Involvement of RNA metabolism in physiological processes: development and response to stress

dr Anna Golisz-Mocydlarz

1

Levels of regulation

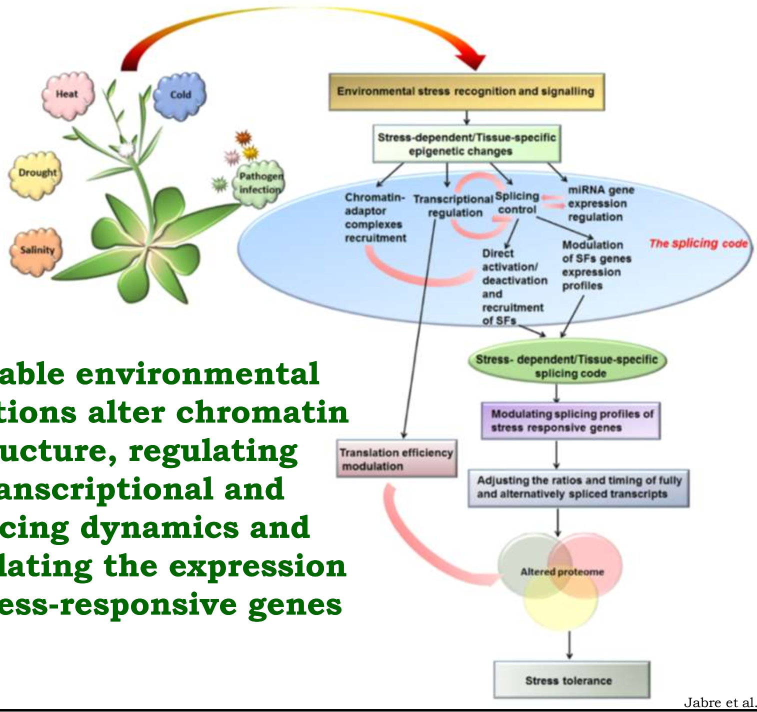
I. Chromatin and transcription

II. RNA processing: pre-mRNA splicing (alternative splicing - AS) and 3' formation

III. RNA stability

IV. Regulation via microRNA and lncRNA

2



Variable environmental conditions alter chromatin structure, regulating transcriptional and splicing dynamics and modulating the expression of stress-responsive genes

Jabre et al. 2019 NAR

3

Regulation of plant metabolism

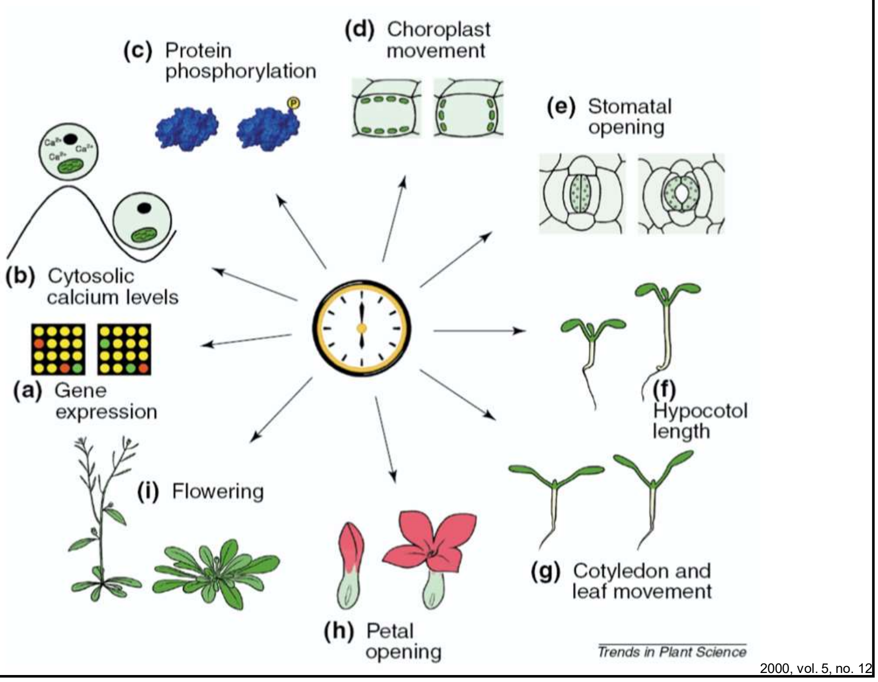
I. Chromatin and transcription

RNA metabolism regulates most of developmental and signaling processes in plants

- ► Germination
- ► Circadian clock
- ► Transition from vegetative to generative development
- ► Flowering
- ► Stress response

4

Plant clocks control a plethora of biological processes



2000, vol. 5, no. 12

5

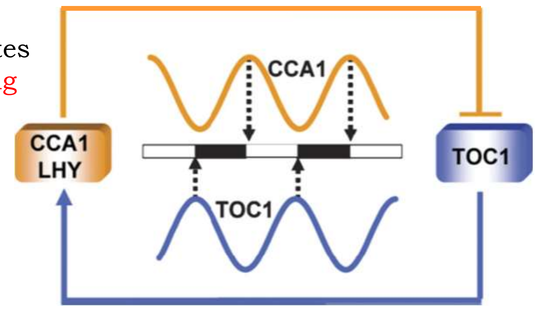
The central oscillator

1) CCA1 – CIRCADIAN CLOCK ASSOCIATED 1
LHY – LATE ELONGATED HYPOCOTYL

- ❖ MYB transcription factors
- ❖ reduction in mRNA levels: negative feedback loop
- ❖ mRNA level peaking at dawn

2) TOC1 – TIMING OF CAB EXPRESSION 1

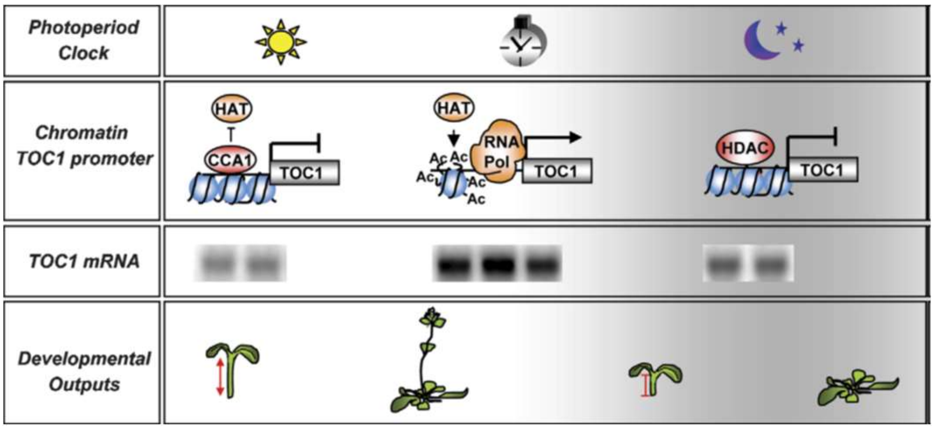
❖ TOC1 expression oscillates peaking during early evening (opposite to CCA1 and LHY)

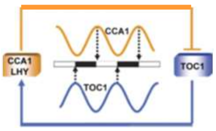


Stratmann & Mas, Seminars in Cell & Developmental Biology (2008) 554–559

6

Chromatin-dependent regulation of *TOC1*



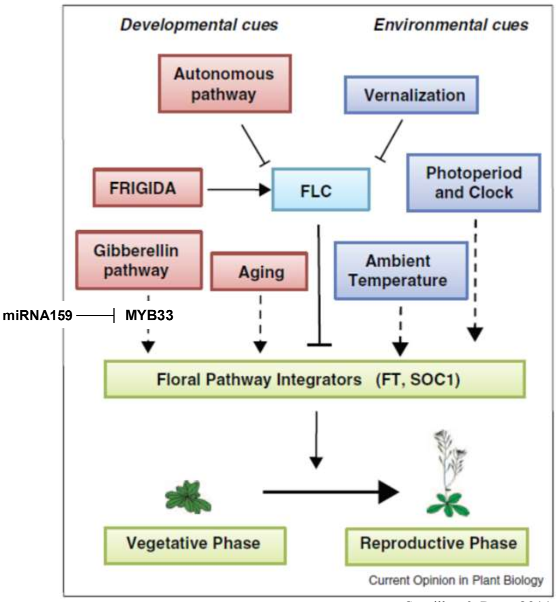


HAT – histone acetyltransferase
HDAC – histone deacetylase

Stratmann & Mas, Seminars in Cell & Developmental Biology 19 (2008) 554–559

7

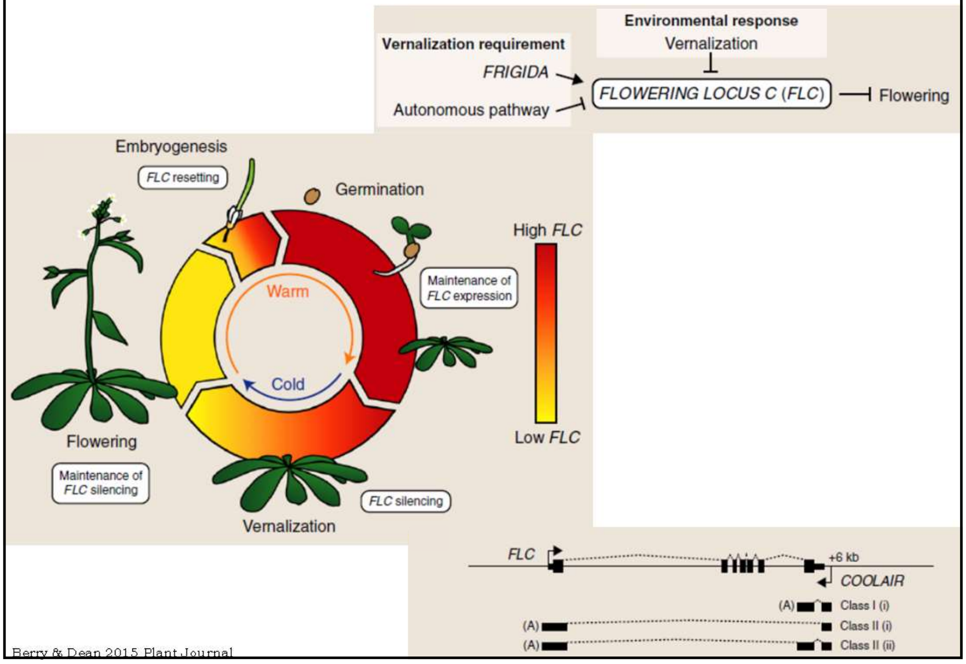
Flowering occurs in response to different developmental and environmental cues



