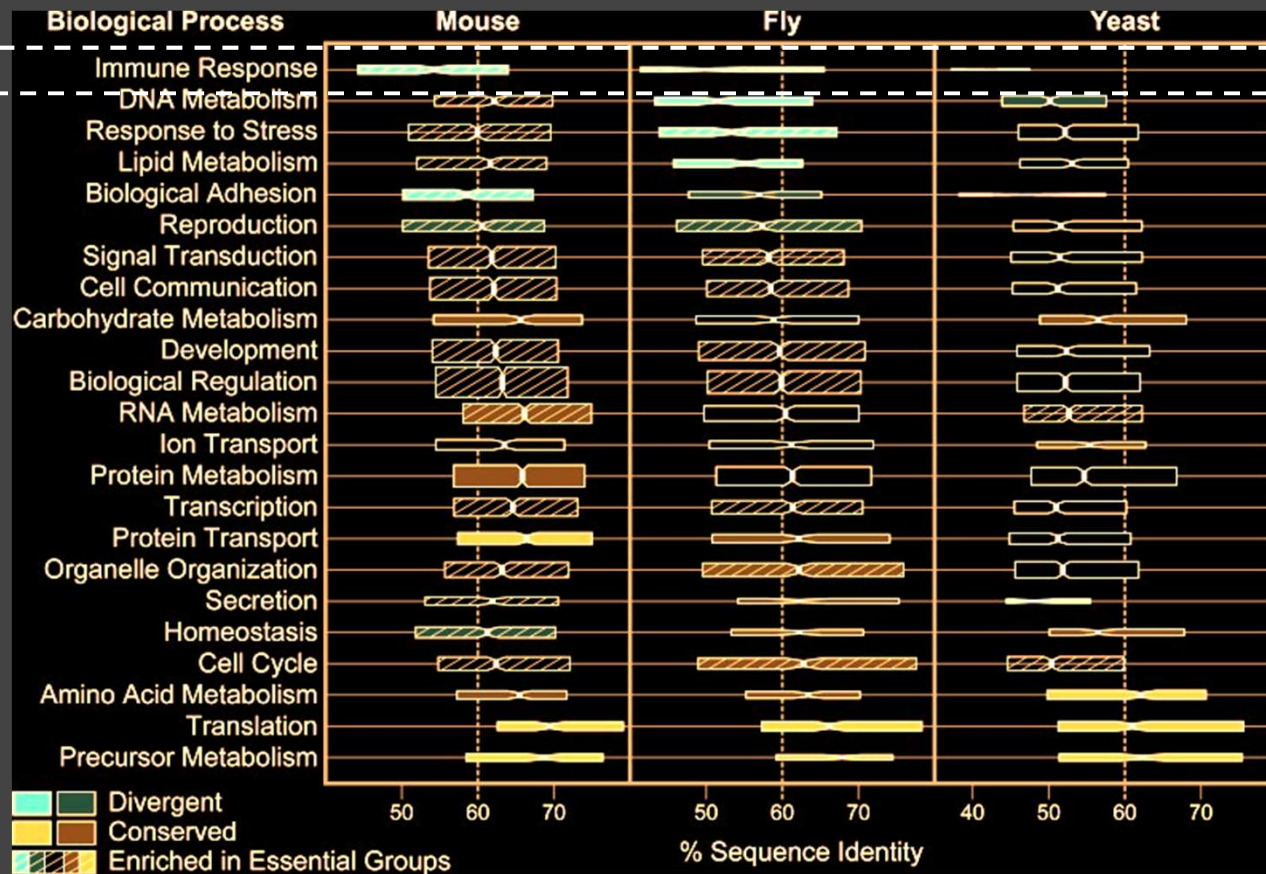
[Waterhouse](#)
et al., (2013)



OrthoDB

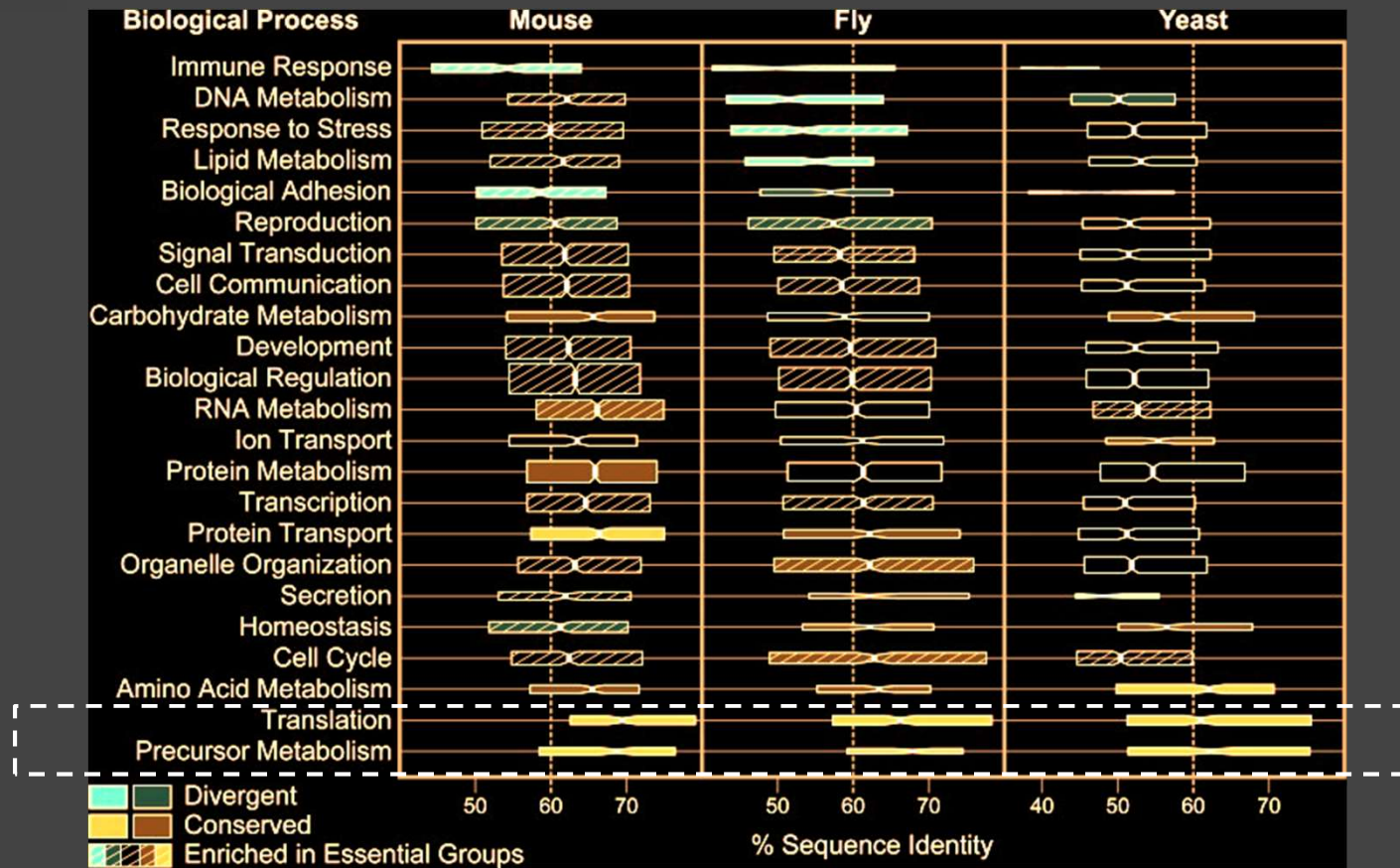
Some genes evolve faster

[Waterhouse et al., \(2013\)](#)



OrthoDB Some functions are more conserved

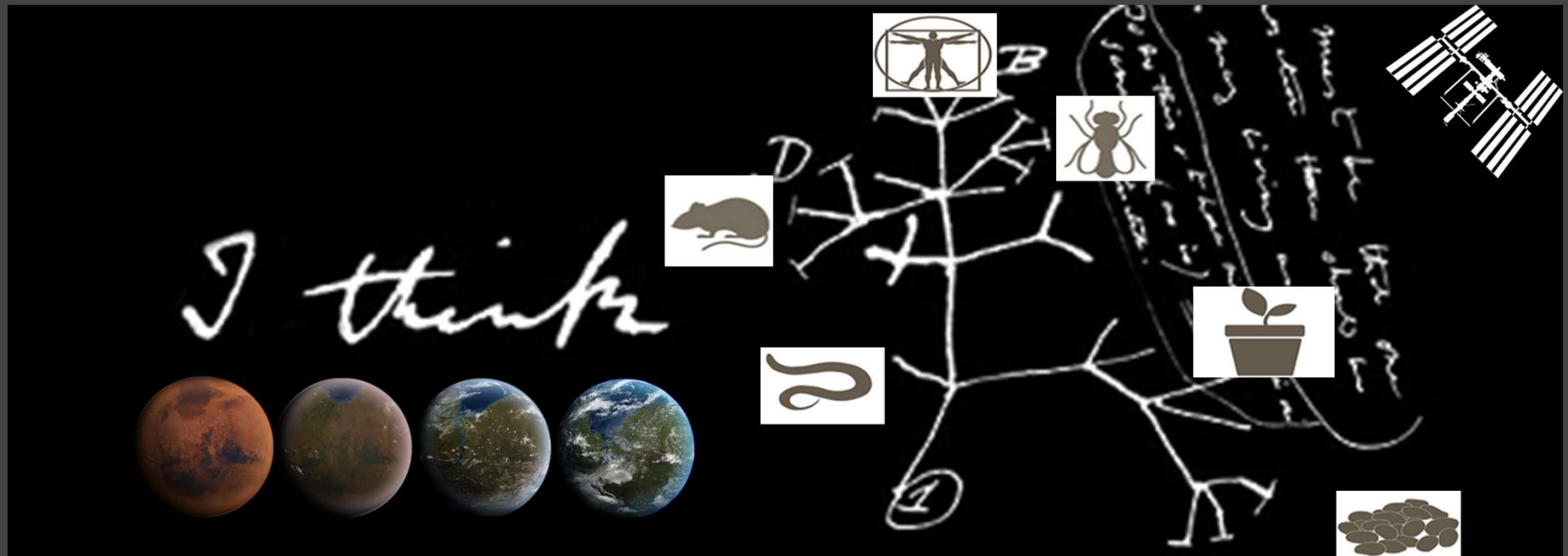
[Waterhouse et al., \(2013\)](#)












GeneLab

Open Science for Life in Space



GLDS datasets used for preliminary analysis

GLDS-172	Dynamic gene expression response to altered gravity in human T cells (parabolic flight).	
GLDS-188	Dynamic gene expression response to altered gravity in human T cells (sounding rocket flight).	
GLDS-021	Effects of spaceflight on murine skeletal muscle gene expression (ISS).	
GLDS-195	Effects of 21 days of bedrest on human skeletal muscle gene expression.	
GLDS-003	<i>Drosophila melanogaster</i> gene expression changes after spaceflight (Shuttle).	
GLDS-042	Gene expression changes in space flown <i>C.elegans</i> exposed to a long period of microgravity.	
GLDS-111	Global gene expression analysis highlights microgravity sensitive key genes in soleus and EDL of 30 days space flown mice.	
GLDS-037	Variation in the transcriptome of different ecotypes of <i>Arabidopsis thaliana</i> reveals signatures of oxidative stress in plant responses to spaceflight.	
GLDS-251	Vandenbink et al., <i>Arabidopsis</i> in a centrifuge on orbit.	

Lots of spaceflight related stresses

GLDS	Species	Assay Summary	Gravity Summary	Radiation Summary
GLDS3	<i>Drosophila melanogaster</i>	Transcription Profiling	Microgravity	Cosmic radiation
GLDS21	<i>Mus musculus</i>	Transcription Profiling	Microgravity	Cosmic radiation
GLDS37	<i>Arabidopsis thaliana</i>	Transcription Profiling	Microgravity	Cosmic radiation
GLDS42	<i>Caenorhabditis elegans</i>	Transcription Profiling	Microgravity	Cosmic radiation
GLDS111	<i>Mus musculus</i>	Transcription Profiling	Microgravity	Cosmic radiation
GLDS172	<i>Homo sapiens</i>	Transcriptomics	Terrestrial	Terrestrial
GLDS188	<i>Homo sapiens</i>	Transcriptomics	Terrestrial / Hypergravity	Terrestrial
GLDS195	<i>Homo sapiens</i>	Transcriptomics	Terrestrial	Terrestrial
GLDS251	<i>Arabidopsis thaliana</i>	Transcription Profiling	Microgravity 1G with transition to Microgravity	Cosmic radiation during centrifugation

GLDS	Species	Growth environment	Vehicle	Organ or cell type
GLDS3	<i>Drosophila melanogaster</i>	Shuttle	3rd instar	Female flies
GLDS21	<i>Mus musculus</i>	ISS	skeletal muscle	Hind limb loading
GLDS37	<i>Arabidopsis thaliana</i>	ISS	Etiolated seedling	BRIC
GLDS42	<i>Caenorhabditis elegans</i>	ISS	Whole Worm	Worm
GLDS111	<i>Mus musculus</i>	BION	mouse soleus and extensor digitorum longus	Dish
GLDS172	<i>Homo sapiens</i>	Parabolic flight	Human T-cells	Nutrimix bags in plastic housing
GLDS188	<i>Homo sapiens</i>	Sounding rocket	Human T-cells	Nutrimix bags in plastic housing
GLDS195	<i>Homo sapiens</i>	Terrestrial	Human skeletal muscle response	21 day bedrest
GLDS251	<i>Arabidopsis thaliana</i>	ISS	Seedlings	EMCS

Mammal ChipSeq analysis

Introduction

Mammal ChipSeq analysis

Introduction

Mammal ChipSeq analysis

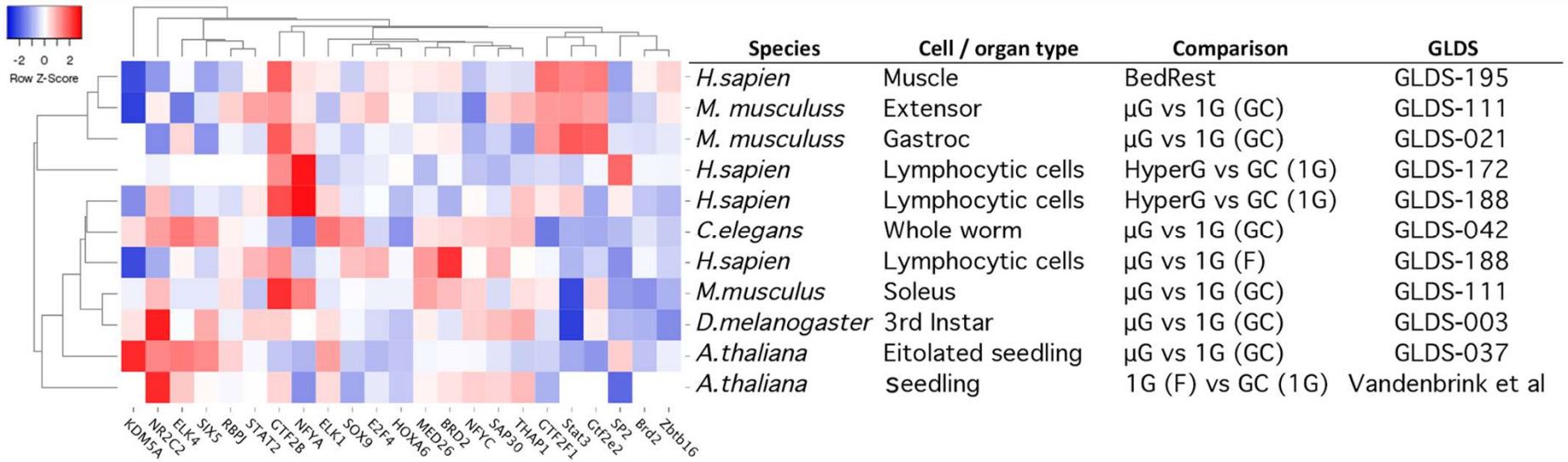
Introduction

Key nodes identified that regulate stress response

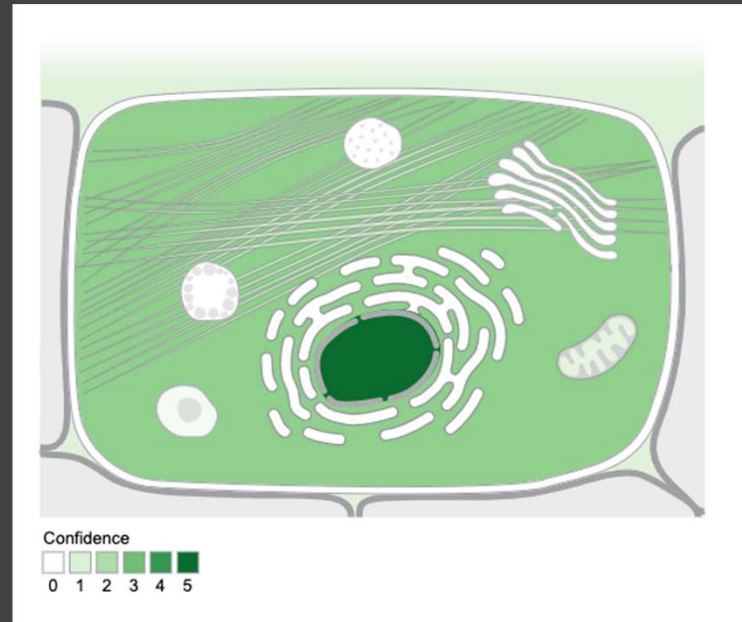
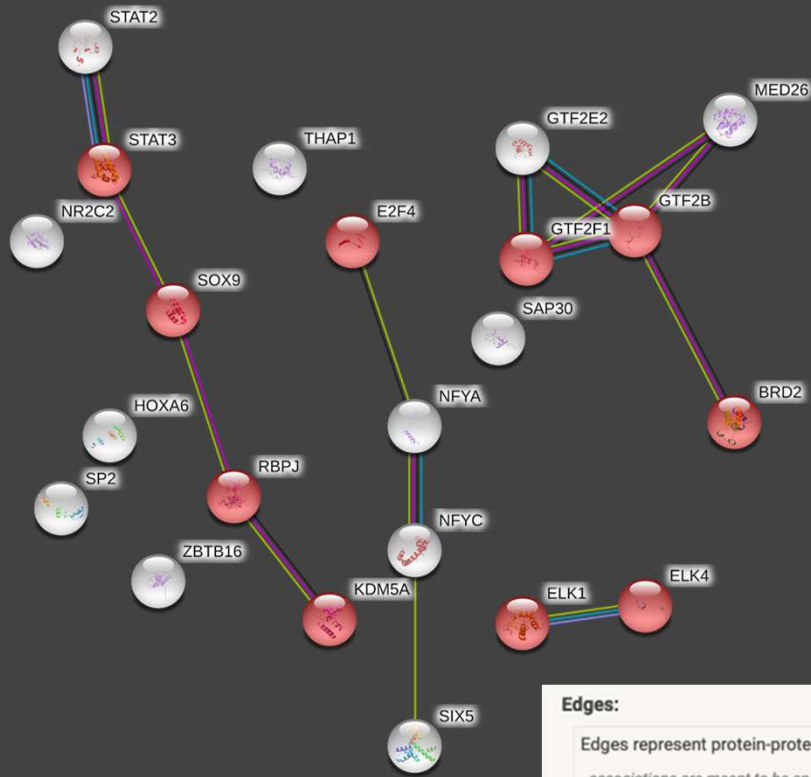
Node	Median Enrichment	Σ data points	Percentile 3	χ^2	Species
GTF2B	1.4	3316	0.79	494.85	Hs
SIX5	1.39	2705	0.77	251.01	Hs
NR2C2	1.57	2159	0.74	327.32	Hs
SAP30	1.34	3652	0.8	208.21	Hs
E2F4	1.33	3769	0.81	60.16	Hs
Brd2	1.33	6414	0.84	99.69	Mm
ELK1	1.29	2094	0.73	213.98	Hs
NFYA	1.26	2065	0.72	212.37	Hs
Stat3	1.26	3791	0.76	42.42	Mm
MED26	1.26	1851	0.7	163.85	Hs

Red is activation of TF regulated network and blue is suppression of TF regulated network

Enrichment analysis



Chromatin binding & nuclear localised



Edges:

Edges represent protein-protein associations

associations are meant to be specific and meaningful, i.e. proteins jointly contribute to a shared function; this does not necessarily mean they are physically binding each other.