Crevillen & Dean 2011 Current Opinion in Plant Biology

8

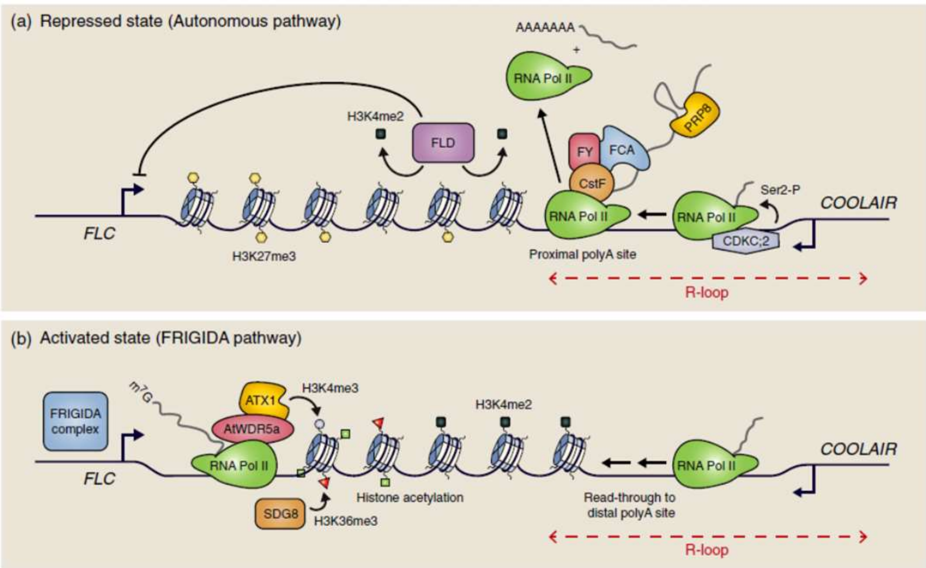
FLC regulation through development



Berry & Dean 2015 Plant Journal

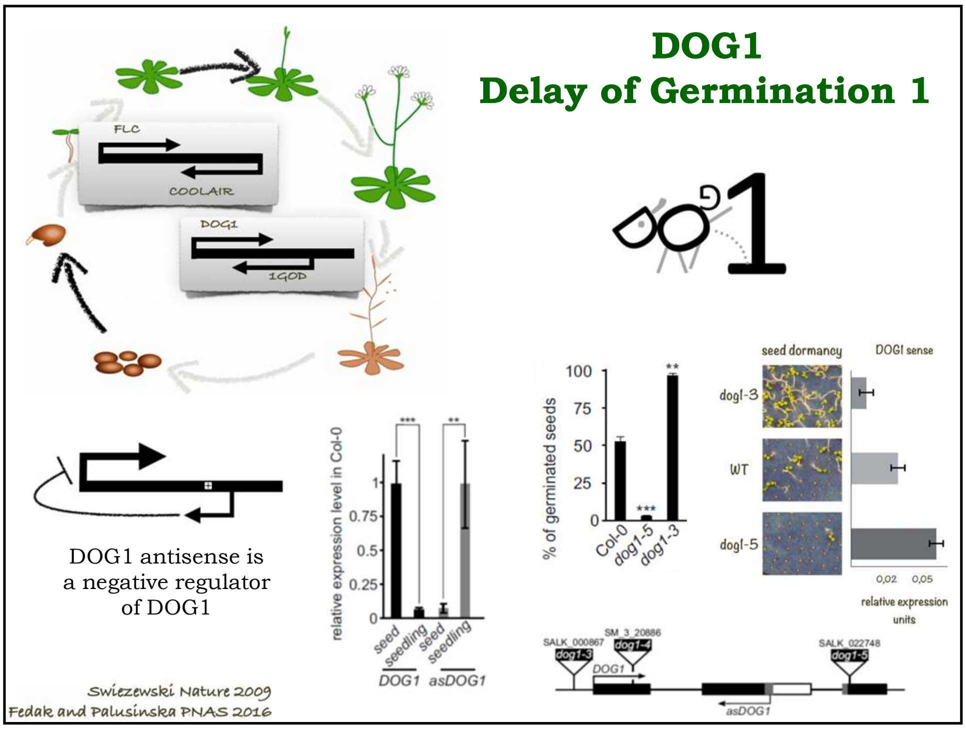
9

Autonomous pathway/FRIGIDA 'tug of war' to set and maintain FLC expression

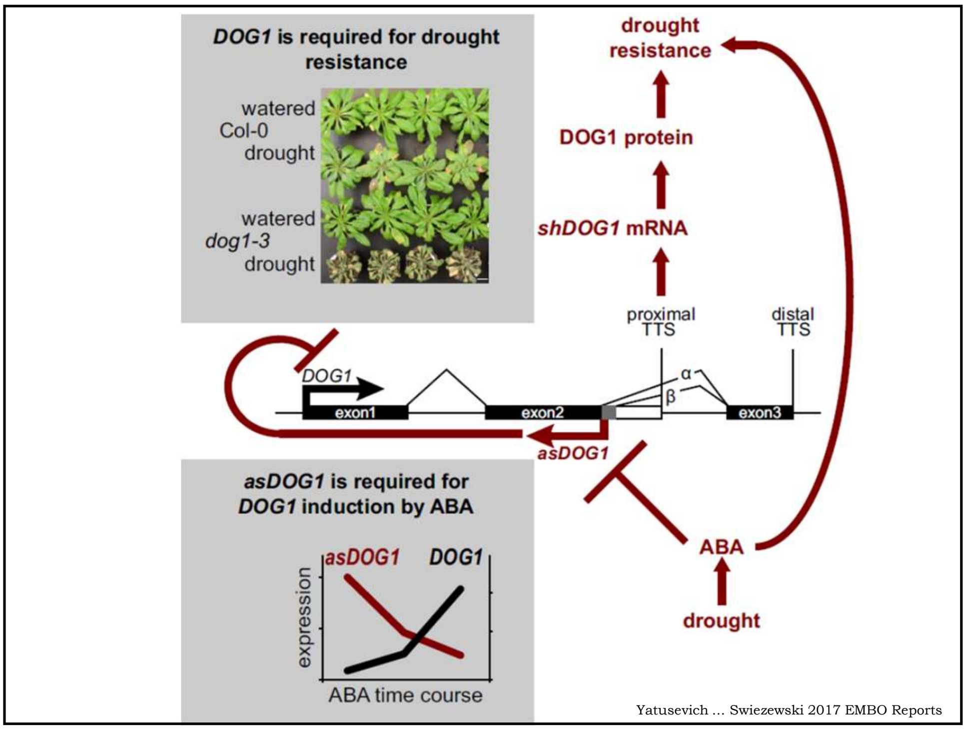


Berry & Dean 2015 Plant Journal

10

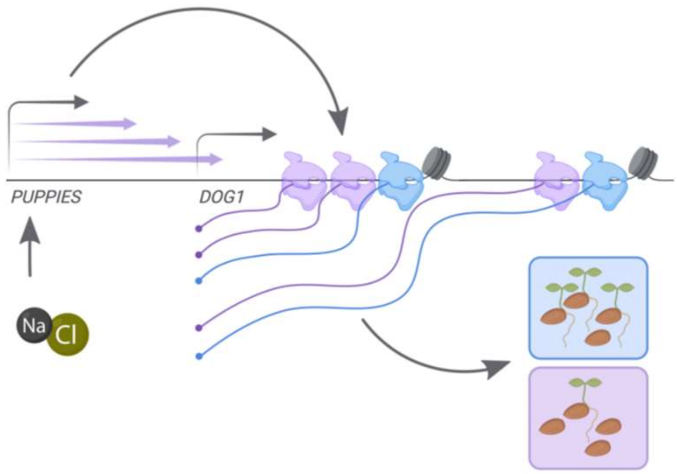

DOG1
Delay of Germination 1
FLC
COOLAIR
DOG1
1GOD
DOG1 antisense is
a negative regulator
of DOG1
relative expression level in Col-0
seed
seedling
seed
seedling
DOG1
asDOG1
% of germinated seeds
Col-0
dog1-5
dog1-3
seed dormancy
DOGI sense
dogl-3
WT
dogl-5
relative expression
units
SALK_000867
dog1-3
SM_3_20886
dog1-4
DOG1
SALK_022748
dog1-5
asDOG1
Swiezewski Nature 2009
Fedak and Palusinska PNAS 2016

11


DOG1 is required for drought
resistance
watered
Col-0
drought
watered
dog1-3
drought
drought
resistance
DOG1 protein
shDOG1 mRNA
proximal
TTS
distal
TTS
DOG1
exon1
exon2
exon3
α
β
asDOG1
asDOG1 is required for
DOG1 induction by ABA
asDOG1
DOG1
expression
ABA time course
ABA
drought
Yatusevich … Swiezewski 2017 EMBO Reports

12

Molecular regulation of DOG1 gene expression mediated by PUPPIES in seeds under salt stress

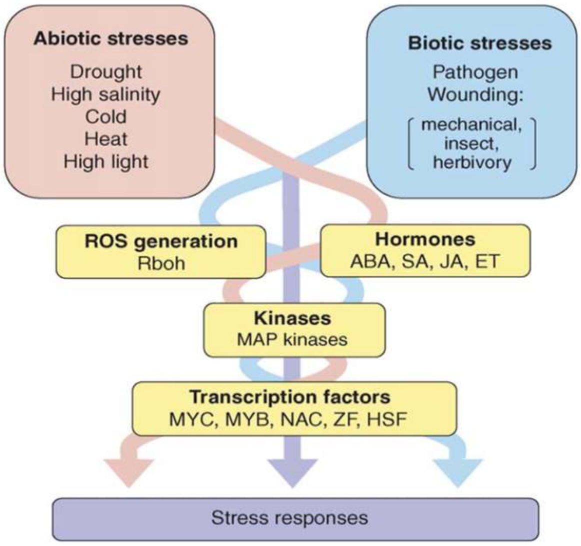


13

Stress response

I and III. Transcription and RNA stability

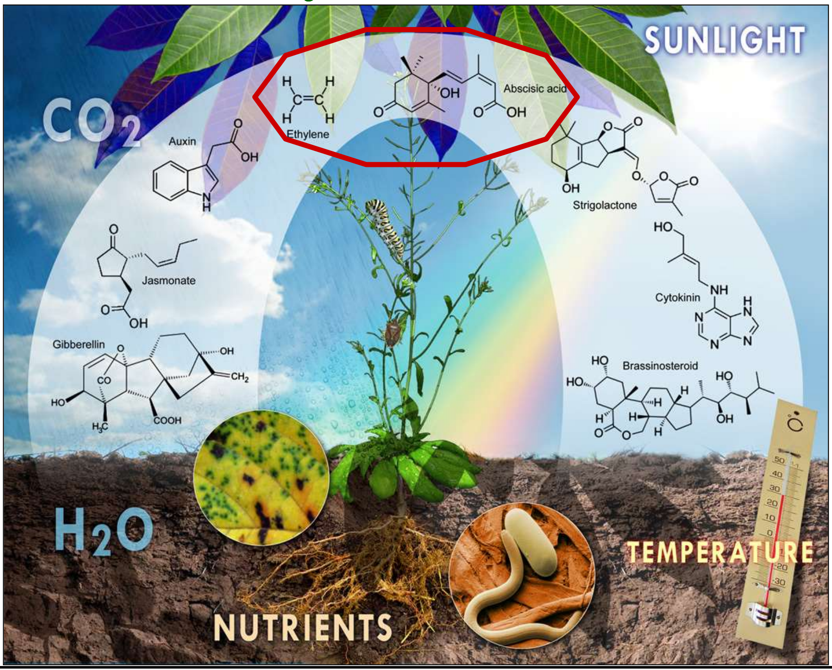
Convergence points in abiotic and biotic stress signaling networks



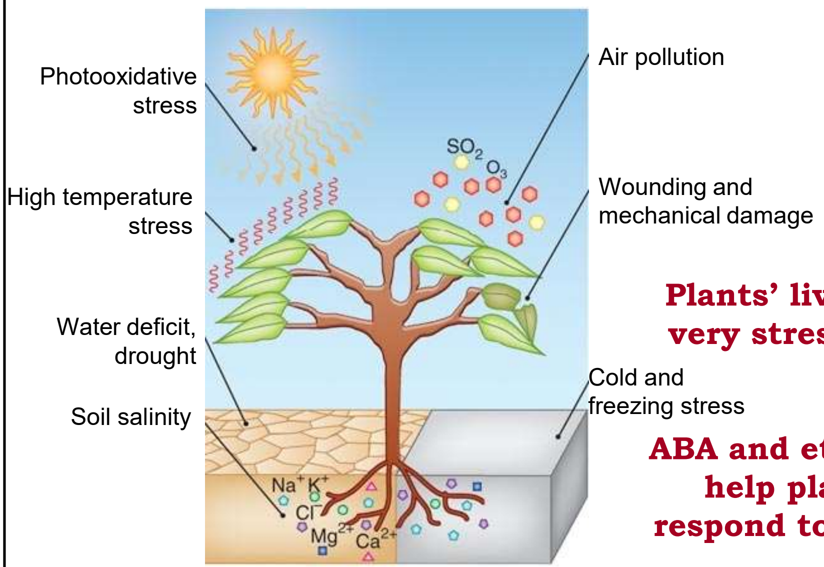
Fujita et al. Current Opinion in Plant Biology 2006, 9:436–442