Known Interactions

- from curated databases
- experimentally determined

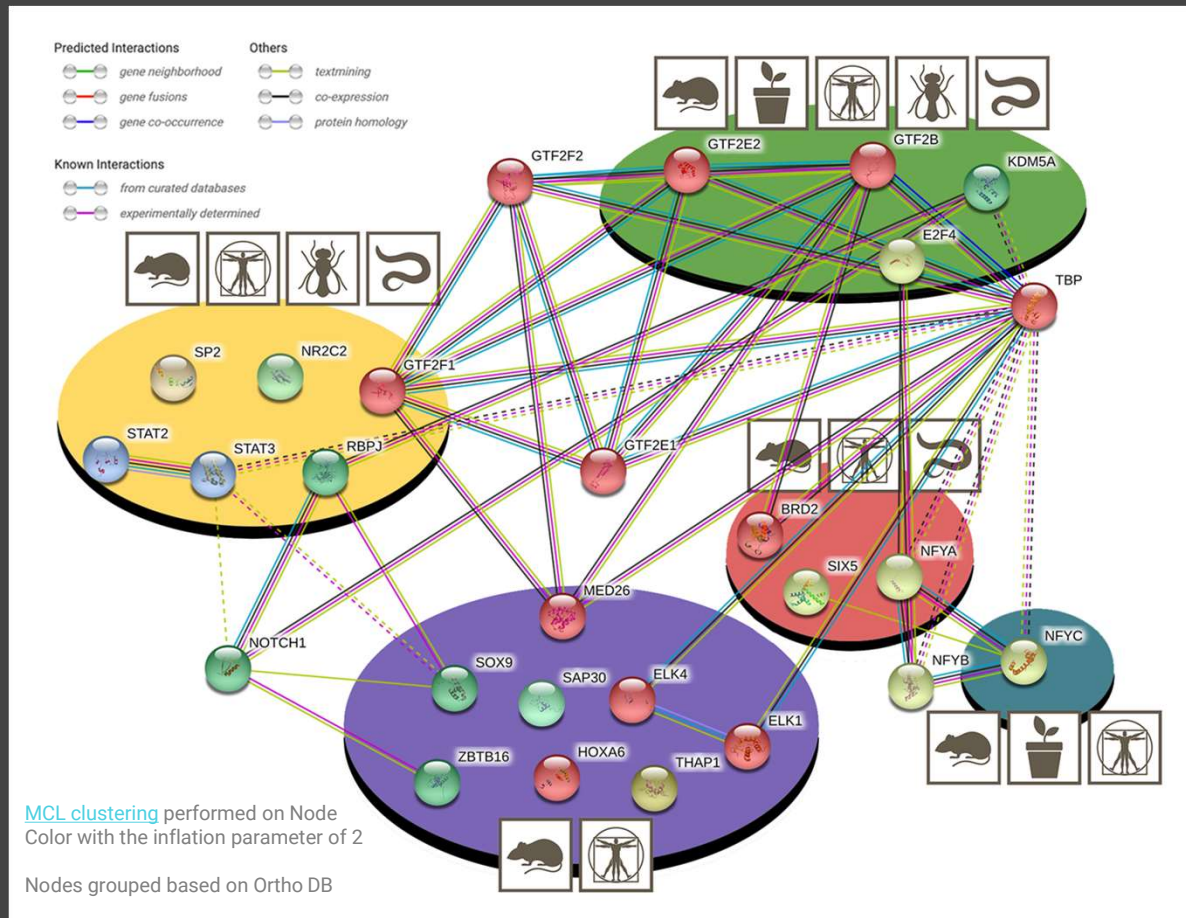
Predicted Interactions

- gene neighborhood
- gene fusions
- gene co-occurrence

Others

- textmining
- co-expression
- protein homology

The Genetic network can be dissected



Predicted Interactions

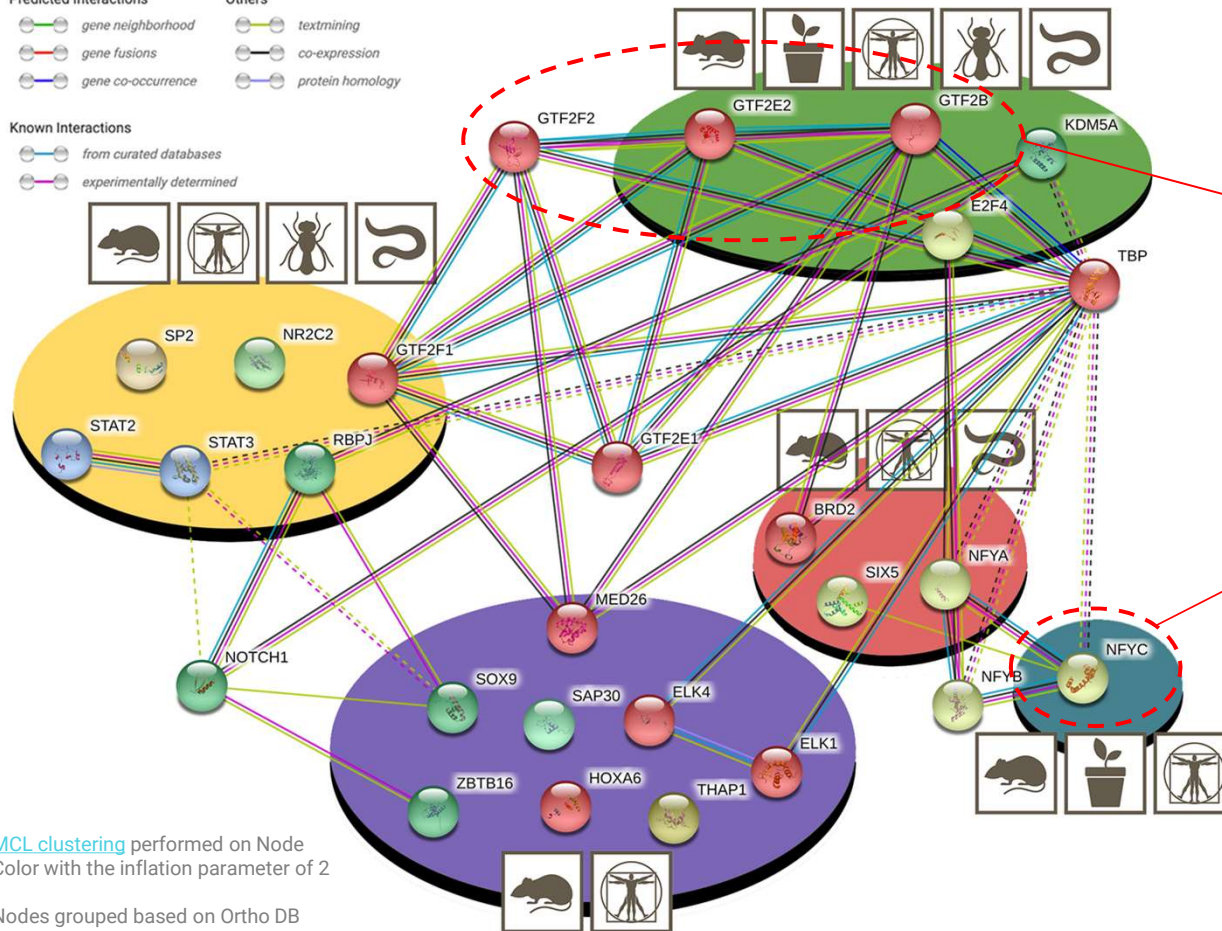
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Known Interactions

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MCL clustering performed on Node Color with the inflation parameter of 2

Nodes grouped based on Ortho DB

Orthologs | Ideogram

[Overview](#) | [Previous](#) | [Next](#) | [Source](#)

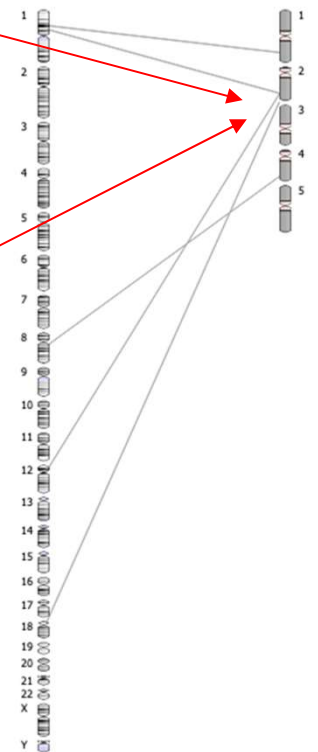
Compare gene locations across organisms.

Genes:

Source organism:

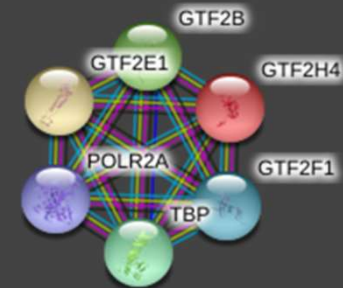
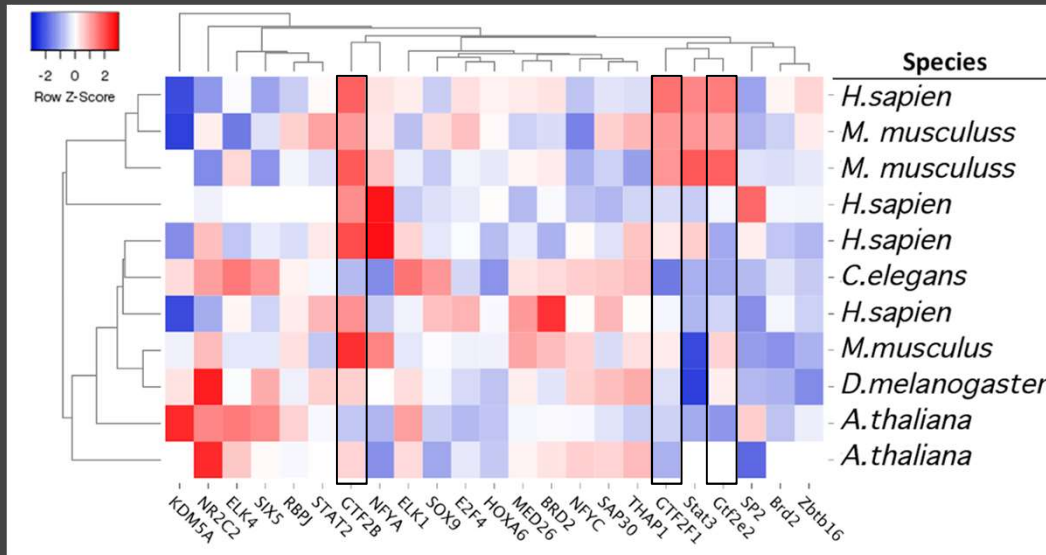
Target organism:

Orthology backend:



The general transcription factor complex is identified

Enrichment analysis



Transcription Initiation And Promoter Clearance

- Transcription of mRNA
- Basal transcription factors
- Eukaryotic Transcription Initiation
- Protein Acetylation and Deacetylation

PEDF Induced Signaling

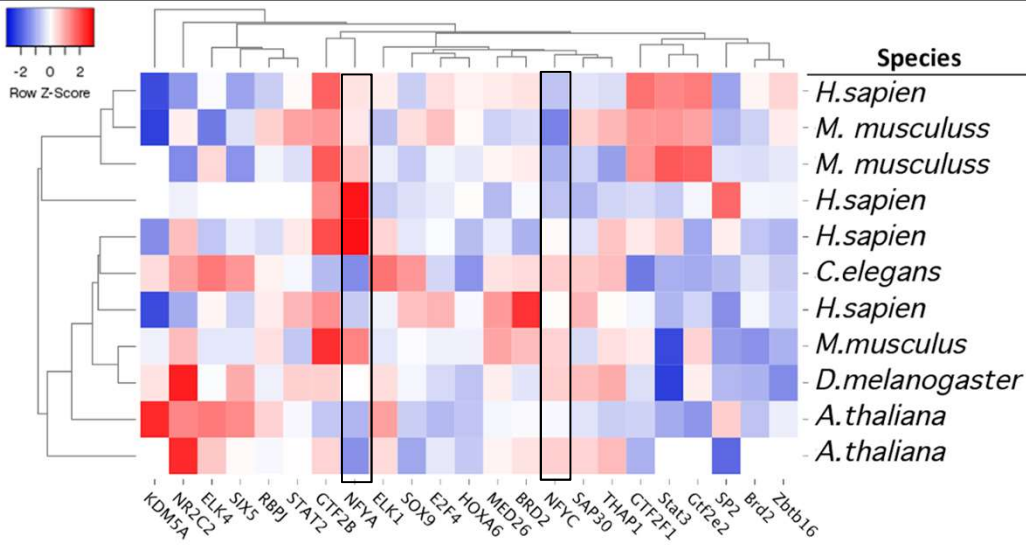
- RAR-Gamma-RXR-Alpha Degradation
- Glucocorticoid Receptor Signaling