14

Phytohormones



Hormonal responses to abiotic stress

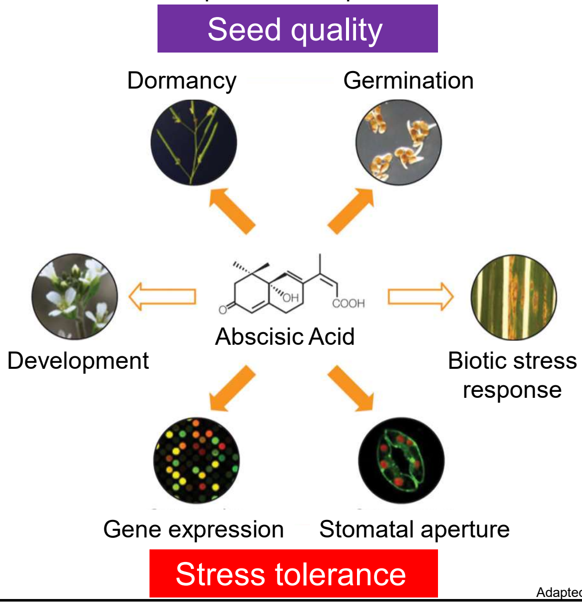


Plants' lives are very stressful…

ABA and ethylene help plants respond to stress

ABSCISIC ACID (ABA)

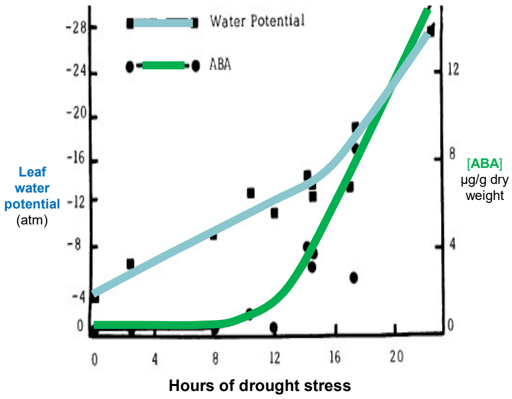
controls many plant processes including stress responses, development and reproduction



Adapted with permission from RIKEN

17

ABA synthesis is strongly induced in response to stress

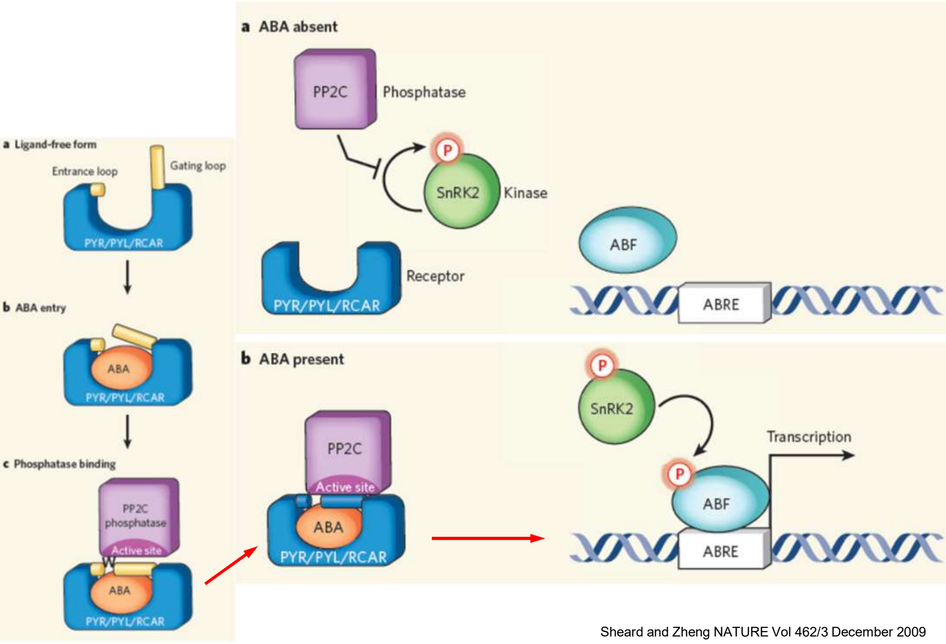


ABA levels rise during drought stress due in part to increased biosynthesis

R.L. Croissant, , Bugwood. www.forestryimages.org . Zabadel, T. J. Plant Physiol. (1974) 53: 125-127.

18

Abscisic acid (ABA) signaling pathway

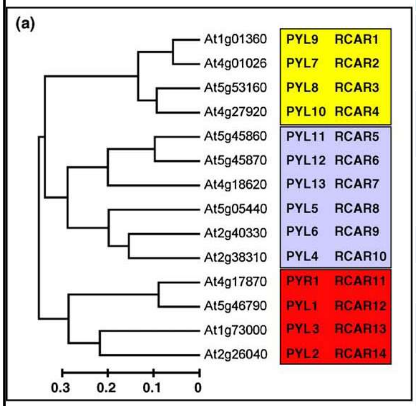


Sheard and Zheng NATURE Vol 462/3 December 2009

19

There are many genes encoding PYR/PYL/RCARs

The 14 PYR/PYL/RCARs in *Arabidopsis*

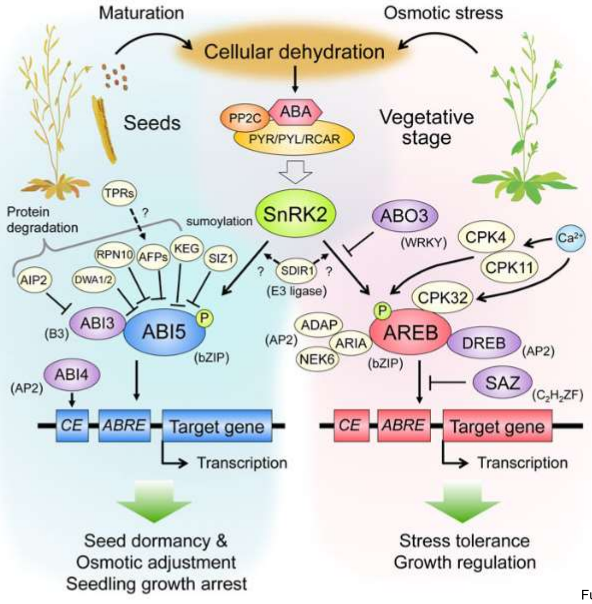


Common Name	Species	Number of genes
Soybean	*Glycine max*	23
Corn	*Zea mays*	20
Western poplar	*Populus trichocarpa*	14
Arabidopsis	*Arabidopsis thaliana*	14
Rice	*Oryza sativa*	11
Grape	*Vitis vinifera*	8
Sorghum	*Sorghum bicolor*	8
Barrel medic (a model legume)	*Medicago truncatula*	6

Klingler, J.P., Batelli, G., and Zhu, J.-K. J. Exp.Bot. 61: 3199-3210
Raghavendra, A.S., Gonugunta, V.K., Christmann, A., and Grill, E. (2010) Trends Plant Sci. 15: 395-401.

20

Transcriptional regulation of ABA signaling by AREB/ABF and ABI5 family TFs



Fujita et al. 2011 J Plant Res

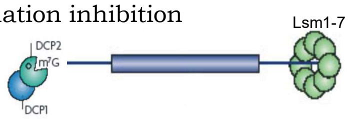
21

ABA response in RNA metabolic mutants

sad1 – supersensitive to ABA and drought
LSM complex (Sm-like) snRNP proteins
mRNA splicing and degradation

ahg2 – ABA hypersensitive germination
poly(A)-specific ribonuclease **AtPARN**
deadenylation, **mRNA degradation**

abh1 – hypersensitive response to ABA in germination inhibition
nuclear cap-binding protein **CBP80**
mRNA splicing and stability



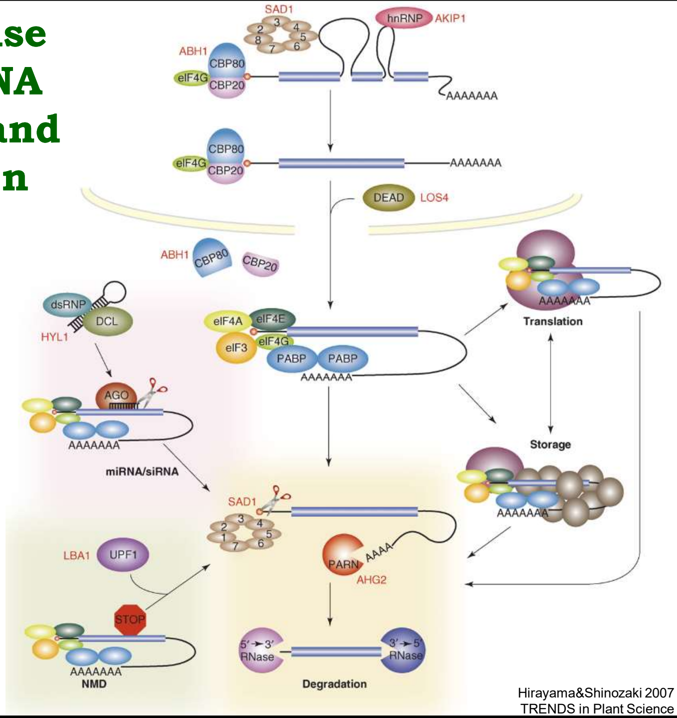
los4 – sensitive to ABA and cold
putative DEAD box RNA helicase LOS4
mRNA export

lba1 – ABA-hypersensitive seed germination
RNA helicase **UPF1** Nonsense-Mediated decay (NMD)
Nonsense-Mediated mRNA decay

hyl1 – hypersensitive to salt and ABA
RNA binding protein HYL1
miRNA processing and accumulation

22

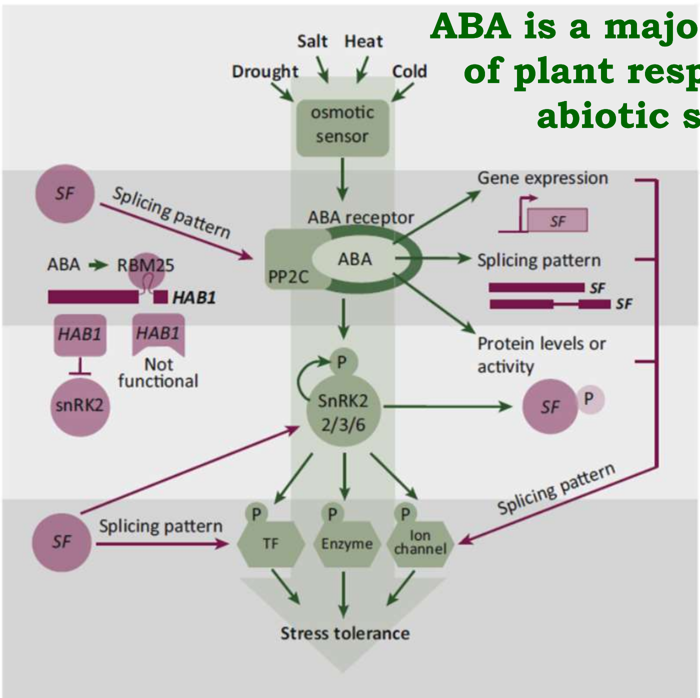
ABA response involves RNA processing and degradation systems