Chromatin Regulation / Acetylation

- Chromatin Regulation / Acetylation

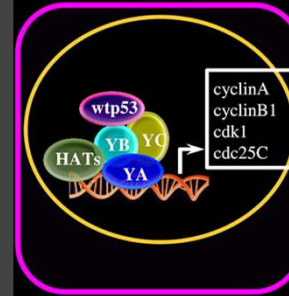
NFY complex ratio's are changing

Enrichment analysis

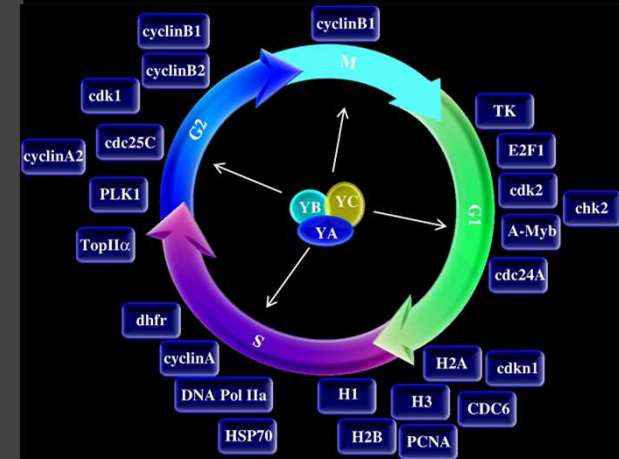
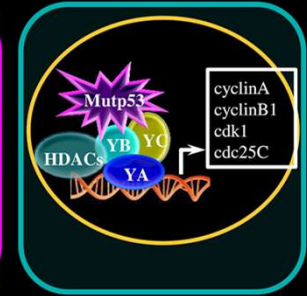


NF-Y-interacting partners: the p53 example

Wild type p53 context



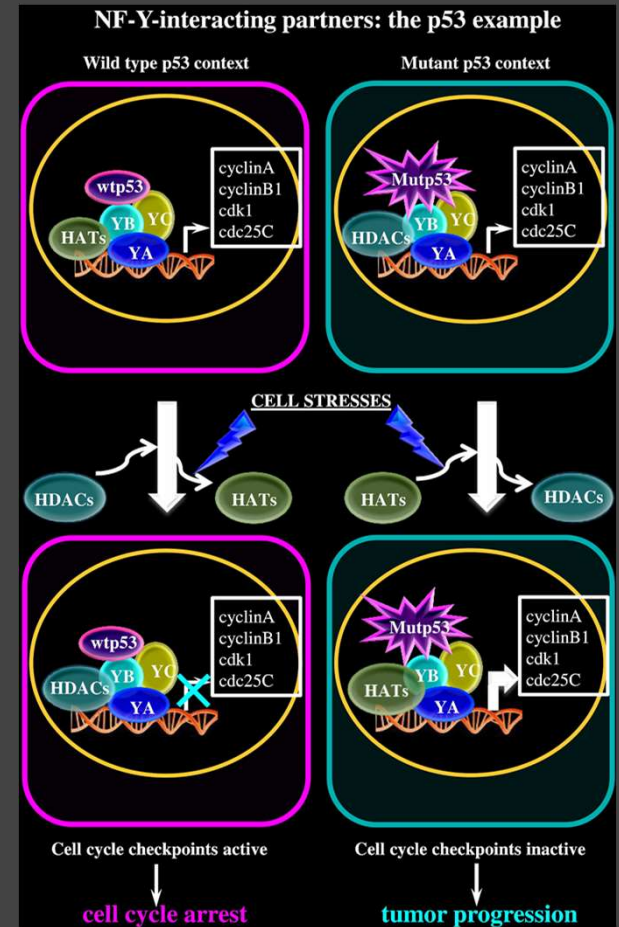
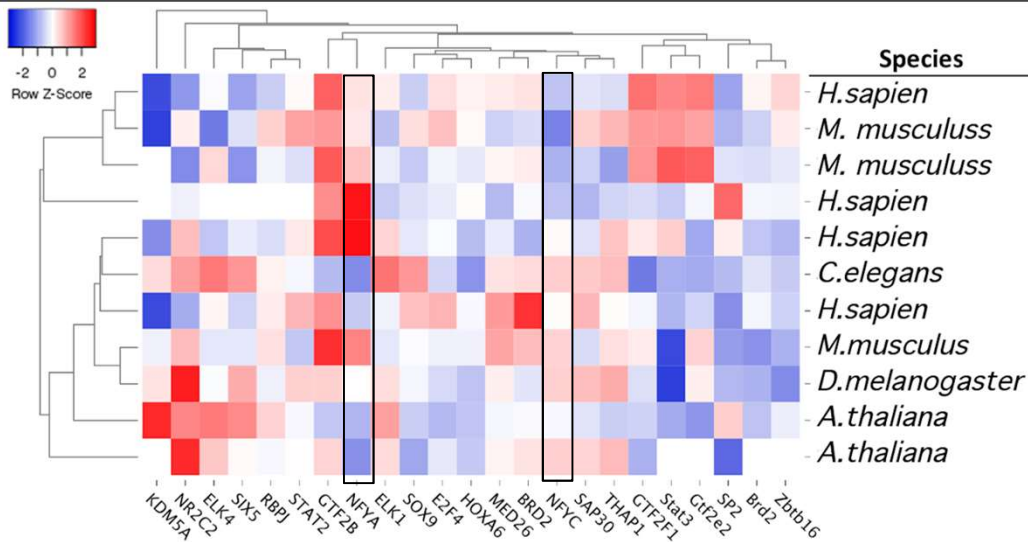
Mutant p53 context



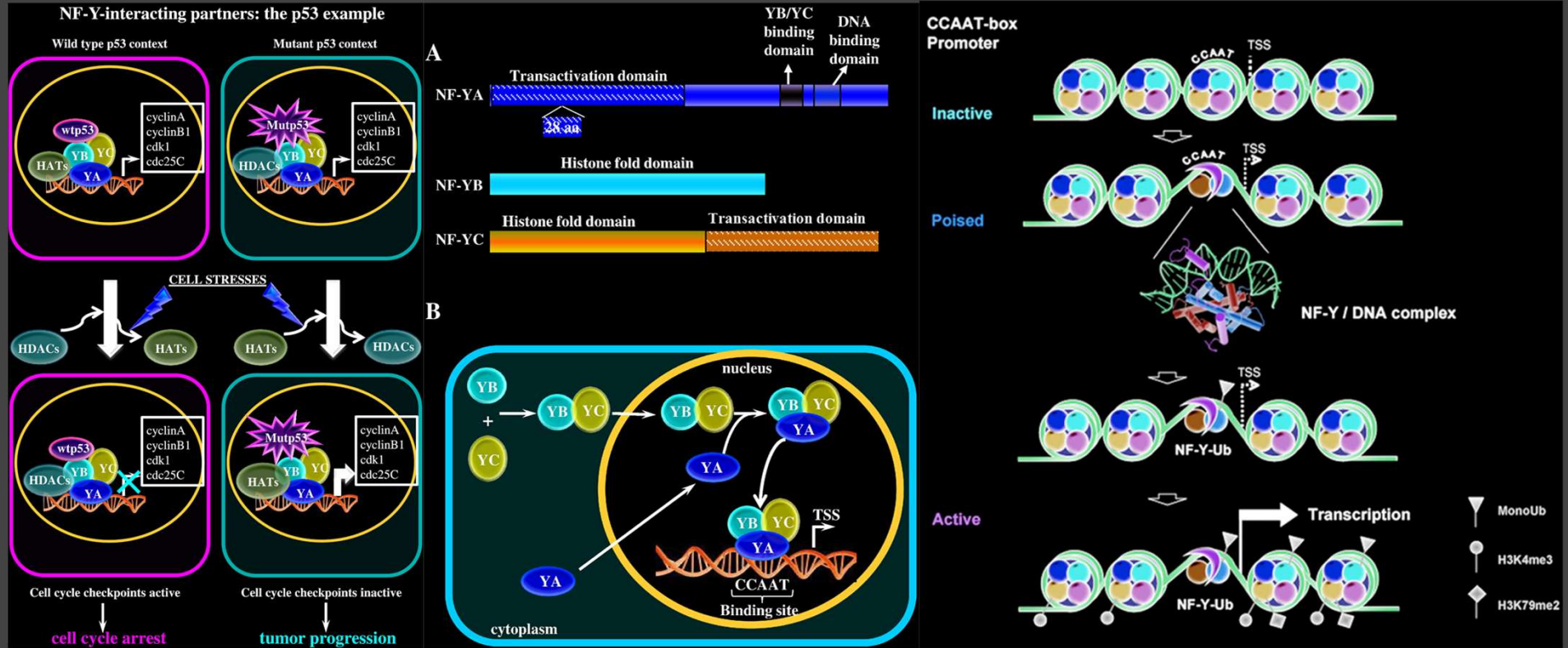
Reviewed: Gurtner et al., (2016)

Which can lead to cancer...

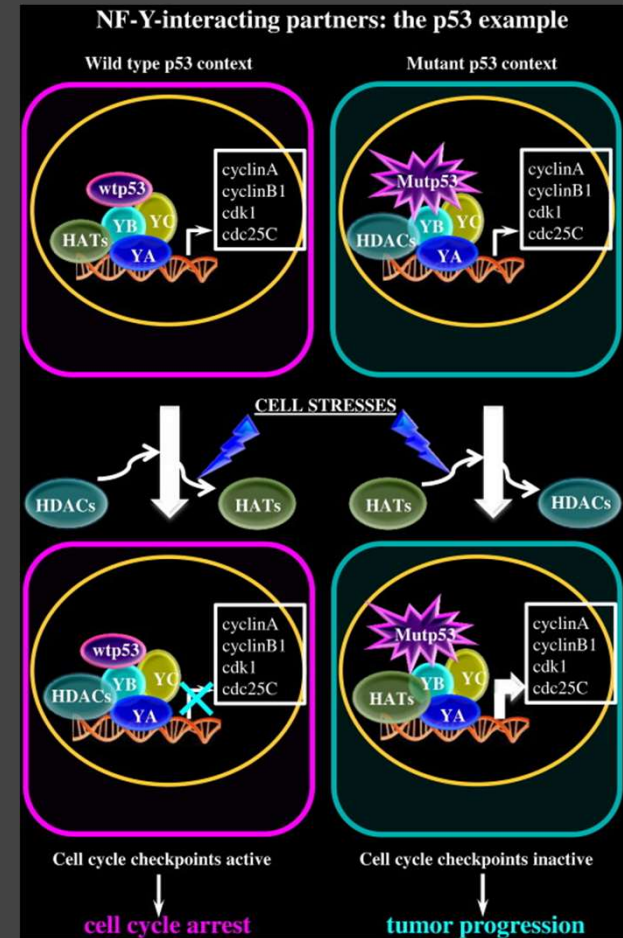
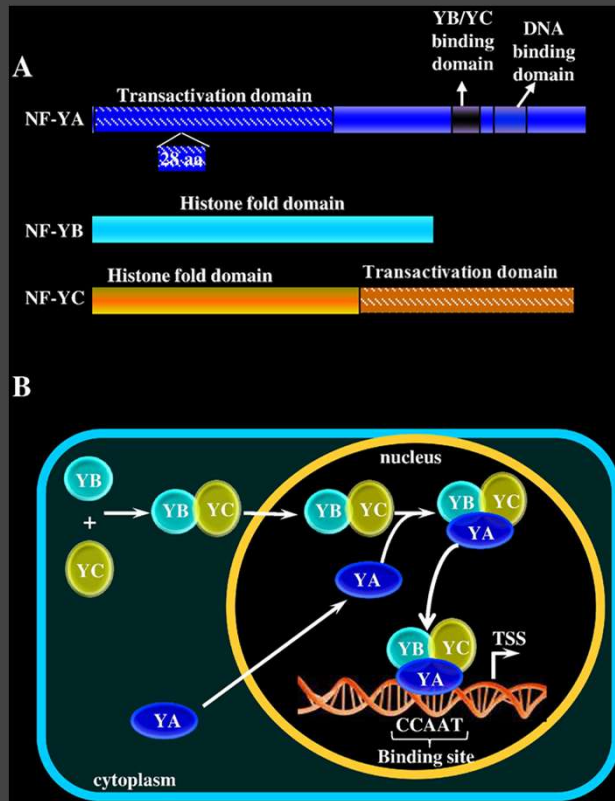
Enrichment analysis