Hirayama&Shinozaki 2007
TRENDS in Plant Science

23

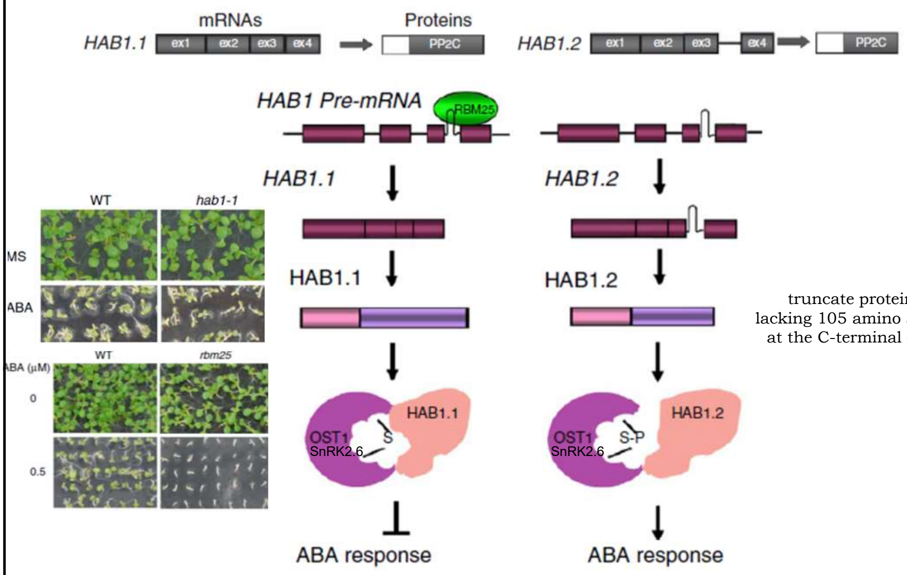
ABA is a major mediator of plant responses to abiotic stress



Laloum et al. 2017
Trends in Plant Science

24

HAB1 splice variants control ABA signalling



truncate protein lacking 105 amino acids at the C-terminal end

Wang et al. 2015 Nature Communications

25

Splicing factors involved in plant abiotic stress responses

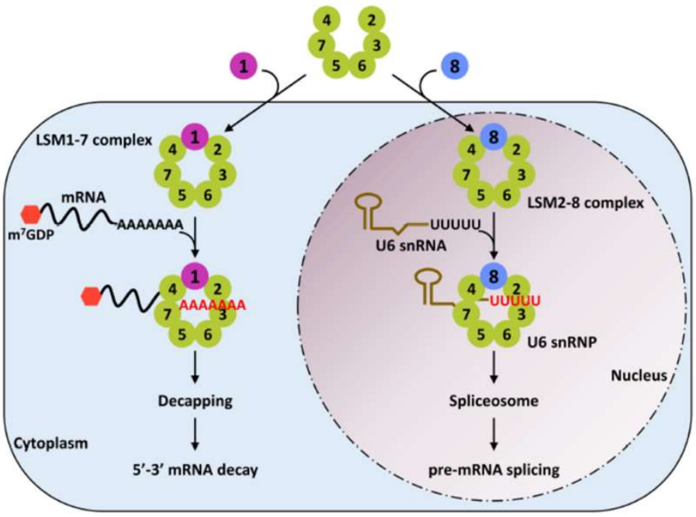
Splicing factor		Abiotic stress under which an *in vivo* role was reported[a]					
		ABA	Drought	Salt	Cold	Heat	Cadmium
SR proteins	SR45	✓	X	X	X	X	X
	SR34b	X	X	X	X	X	✓
	RS40	✓	X	✓	X	X	X
	RS41	✓	X	✓	X	X	X
GRPs	GRP2	X	✓	X	X	X	X
	GRP7	X	✓	✓	✓	X	X
	RZ-1a	✓	✓	✓	X	X	X
CBPs	CBP20	✓	✓	✓	X	X	X
	CBP80/ABH1	✓	✓	✓	X	X	X
Spliceosome components	SKIP	X	✓	✓	X	X	X
	SAD1	✓	✓	✓	X	X	X
	LSm4	✓	X	✓	X	X	X
	RDM16	✓	X	✓	X	X	X
	STA1	✓	✓	✓	✓	✓	X
	RBM25	✓	✓	✓	X	X	X
	SMD3	✓					

[a]Symbols: ✓, *in vivo* stress response role reported; X, no *in vivo* stress response role reported.

Laloum et al. 2017 Trends in Plant Science

26

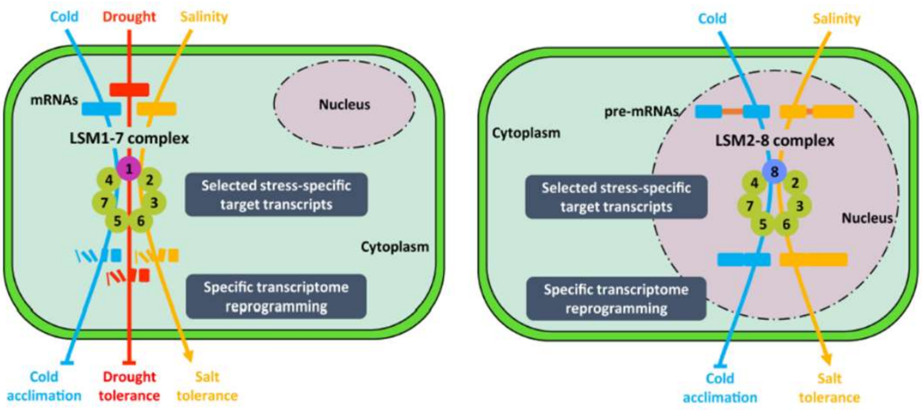
Subcellular localization and function of the eukaryotic LSM complexes



Catala et al. 2019 Frontiers in Plant Science

27

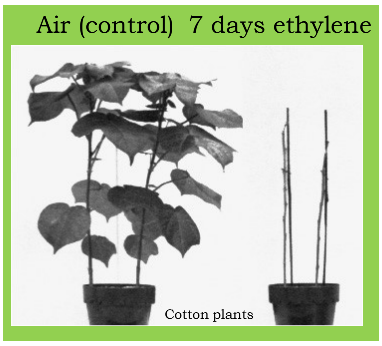
Function of LSM complex in plant response to abiotic stresses



Catala et al. 2019 Frontiers in Plant Science

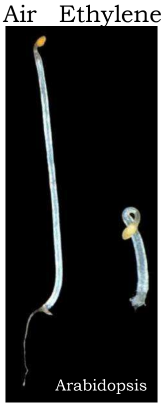
28

Ethylene (C_2H_4) is a gaseous hormone with diverse actions



Ethylene regulates:

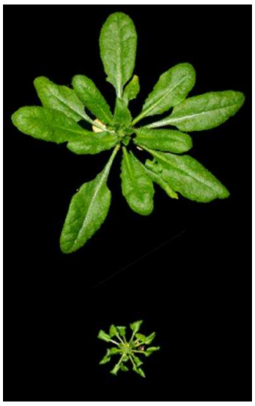
- fruit ripening
- organ expansion
- senescence
- gene expression
- stress responses



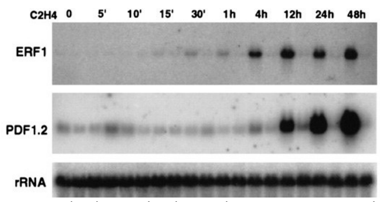
Beyer, Jr., E.M. (1976) Plant Physiol. 58: 268-271.

29

Ethylene responses in *Arabidopsis*



Inhibition of leaf cell expansion



Ethylene-induced gene expression

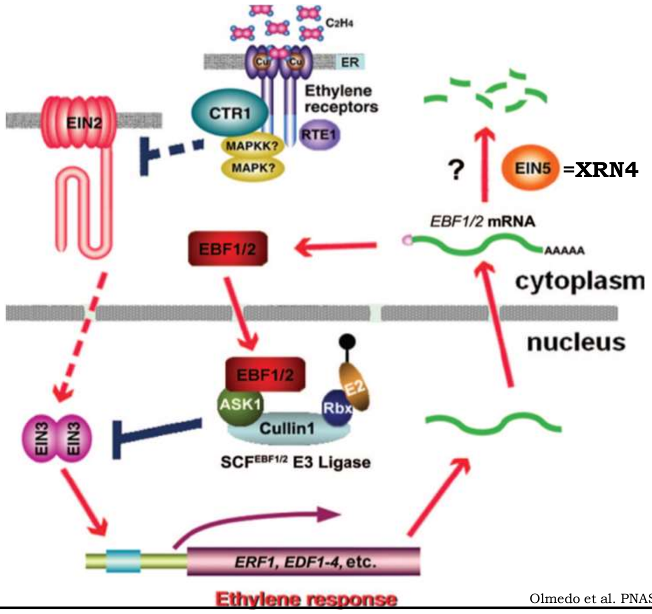
Acceleration of leaf senescence

Inhibition of root elongation

Lorenzo, O., Piqueras, R., Sanchez-Serrano, J.J., and Solano, R. (2003). Plant Cell 15: 165-178;
Růžička, K., Ljung, K., Vanneste, S., Podhorská, R., Beeckman, T., Friml, J., and Benková, E. (2007). Plant Cell 19: 2197-2212.

30

Ethylene signal transduction pathway: XRN4 - 5'-3' cytoplasmic exoribonuclease



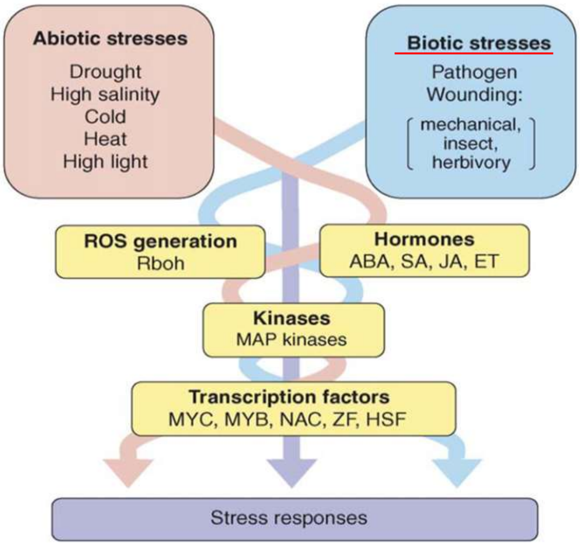
Olmedo et al. PNAS 2006 vol. 103 no. 36

31

Stress response

I and III. Transcription and RNA stability

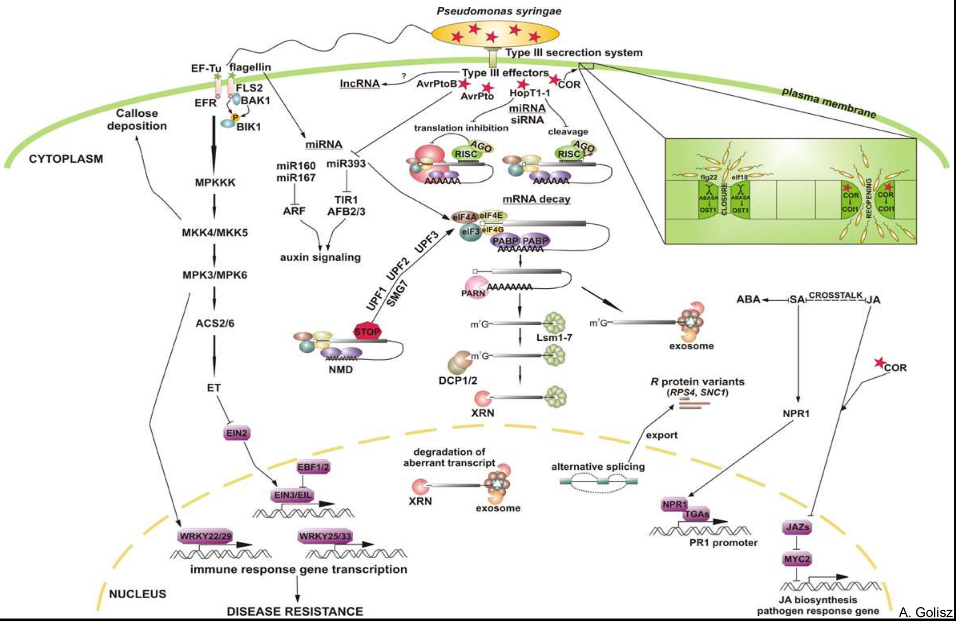
Convergence points in abiotic and biotic stress signaling networks



Fujita et al. Current Opinion in Plant Biology 2006, 9:436–442

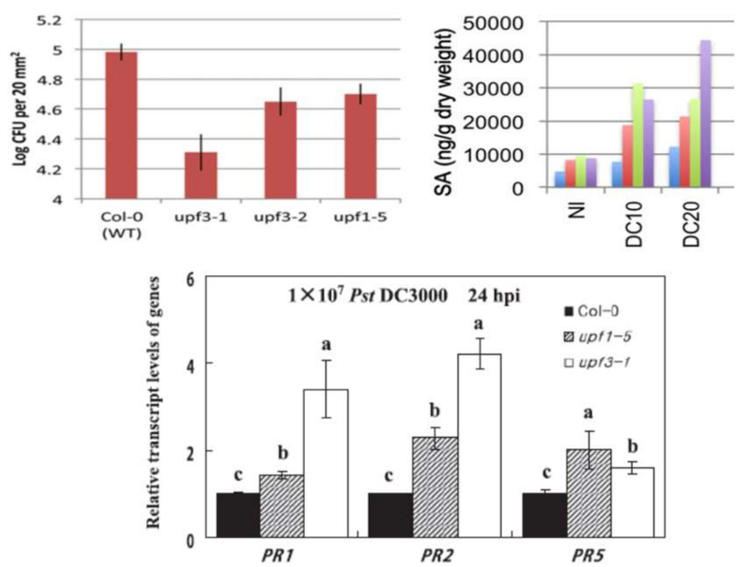
32

Pathways of the interplay between bacterial pathogenesis and plant innate immunity



33

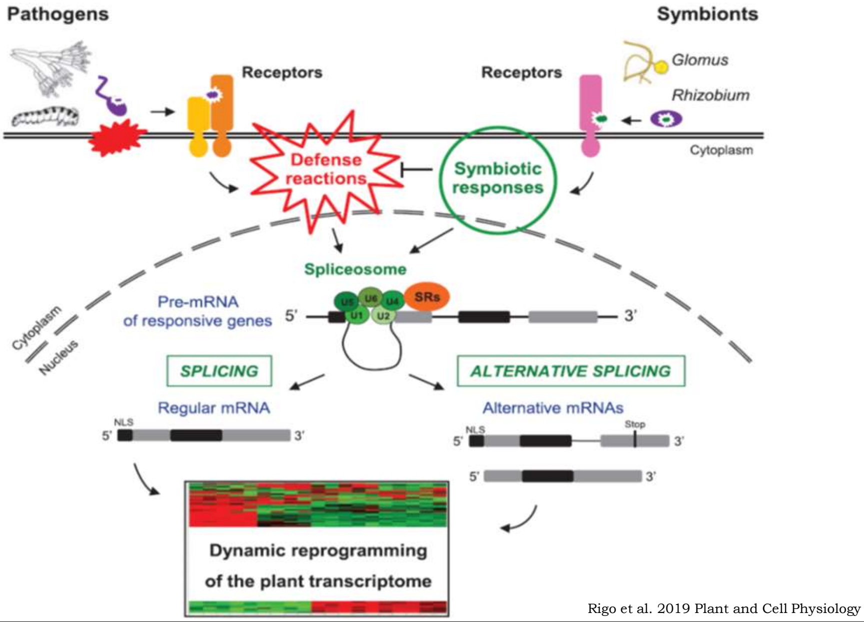
RNA metabolism contribute to plant defense



Rayson et al. PLOS One (2012), 7
Jeong et al. Plant Cell Physiol. 52(12): 2147–2156 (2011)

34

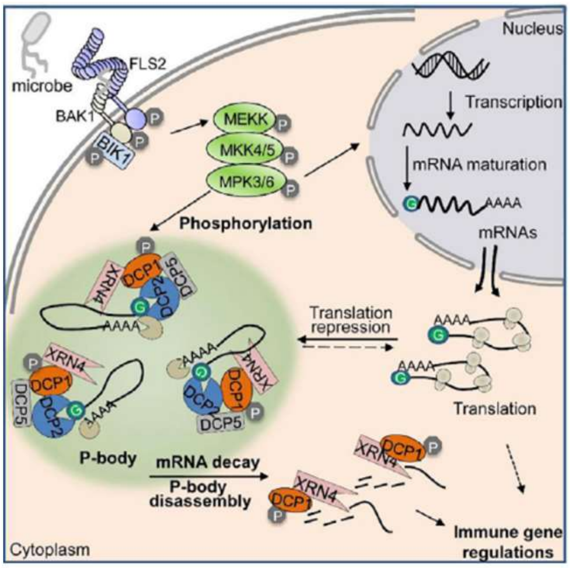
Dynamic reprogramming of the plant transcriptome in response to biotic interactions



Rigo et al. 2019 Plant and Cell Physiology

35

P-body dynamics in plant immunity

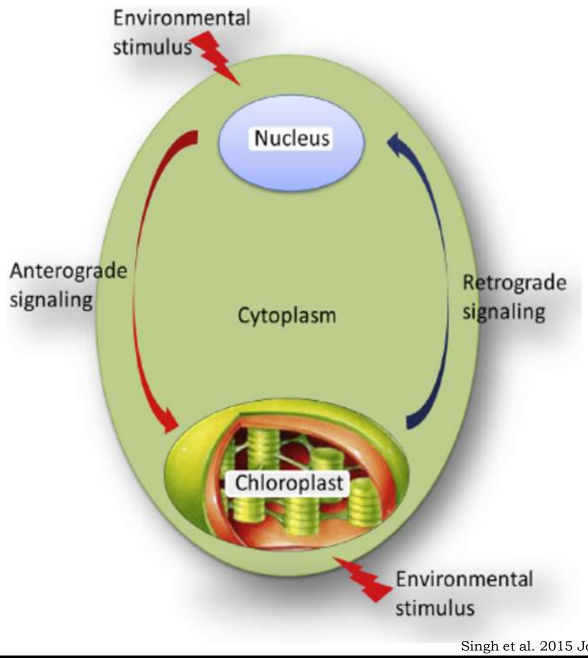


- ❖ P-body dynamics is regulated in plant pattern-triggered immunity (PTI)
- ❖ P-body components DCP1 and DCP2 positively regulate plant PTI
- ❖ Microbe-associated molecular pattern-activated MAP kinases phosphorylate DCP1
- ❖ DCP1 phosphorylation contributes to mRNA decay of certain immune-related genes

Yu et al. 2019 Cell Reports

36

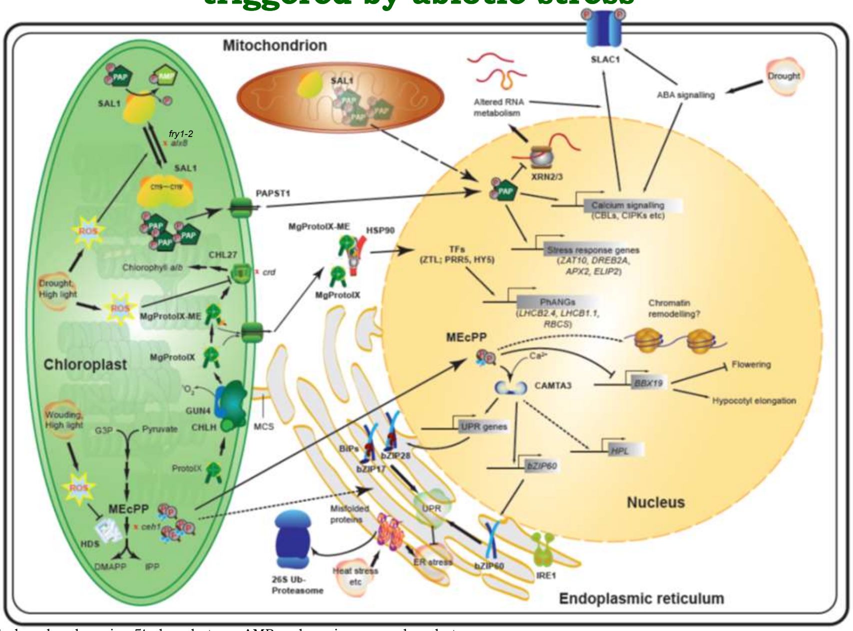
Anterograde and retrograde signaling in plant cells



Singh et al. 2015 Journal of Plant Physiology

37

Metabolite-mediated retrograde signaling pathways triggered by abiotic stress



PAP: 3′-phosphoadenosine 5′-phosphate AMP - adenosine monophosphate
MEcPP: 2-C-methyl-D-erythritol 2,4-cyclodiphosphate

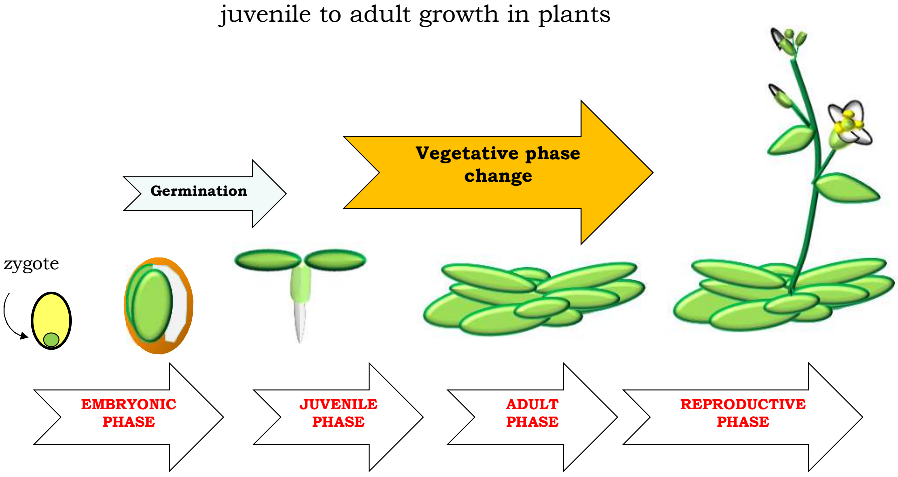
Crawford et al., 2018 J Exp Bot

38

IV. Regulation via miRNA and lncRNA

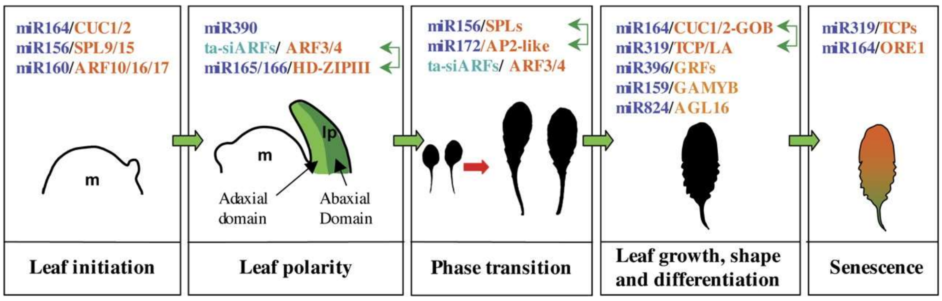
miRNAs and vegetative phase change

Vegetative phase change is the transition from juvenile to adult growth in plants



39

Leaves are modulated by miRNA activity throughout development



Pulido, A., and Laufs, P. (2010). J.Exp.Bot. 61: 1277-1291

40

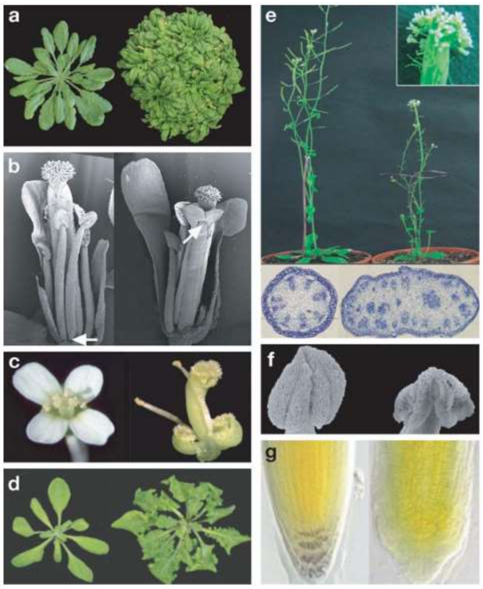
Phenotypes resulting from microRNA overexpression in Arabidopsis

miRNA156

miRNA164

miRNA172

miRNA319



miRNA166

miRNA159a

miRNA160

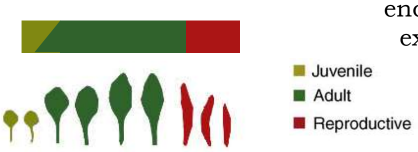
M.W. Jones-Rhoades et al. Annu. Rev. Plant Biol. 2006. 57:19–53