NFY complex ratio's are changing

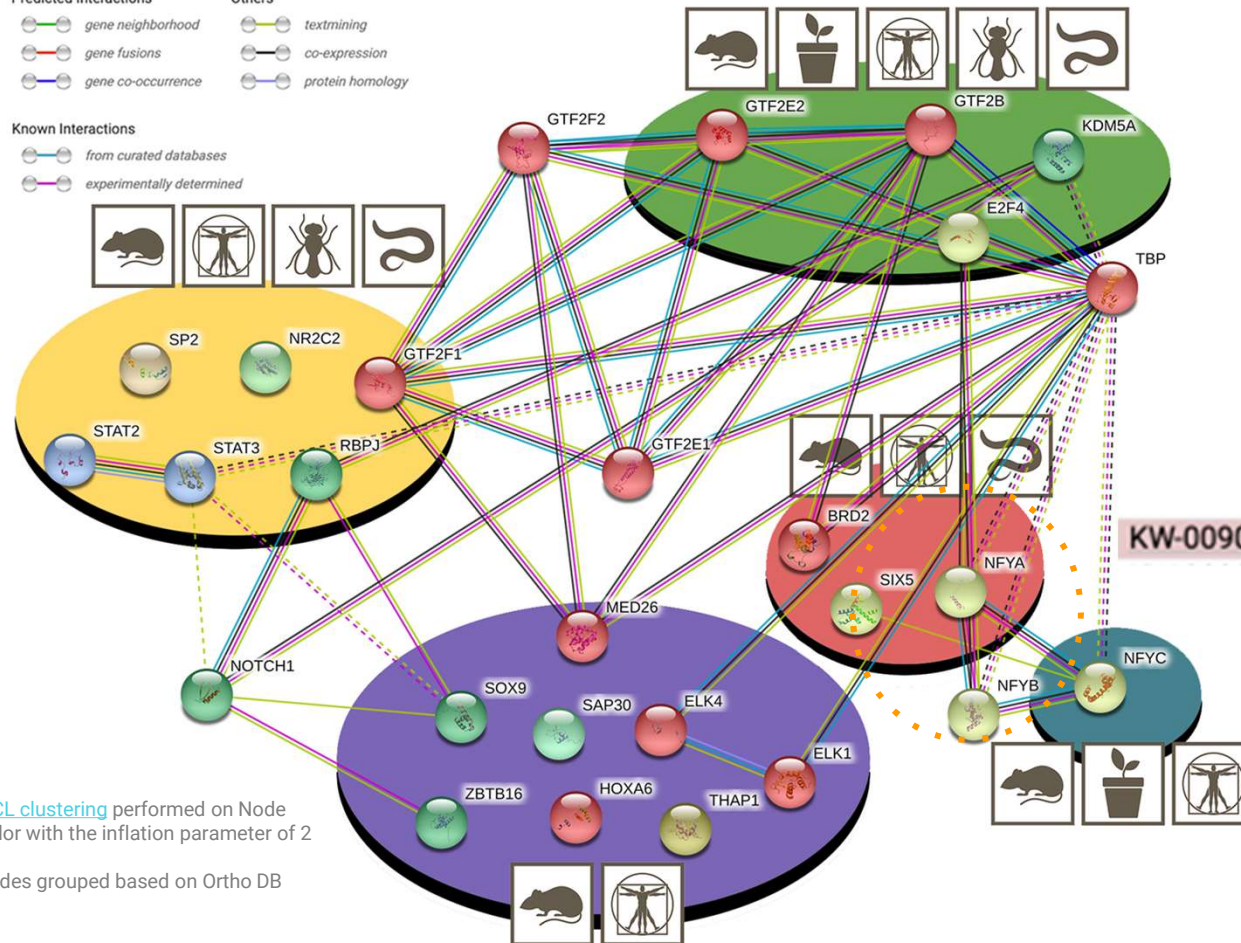


NFY complex ratio's are changing



- Predicted Interactions**
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- Others**
- textmining
 - co-expression
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- Known Interactions**
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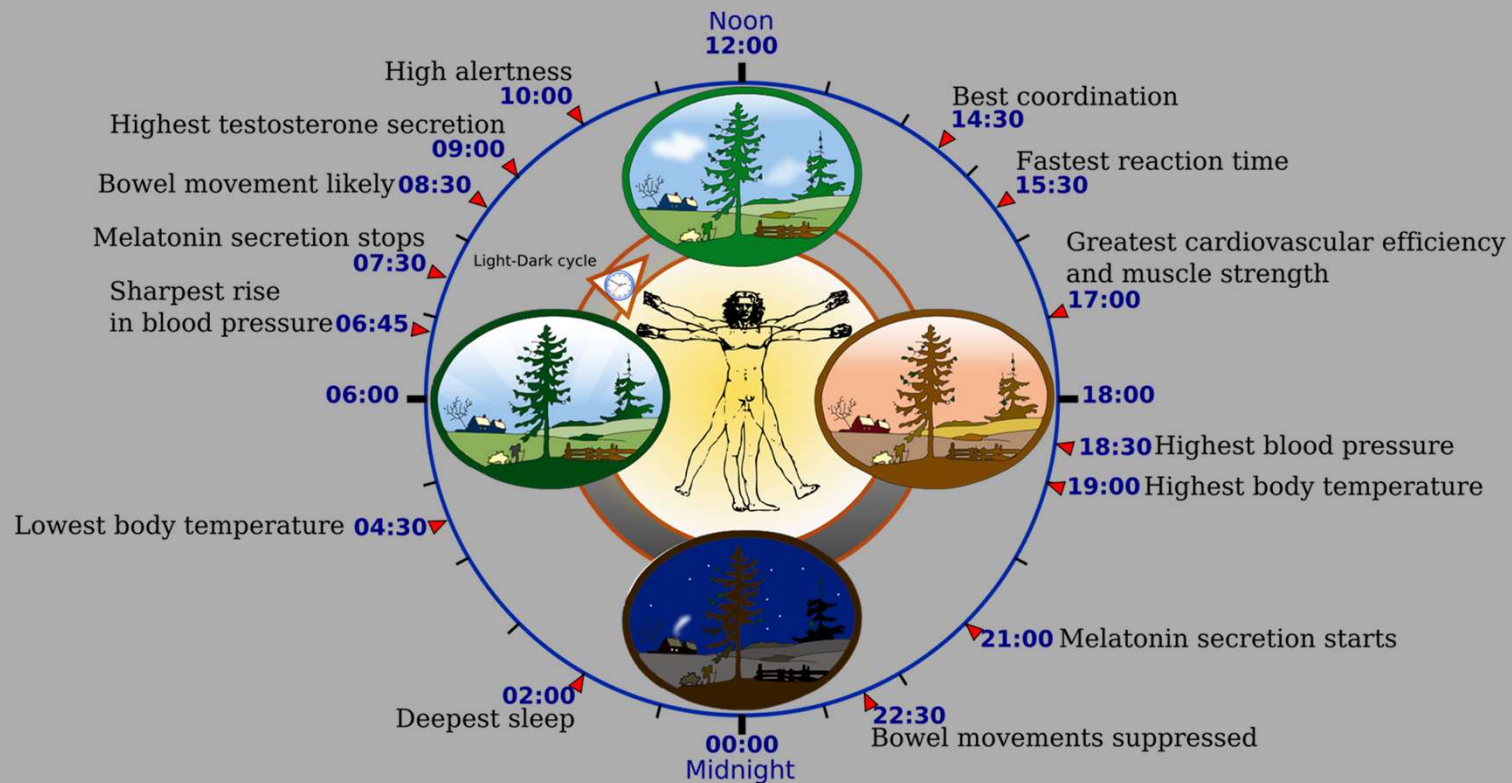
MCL clustering performed on Node Color with the inflation parameter of 2