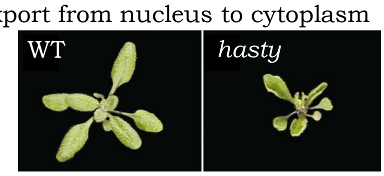
41

Phase change is specified by miRNAs

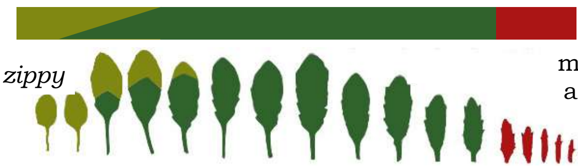
HASTY, with a shortened juvenile phase, encodes a protein needed for miRNA export from nucleus to cytoplasm

hasty



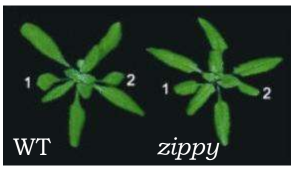


zippy



Loss-of-function *zippy* mutants prematurely express adult vegetative traits. *ZIPPY* encodes an ARGONAUTE protein, AGO7

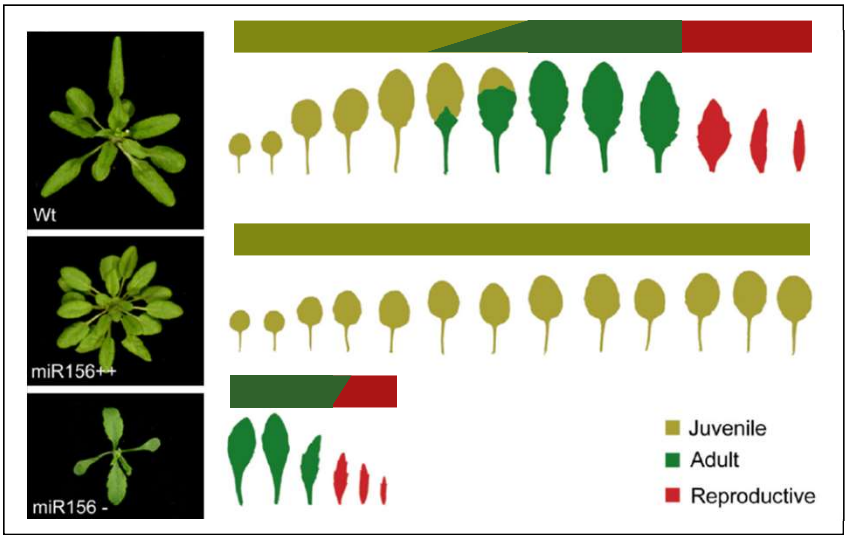
Wild-type



Bollman, et al. (2003) Development 130: 1493-1504
Hunter et al. (2003) Curr. Biol. 13: 1734–1739

42

miR156 overexpression prolongs juvenile phase in *Arabidopsis*



Poethig, R.S. (2009) Curr. Opin. Genet. Devel.

43

Role of conserved plant miRNAs

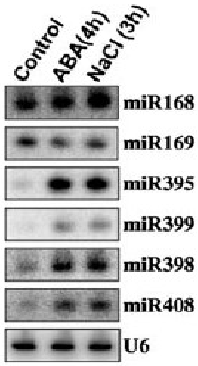
Role	miRNA family	Target families/genes	Reference(s)
Auxin signaling	miR160	ARF10	[122,123]
	miR164	NAC1	[130]
	miR167	ARF8	[122]
	miR390	ARF	[114]
	miR393	TIR1/F-box AFB	[15,124]
Leaf development	miR159	MYB	[48,127,128
	miR164	NAC1	[132]
	miR166	HD-ZIPIII	[131]
	miR172	AP2	[127]
	miR319	TCP	[128]
Leaf polarity	miR166	HD-ZIPIII	[121,131]
	miR168	AGO1	[120]
	miR390	ARF	[114]
Floral organ identity	miR160	ARF10	[122,123,1
	miR164	NAC1	[132,133]
	miR172	AP2	[134]
	miR319	TCP	[127,128]
Flowering time	miR156	SBP	[125–127]
	miR159	MYB	[48]
	miR172	AP2	[127,135]
	miR319	TCP	[127]

Role	miRNA family	Target families/genes	Reference(s)
Adaptive responses to stress	miR156	SBP	[37,43,44,103]
	miR159	MYB	[16,37,43,48,49]
	miR160	ARF10	[37,50,100]
	miR167	ARF8	[37,42,43]
	miR168	AGO1	[37]
	miR169	NFY/MtHAP2-1	[37,43,52,110,136
	miR171	SCL	[37,43]
	miR319	TCP	[16,37,43]
	miR393	TIR1/F-box AFB	[15,16,37,42,43]
	miR395	APS/AST	[15,16,37]
	miR396	GRF	[16,37]
	miR397	Laccases, Beta-6-tubulin	[15,16,37]
	miR398	CSD	[15,19,37,43,53,72
	miR399	UBC24/PHO2	[36,37,75,76]
	miR408	Plastocyanin	[16,37,44]
Regulation of miRNA	miR162	DCL1	[137]
	miR168	AGO1	[120]
	miR403	AGO2	[114]
Others	miR158	At1g64100	
	miR161	PPR	
	miR163	At1g66700, At1g66690	
	miR173	At3g28460	
	miR174	At1g17050	
	miR175	At5g18040, At3g43200, At1g51670	
	miR394	F-box	

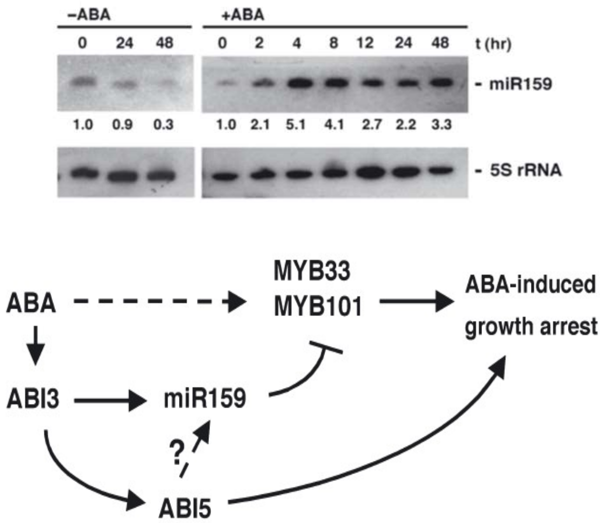
Khraiwesh et al. 2011 Biochimica et Biophysica Acta

44

Regulation of miRNA and their target genes by ABA and salt stress in *Arabidopsis*



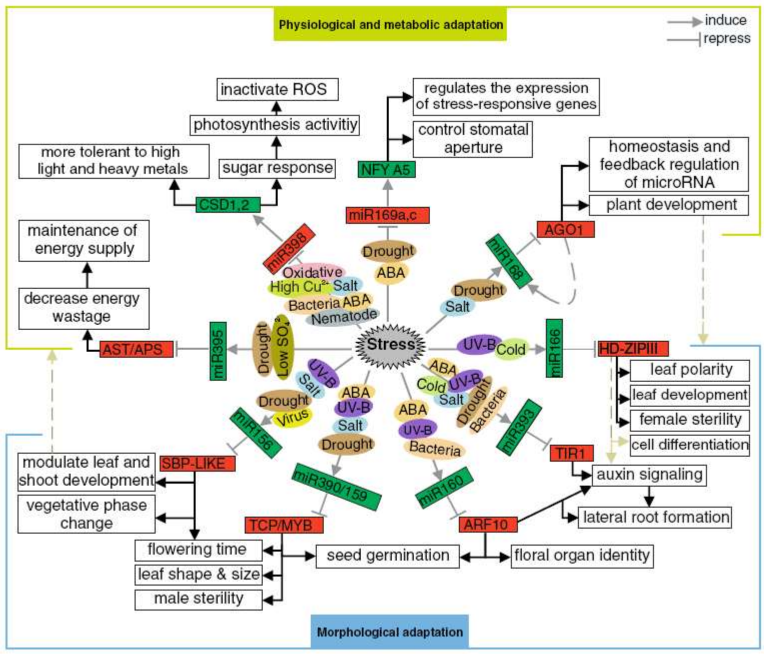
Plant Mol Biol (2009) 71:51–59



The Plant Journal (2007) 49, 592–606

45

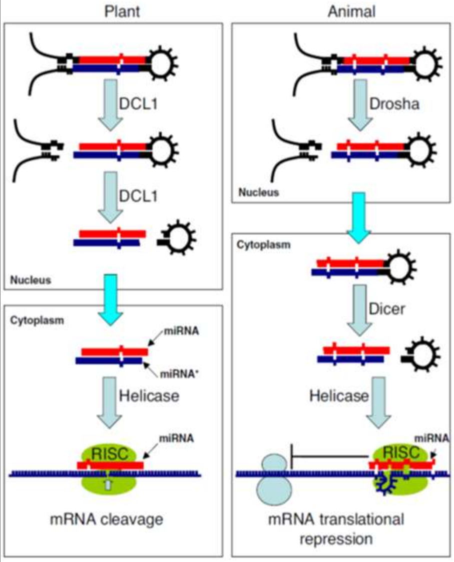
Regulatory network of stress-responsive miRNAs in *Arabidopsis*



B. Khraiwesh et al. Biochimica et Biophysica Acta 1819 (2012) 137–148

46

Distinctions between animal and plant miRNAs



	Plants	Animals
Number of miRNA genes present	100> number <200 of genes	100> number <500 of genes
Location within genome	Predominantly intergenic regions	Intergenic regions introns
Presence of miRNA clusters	Uncommon	Common
MiRNA biosynthesis	Dicer-like	*Drosha*, Dicer
Mechanism of repression	mRNA-cleavage (methylation?)	Translational repression
Location of miRNA-binding motifs within target genes	Predominantly the open-reading frame	Predominantly the 3′-UTR
Number of miRNA-binding sites within target genes	Generally one	Generally multiple
Function of known target genes	Regulatory genes—crucial for development, enzymes	Regualatory genes—crucial for development, structural proteins, enzymes

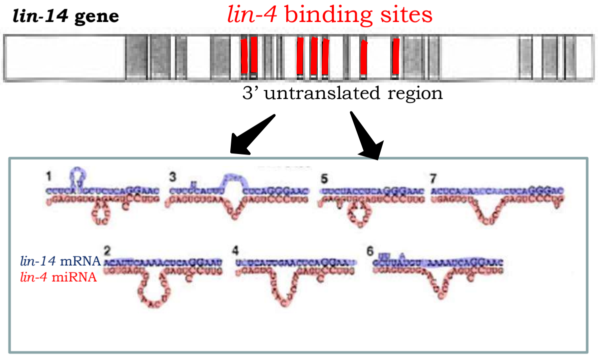
Millar & Waterhouse Funct Integr Genomics (2005) 5: 129–135

47

miRNAs regulate developmental timing

miRNAs were discovered in studies of developmental progressions in the nematode *C. elegans*

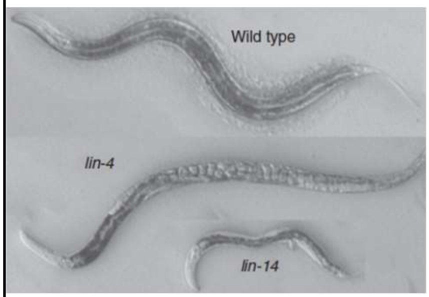
miRNA encoded by *lin-4* is required for proper larval development



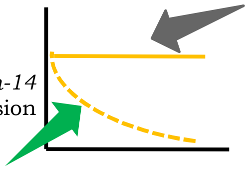
Lee, R.C., Feinbaum, R.L., and Ambrose, V. (1993). Cell 75: 843–845.
Wightman, B., Ha, I., and Ruvkun, G. (1993). Cell 75: 855–862.