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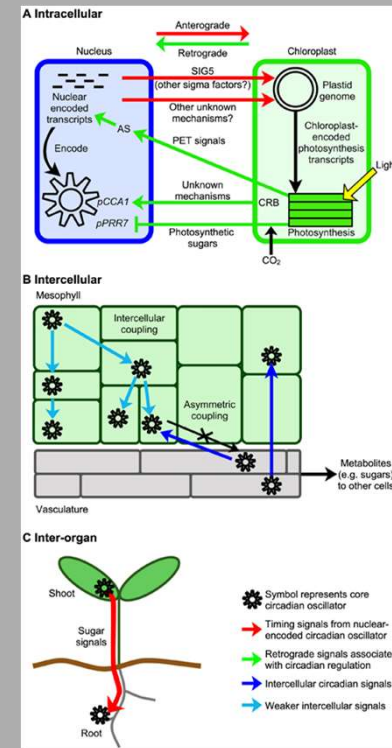
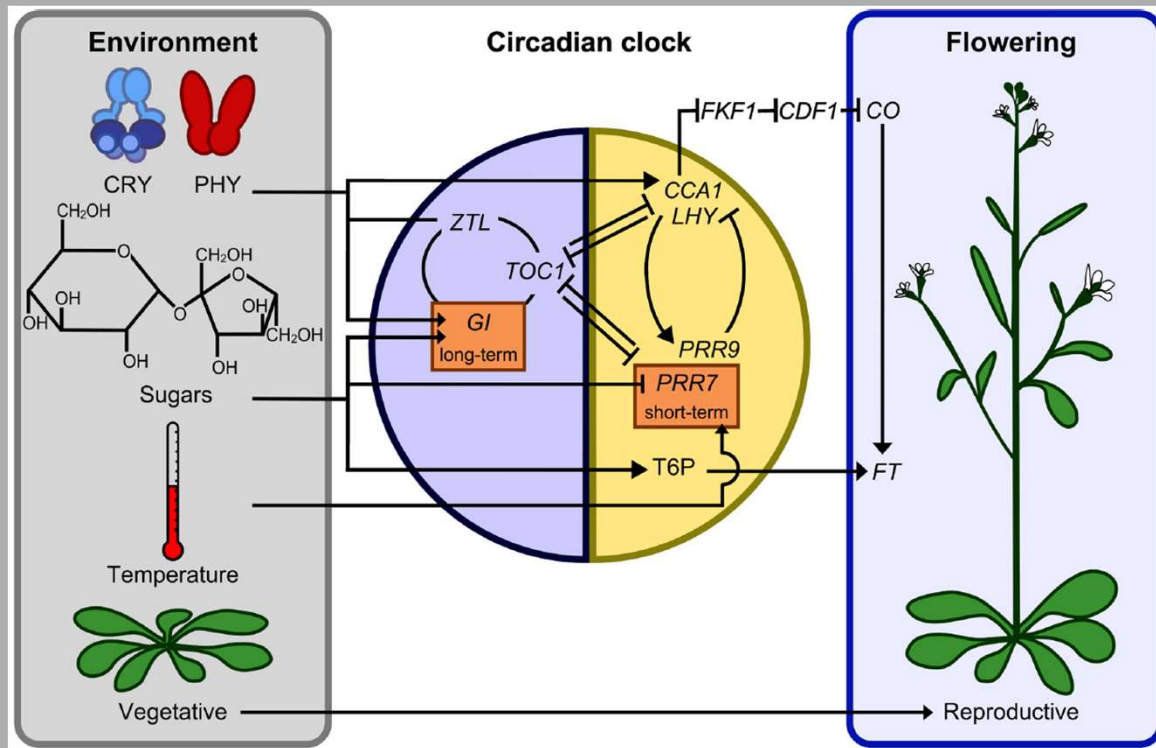
KW-0090

Biological rhythms

Biological Rhythms Exist in both plants and animals.

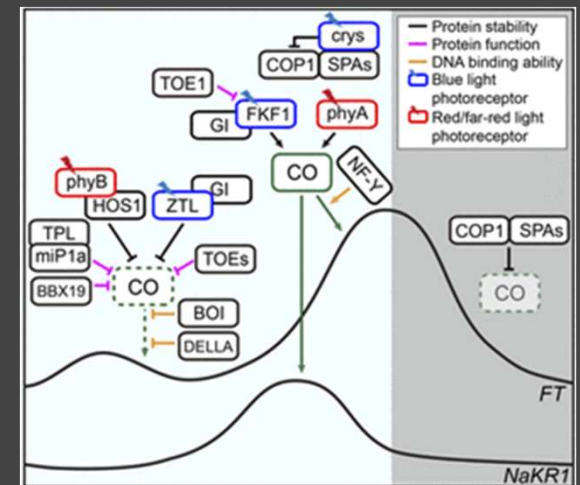
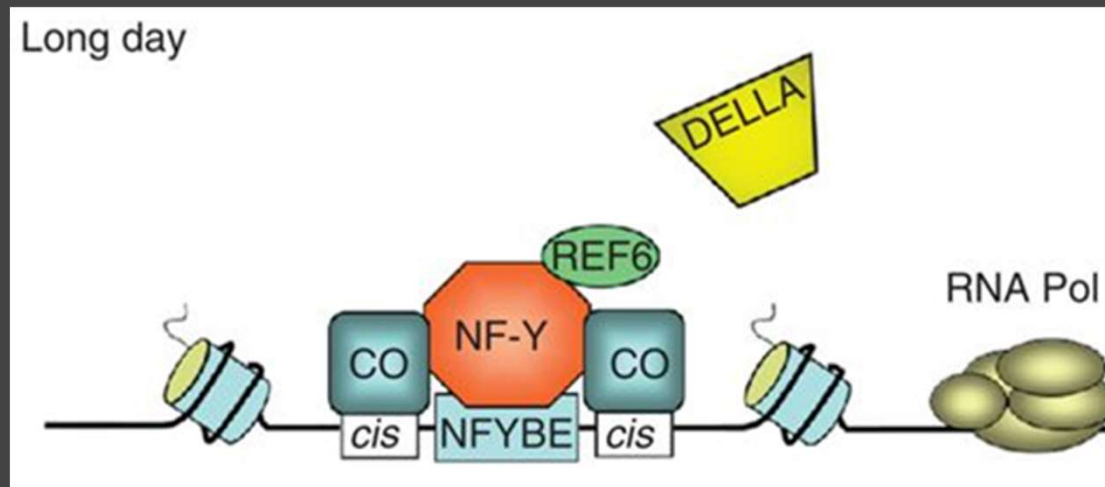


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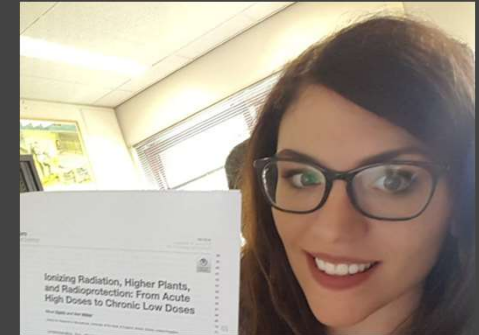


Dodd et al., 2015

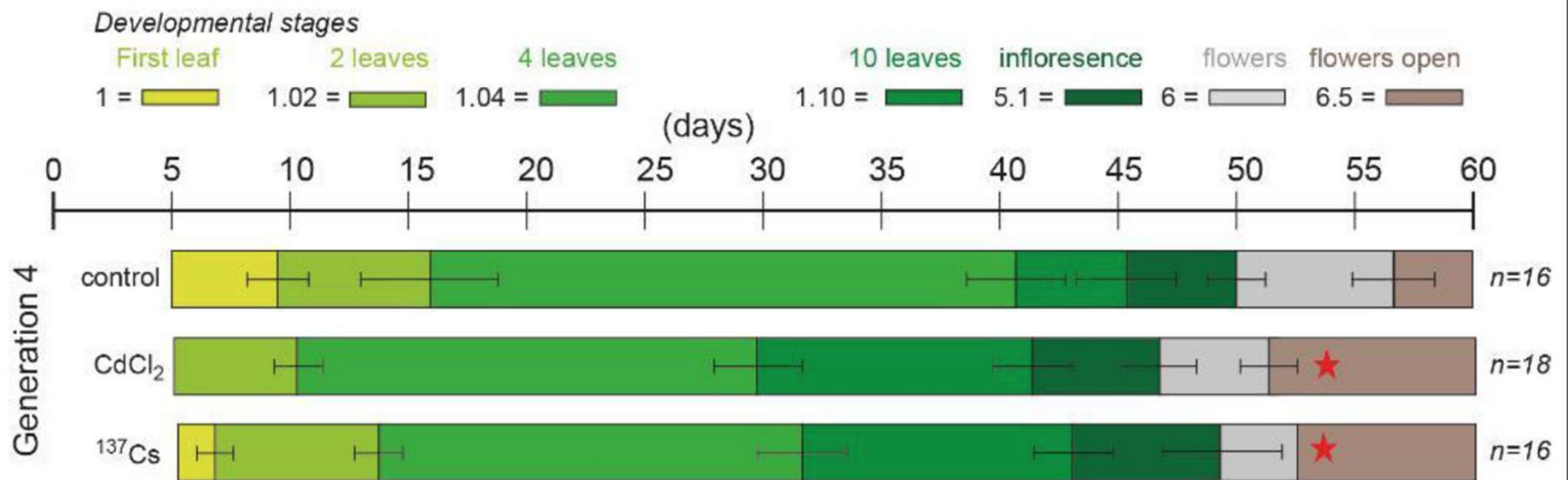
Biological Rhythms regulate size and Flowering Time



Changes to NFY can cause changes in flowering time and plant size



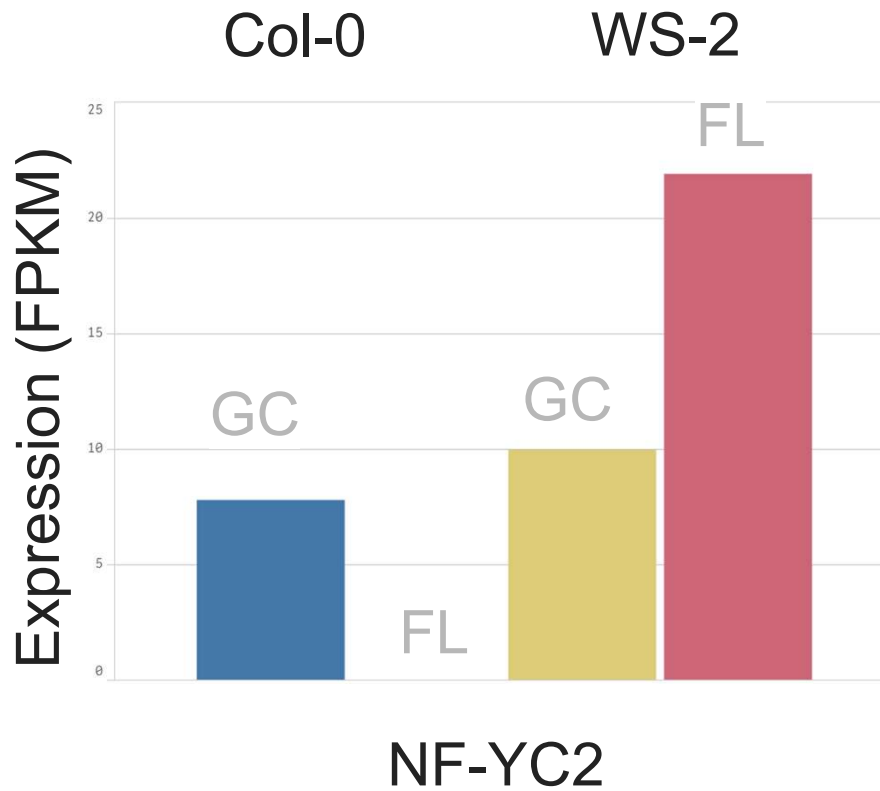
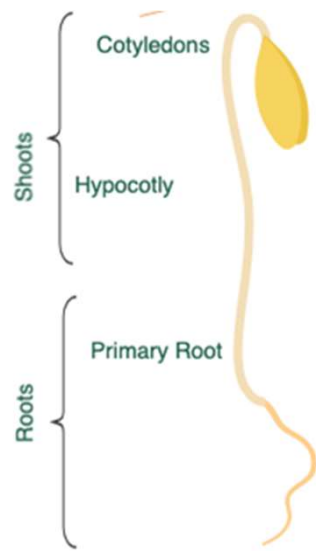
Developmental, Morphological and Physiological Traits in Plants Exposed for Five Generations to Chronic Low-Level Ionising Radiation

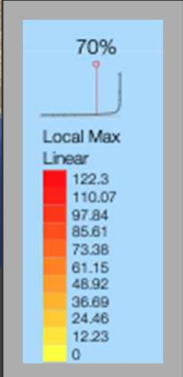
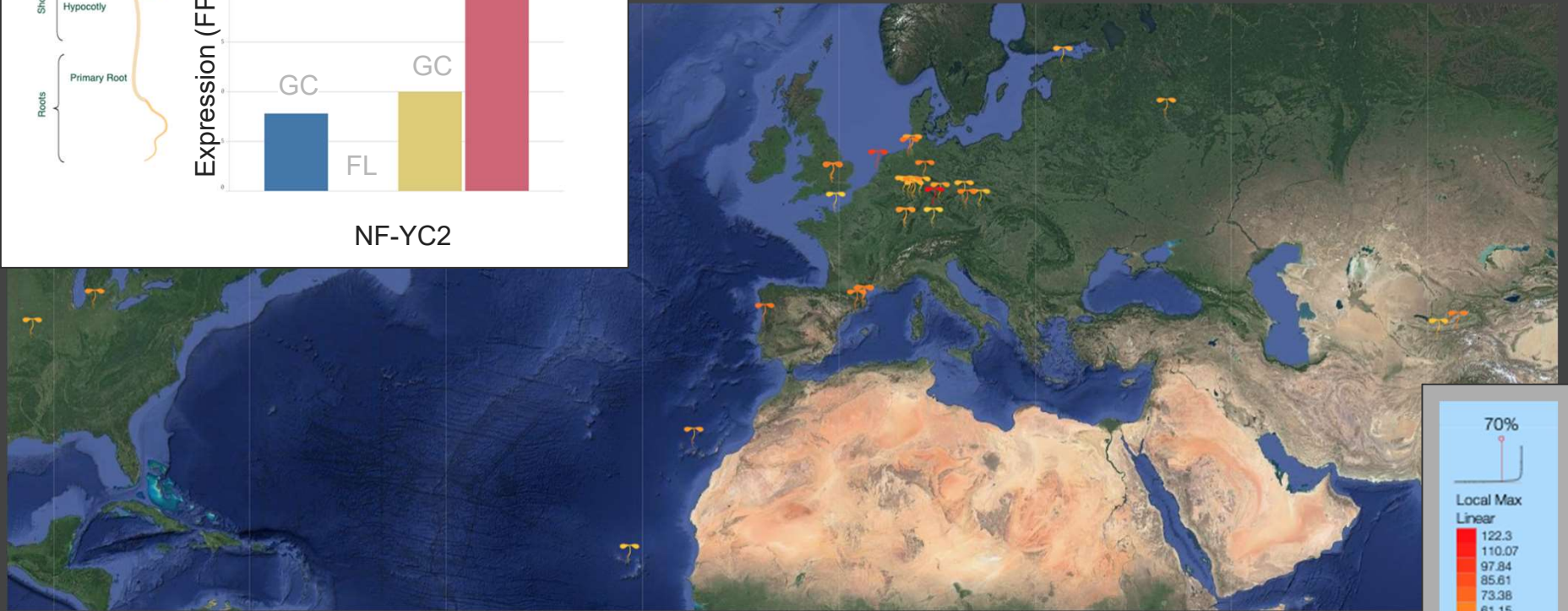
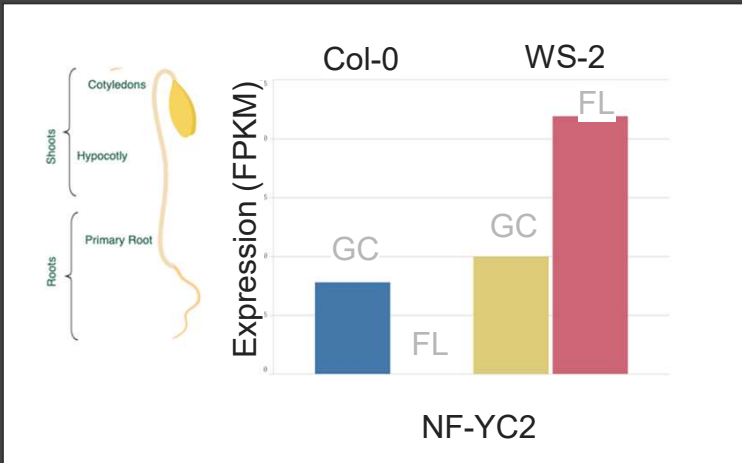


The end....

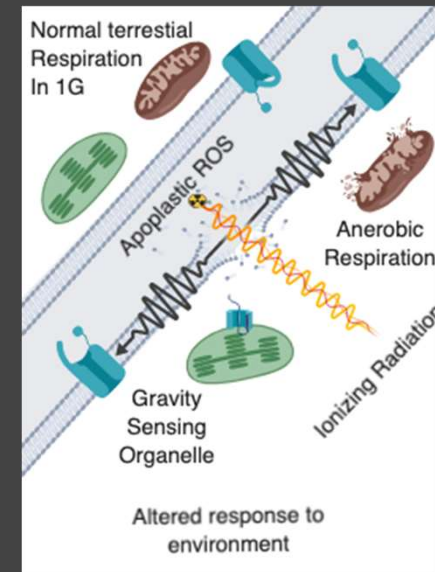
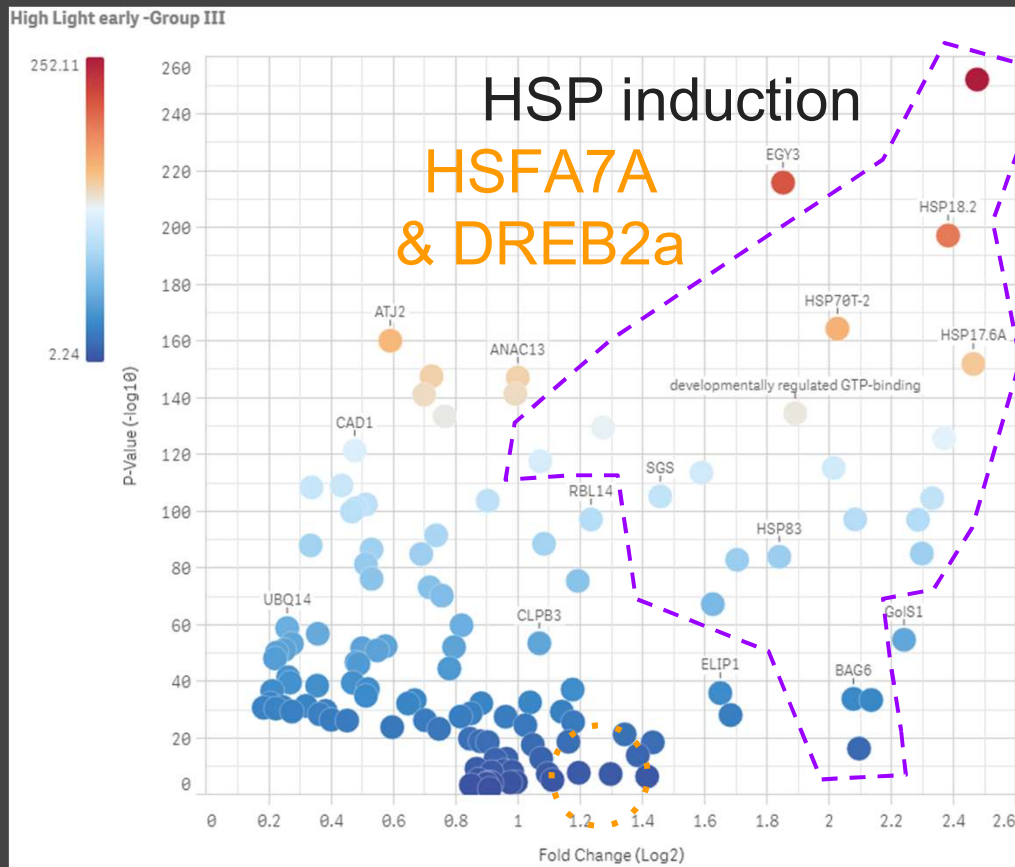


NF-YC2: Suppressed in Col-0 & Induced in WS-0





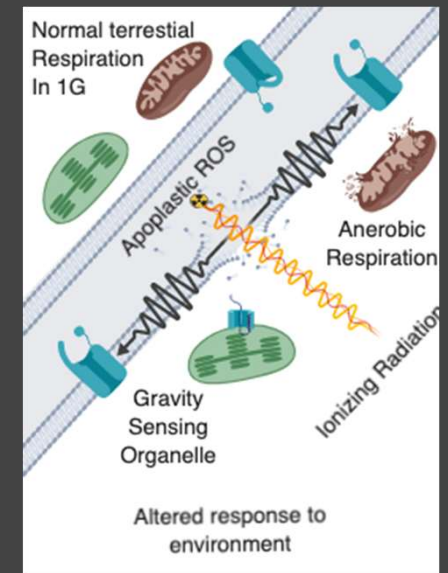
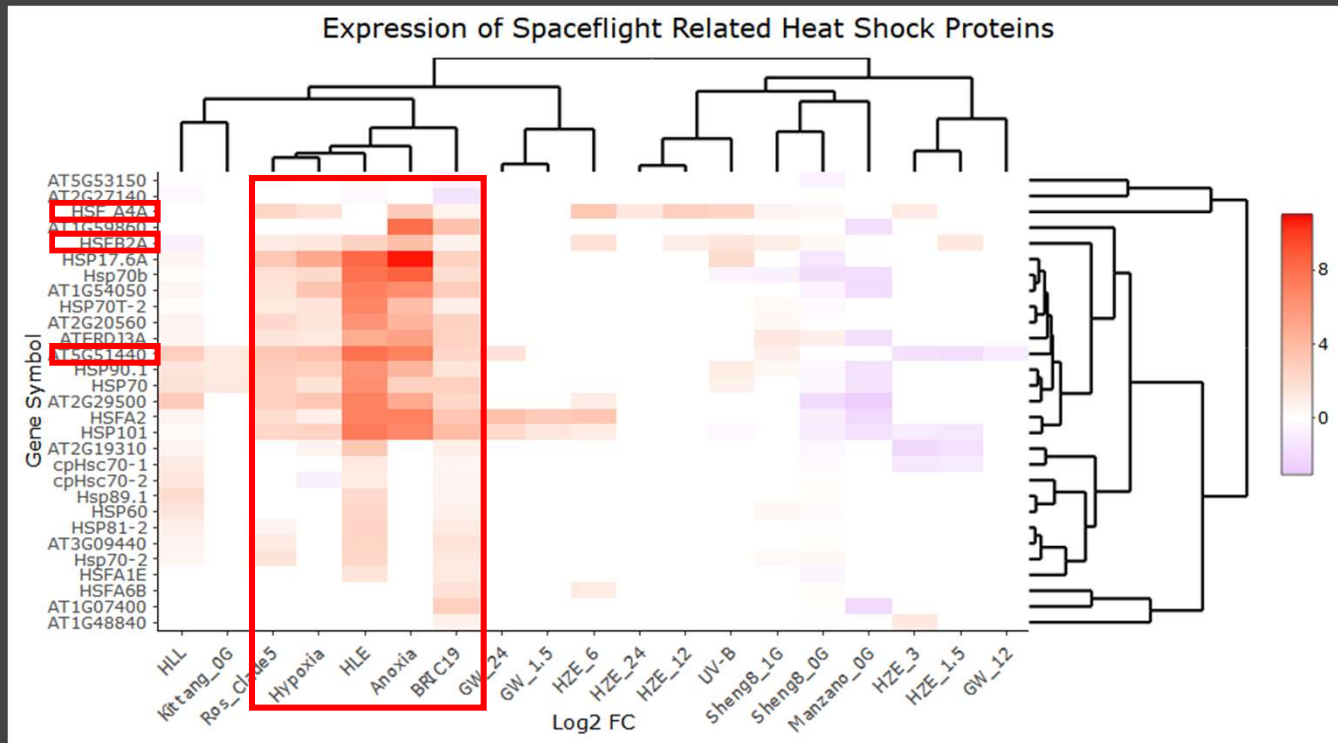
NFYC2 was always significant in the data!