48

Downregulation of *lin-14* by *lin-4* is necessary for normal development



lin-14 expression



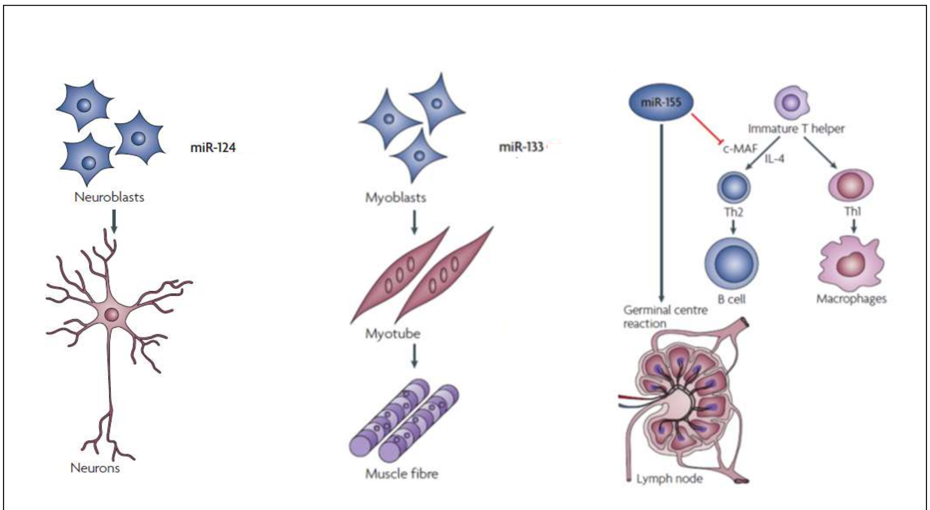
lin-4 loss-of-function causes *lin-14* expression to remain high.

In wild-type worms, *lin-14* is expressed early and then shut off.

lin-4* is a negative regulator of *lin-14

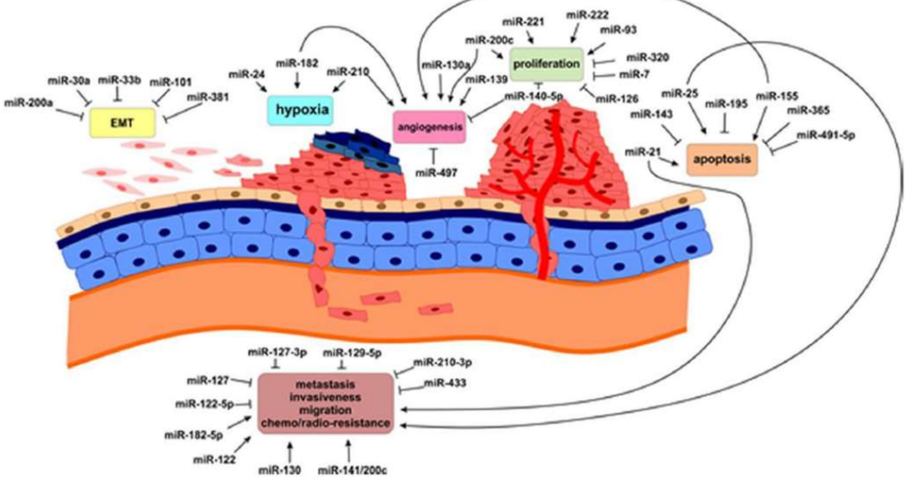
Lee, R.C., Feinbaum, R.L., and Ambrose, V. (1993). Cell 75: 843–845.
Wightman, B., Ha, I., and Ruvkun, G. (1993). Cell 75: 855–862.
Ambros 2008 Nature

miRNA in animal development



Stefani G., Slack F. J., (2008) Mol Cell Biol

MicroRNAs regulate proliferation, apoptosis, EMT, invasiveness, migration, metastases, angiogenesis, and adaptation to hypoxia of cancer cells



Samec et al. Journal of Cancer Research and Clinical Oncology (2019) 145:1665–1679

51

Table 1 Detailed overview of selected miRNAs involved in cancer regulation

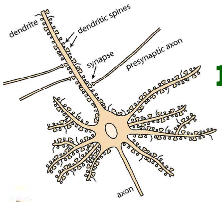
Mechanism of miRNAs regulation of cancer	MicroRNAs	Target pathway/gene product	References
↑ Proliferation	↑ miR-93; ↑ miR-200c; ↑ miR-221; ↑ miR-222; ↓ miR-7; ↓ miR-126; ↓ miR-140-5p; ↓ miR-320	TIMP2, $P27^{Kip1}$, SOX4, EGFR, ADAM9, PDGFRA	Bai et al. (2017), Guan et al. (2017), Lan et al. (2015), le Sage et al. (2007), Wang et al. (2015, 2016), Webster et al. (2009)
↓ Apoptosis	↑ miR-10b; ↑ miR-21; ↑ miR-25; ↑ miR-155; ↑ miR-222; ↓ miR-143; ↓ miR-195; ↓ miR-365; ↓ miR-491-5p	Bcl-2, Bcl-xL, PUMA, PTEN, DR4, TP53, SOCS1, SOCS6, AKT, Ras/MEK/ERK	Bahena-Ocampo et al. (2016), Gu et al. (2018), Guo et al. (2012), Hatley et al. (2010), Jiang et al. (2014), Li et al. (2017c), Liu et al. (2012), Razumilava et al. (2012), Song et al. (2017), Wu et al. (2017), Xue et al. (2016), Zhu et al. (2015)
↑ EMT	↓ miR-30a; ↓ miR-33b; ↓ miR-101; ↓ miR-381; ↓ miR-200 family (miR-200a)	ZEB1/ZEB2, vimentin, Wnt/β-catenin/ZEB1, SOX4, Snai1	Cheng et al. (2012), Cong et al. (2013), Guo et al. (2014), Korpal et al. (2008), Kumarswamy et al. (2012), Liu et al. (2014), Pang et al. (2017), Qu et al. (2015
↑ Invasiveness ↑ Migration ↑ Metastases ↑ Chemo/radio-resistance	↑ miR-21; ↑ miR-25; ↑ miR-122; ↑ miR-130; ↑ miR-141/200c; ↑ miR-182-5p; ↑ miR-548j; ↓ miR-122-5p; ↓ miR-127; ↓ miR-127-3p; ↓ miR-129-5p; ↓ miR-210-3p; ↓ miR-433	TIMP3, PTEN, FBXW7, KRAS, MAPK, ITGA6, TGFβR2, VEGF-A, DUSP4, FGFRL1, RAB27A, FNDC3B, Dicer, TNS1	Choi et al. (2016), Duan et al. (2016), Fan et al. (2018), Gong et al. (2015), Guo et al. (2013), Li et al. (2017a), Liu et al. (2013), Martin del Campo et al. (2015), Wang et al. (2018a), Xu et al. (2017, 2018), Yang et al. (2017), Zhan et al. (2016
↑ Adaptation to hypoxia	↑ miR-24; ↑ miR-182; ↑ miR-210	FIH1, HIF-1α, PHD2, PTPN1	Li et al. (2014b, 2015c), Roscigno et al. (2017)
↑ Angiogenesis	↑ miR-130a; ↑ miR-139; ↑ miR-155; ↑ miR-182; ↑ miR-200c; ↑ miR-210; ↑ miR-449a; ↓ miR-140-5; ↓ miR-497	VEGF-A, VEGFR2, RASA1, c-MYB, VHL, FGFRL1, CRIP2, HIF-1α	Du et al. (2015), Kong et al. (2014), Li et al. (2015a), Lu et al. (2017), Shi et al. (2016), Wang et al. (2014a), Yang et al. (2016, 2018)

Explanatory notes: ↑ increase, ↓ decrease

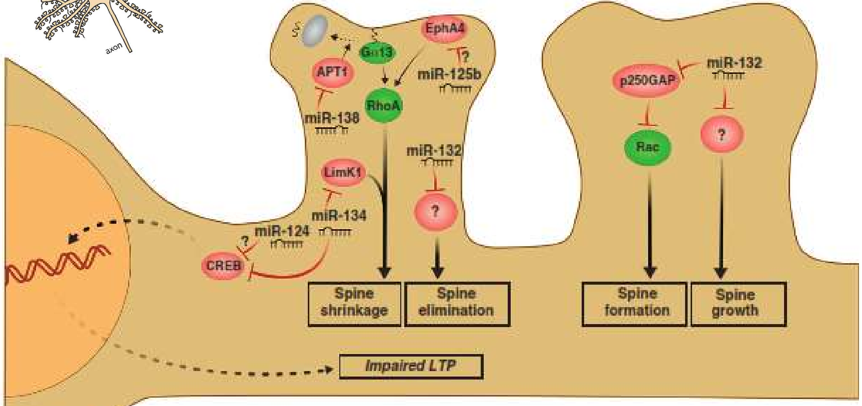
ADAM9 A disintegrin and metalloproteases 9, *AKT* protein kinase B, *Bcl-xL* B-cell lymphoma-extra large, *Bcl-2* B-cell lymphoma, *CRIP2* cysteine-rich protein 2, *DR4* Death Receptor-4, *DUSP4* Dual Specificity Phosphatase 4, *FBXW7* F-box and WD-40 domain protein 7, *FGFRL1* fibroblast growth factor receptor-like 1, *FIH1* factor-inhibiting HIF hydroxylase 1, *FNDC3B* Fibronectin Type III Domain Containing 3B, *HIF1α* hypoxia-inducible factor 1α, *ITGA6* integrin subunit-α 6, *KRAS* Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, *MAPK* mitogen-activated protein kinase 4, *PDGFRA* platelet-derived growth factor receptor A, *PHD2* hypoxia-inducible factor prolyl hydroxylase 2, *PTEN* phosphatase and tensin homolog, *PTPN1* tyrosine-protein phosphatase non-receptor type 1, *PUMA* the p53 upregulated modulator of apoptosis, $p27^{Kip1}$ cyclin-dependent kinase inhibitor 1B, *RAB27A* Ras-related protein Rab-27A, *RASA1* RAS p21 protein activator 1, *SNAI1* snail family zinc finger 1, *SOCS1* suppressor of cytokine signaling 1, *SOCS6* suppressor of cytokine signaling 6, *SOX4* the SRY-box 4, *TGFβR2* the transforming growth factor beta receptor-2, *TIMP2* tissue inhibitor of metalloproteinase 2, *TIMP3* tissue inhibitor of metalloproteinases 3, *TNS1* Tensin 1, *TP53* tumor protein p53, *VEGF* vascular endothelial growth factor, *VHL* von Hippel–Lindau tumor suppressor, *ZEB1* Zinc finger E-box-binding homeobox 1, *ZEB2* Zinc finger E-box-binding homeobox 2

Samec et al. Journal of Cancer Research and Clinical Oncology (2019) 145:1665–1679

52



Regulation of dendritic spine morphogenesis by microRNAs



miR-134 and miR-138 – reduced dendritic spine volume

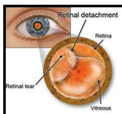
miR-132 – increased dendritic spine density