Could be radiation
Could be respiration

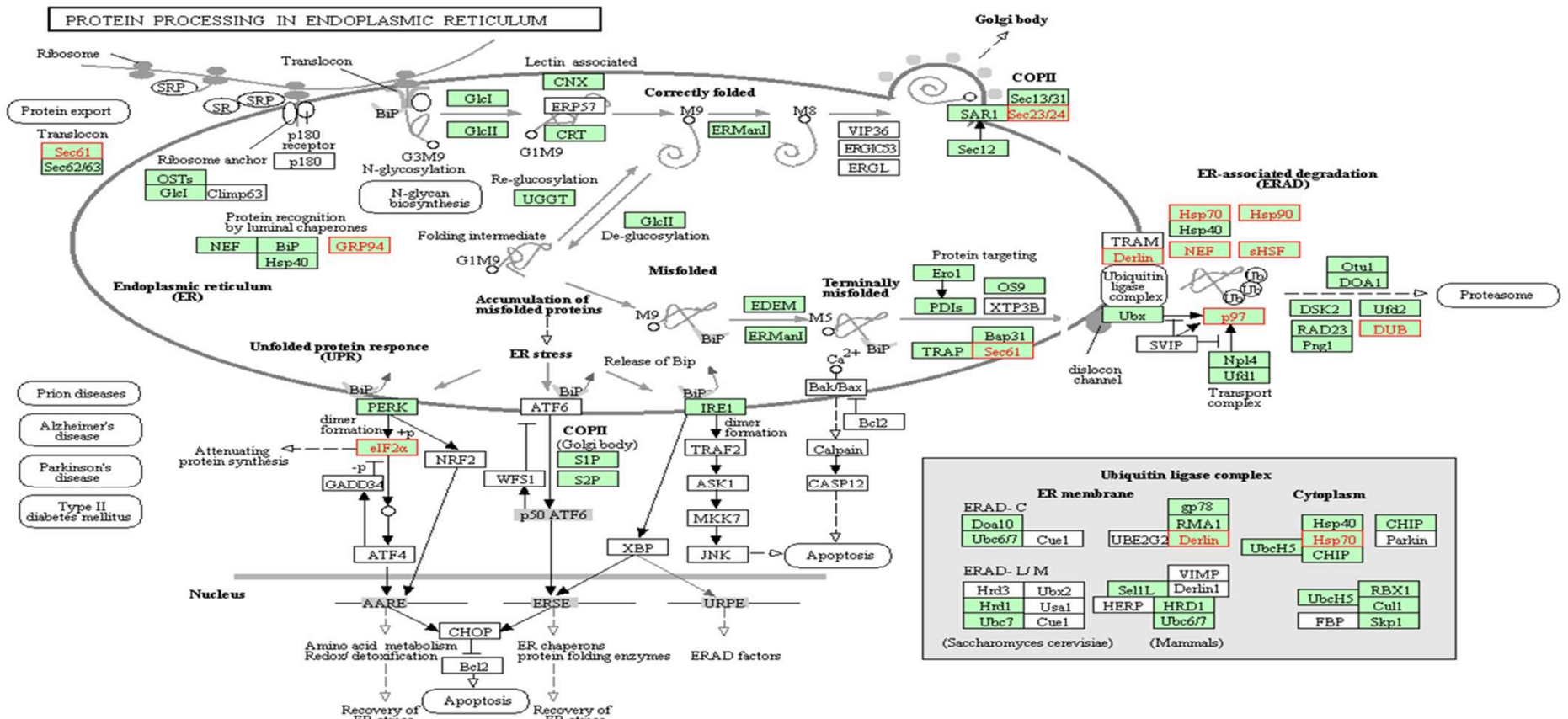
NF-YC2: 2.29 fold change in HighLight ROS response pathway

Plants in BRIC19 showed evidence of anoxia and high light

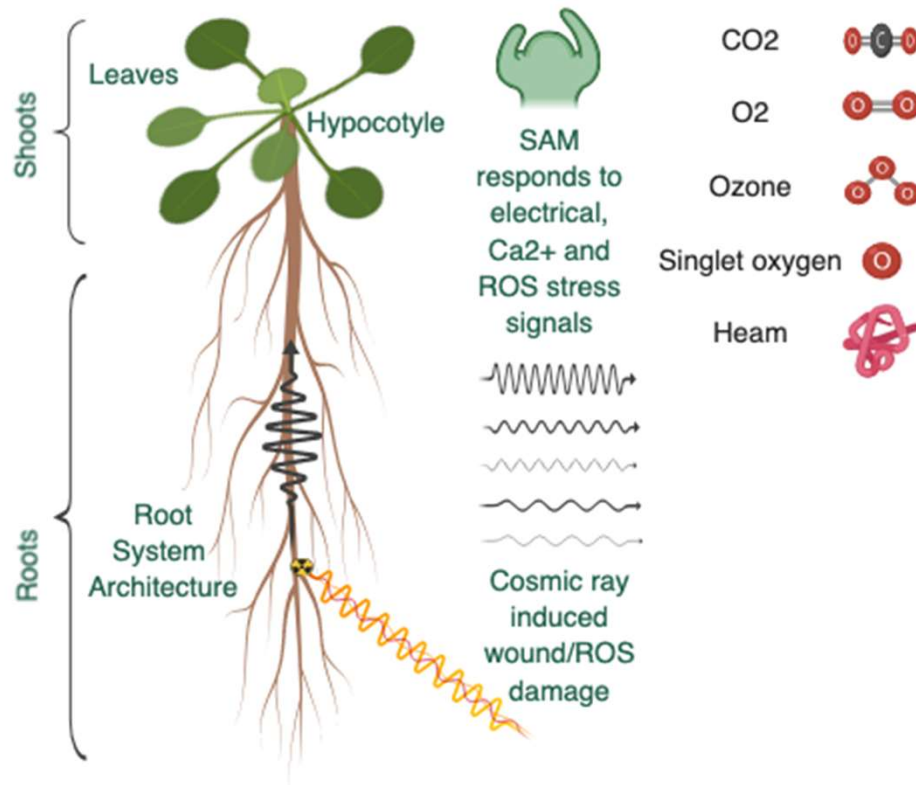


Could be radiation
Could be respiration

The ERAD response is induced both in BRIC19 and during high light stress

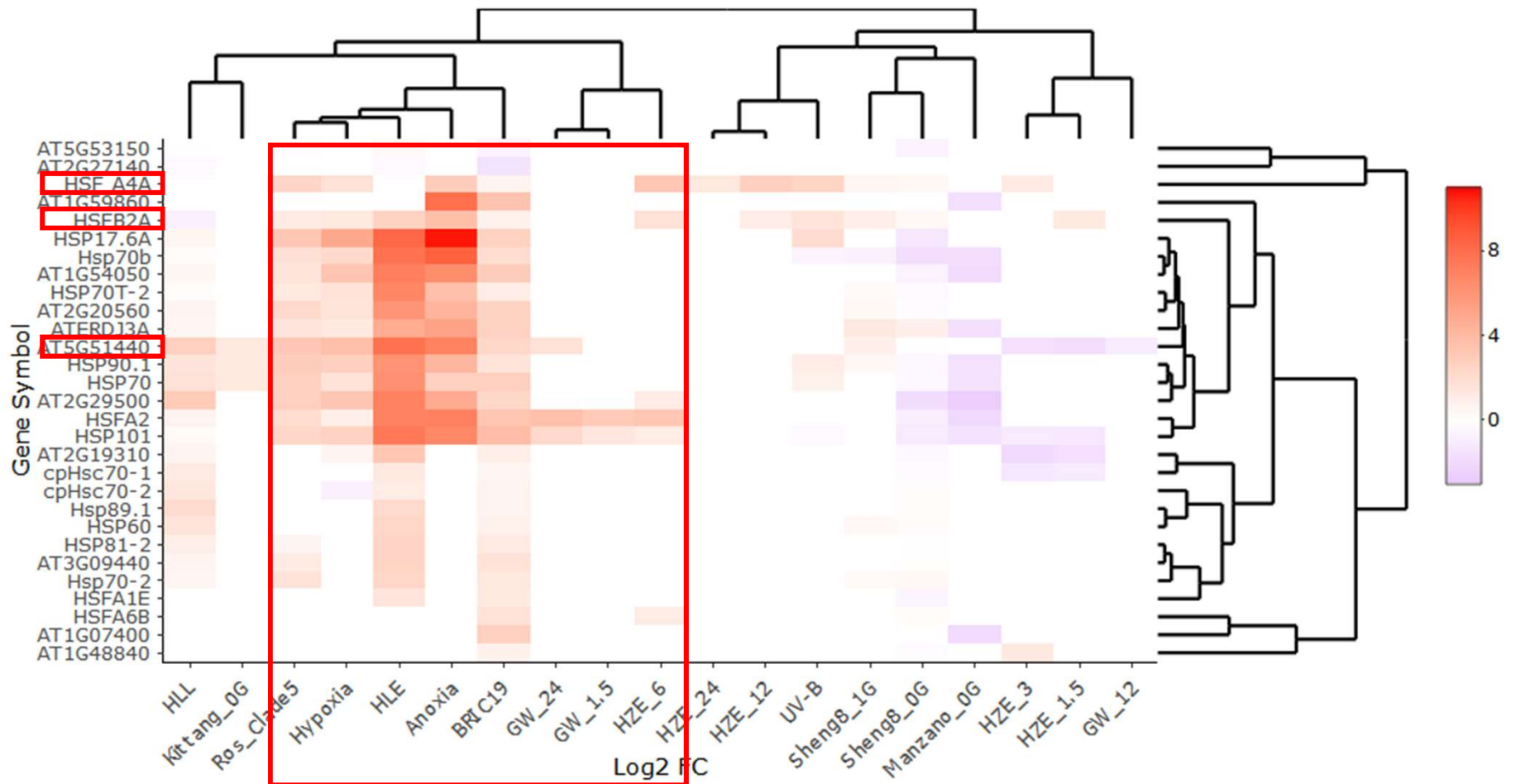


Arabidopsis thaliana - APEX5



Part radiation?
& part hypoxia?

Expression of Spaceflight Related Heat Shock Proteins



Unpublished data courtesy of John Lombardino