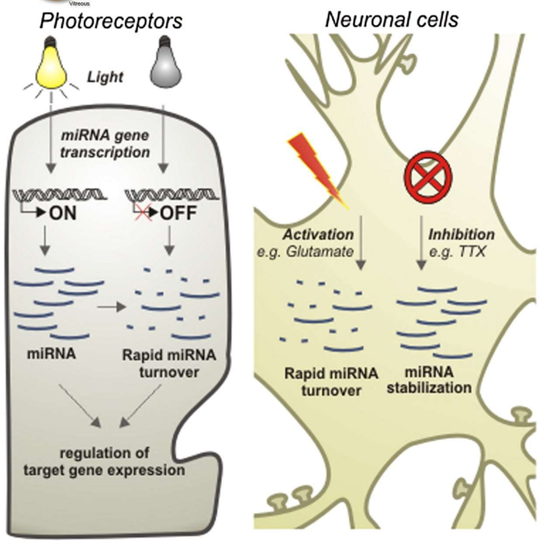
miR-125 – decreased dendritic spine width and increased lenght

Current Opinionin Genetics&Development 2011, 21:491–497

53

Light-Regulated Retinal MicroRNAs





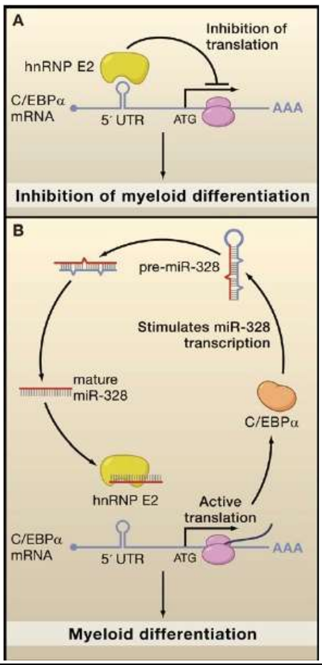
- ► **Several miRNAs** (*miR183/96/182, miR204, miR211*) **are transcriptionally upregulated by light in mouse retinal neurons**
- ► **Glutamate transporter SLC1A1** (*voltage-dependent*) **is one of the targets of the light-regulated miRNAs**
- ► **miRNAs in retinal neurons decay much faster than in nonneuronal cells**
- ► **Blocking action potentials or glutamate receptors strongly affects miRNA turnover**

microRNA metabolism in neurons is higher than in most other cells types

Filipowicz et al. Cell 2010, 141, 618-631

54

miRNA as a DECOY in myeloid cell differentiation



► **RNA binding protein hnRNP E2** *(activated by BCR/ABL kinase in chronic myeloid leukemia patients-CML)* **inhibits translation of C/EBP mRNA by binding to its 5' UTR. This stops MD**

► **miR-328 directly binds hnRNP E2 due to sequence similarity to the E2 binding site on C/EBP mRNA**

► **translation of C/EBP is activated leading to MD**

► **C/EBP stimulates miR-328 transcription** *(positive feedback loop for MD fine-tuning)*

Beitzinger and Meister, Cell, 2010

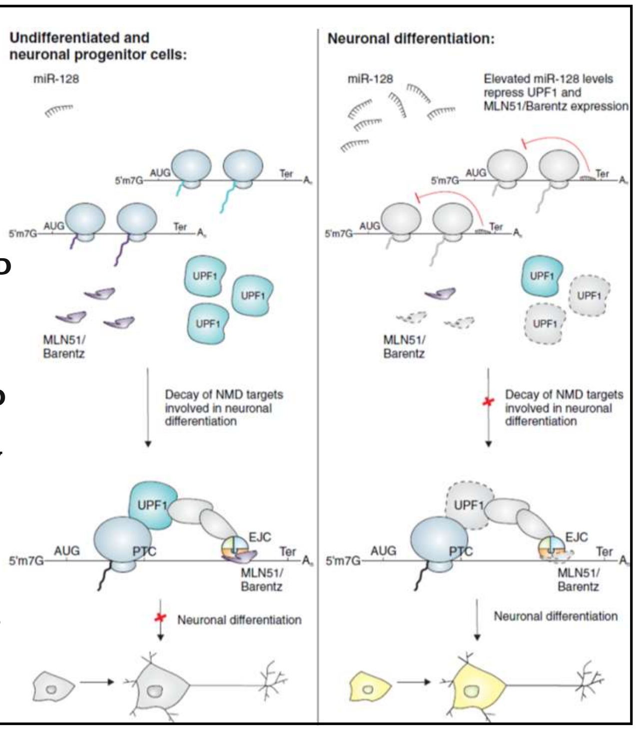
55

A microRNA/NMD circuit regulates neuronal development

► **miR-128 targets the 3' UTR of the central NMD factor UPF1 and the EJC core component MLN51**

► **downregulation of NMD factors by miR-128 represses NMD activity in human and mouse cells**

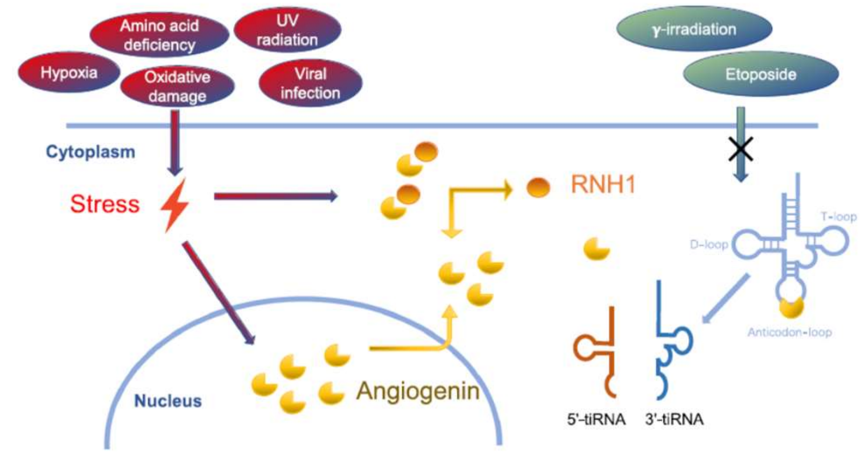
► **miR-128 is drastically upregulated during brain development and neuronal maturation**



Ottens & Gehring 2016 Eur J Physiol

56

Biogenesis of tiRNAs

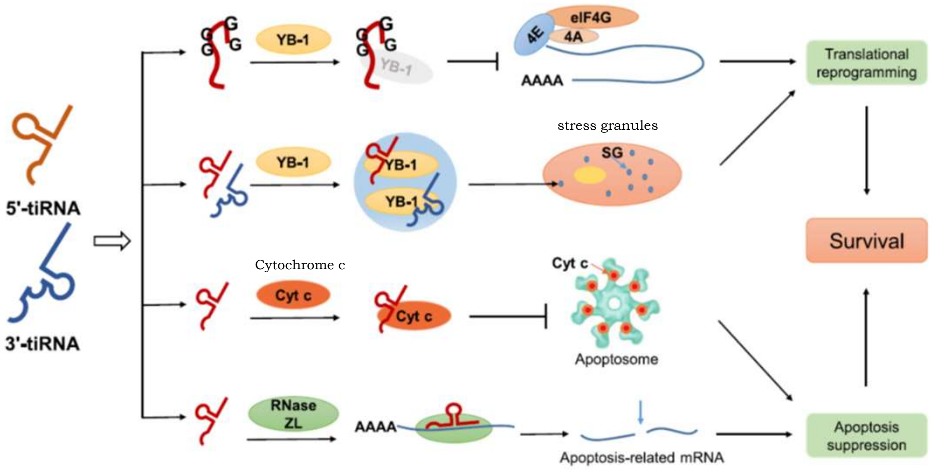


Angiogenin – member of the RNase superfamily
RNH1 – ribonuclease/angiogenin inhibitor 1

Tao et al., 2019 Journal of Cellular Physiology

57

Mechanisms of tiRNAs in response to stress



- 5′-tiRNAs form G-quadruplex structures and disturb translational initiation via sequestering the eIF4F complex from mRNA
- 5′-tiRNAs and 3′-tiRNAs cooperate with Y-box protein 1 (YB-1) to prevent the eukaryotic initiation factor 4F (eIF4F) complex from initiating translation and induce the assembly of stress granules
- under hyperosmotic stresses, tiRNAs directly bind to Cyt c and form a ribonucleoprotein complex, which can inhibit apoptosis by decreasing apoptosome formation or reducing activity
- tiRNAs inhibit apoptosis by reducing mRNAs via a process dependent on the cleavage by tRNase ZL

Tao et al., 2019 Journal of Cellular Physiology

58

Role of tRNA-derived stress-induced RNAs (tiRNAs) in cancer

Cancer type	tiRNA	Sample type	Function	Reference
Brest cancer	5′ tiRNA-Arg/Asn/Cys/Gln/Gly/Leu/Ser/Trp/Val/Asp/Lys	Serum	Associated with clinicopathological characteristics	Dhahbi et al. (2014)
	5′ tiRNA-Val	Cell, tissue, serum	Suppress cell proliferation, migration and invasion	Mo et al. (2019)
Prostate cancer	5′-tiRNA derived from the pseudogene tRNA-Und-NNN-4-1	Seminal fluid	Noninvasive biomarker for cancer screening	Dhahbi et al. (2018)
	5′-tiRNA-Asp-GUC, 5′-tiRNA-Glu-CUC	Serum, tissue	Prognostic parameter	Zhao et al. (2018)
	5′-SHOT-RNA^{AspGUC}, 5′-SHOT-RNA^{HisGUG}, 5′-SHOT-RNA^{LysCUU}	Cell	Enhance cell proliferation	Honda and Kirino (2016), Honda et al. (2015)
Lung cancer	5′-tiRNA-Leu-CAG	Cell, tissue, serum	Promote cell proliferation and cell cycle	Shao et al. (2017)
Gastric cancer	tiRNA-5034-GluTTC-2	Cell, tissue, plasma	Biomarker for diagnosis	Zhu et al. (2019)
Colorectal cancer	5′-tiRNA-Val	Cell, tissue, serum	Promote cell migration, invasion and metastasis	Li et al. (2019)

Tao et al., 2019 Journal of Cellular Physiology

59

Oncogenic or tumor-suppressive non-coding RNAs with in vivo experimental evidence

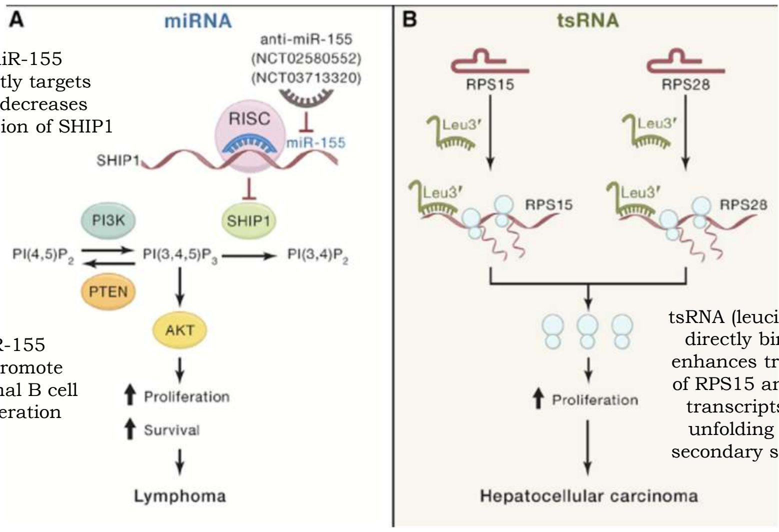
Name	ncRNA Class	Cancer Types Examined	*In Vivo* Experimental Techniques Used	Cancer-Related Mechanisms and/or Functions of ncRNA	References
Oncogenic ncRNAs					
miR-155	miRNA	lymphoma	transgenic overexpression mouse model, treatment with antimiRs	targets SHIP1 transcript, a negative regulator of AKT, to increase proliferation and survival	O'Connell et al., 2009; Babar et al., 2012; Cheng et al., 2015
HOTAIR	lncRNA	breast	siRNA knockdown, overexpression in mouse xenografts	recruits PRC2, LSD1/CoREST/REST chromatin modifying complexes, scaffolds transcription factors at target promoters of genes involved in invasion, metastasis, and proliferation	Gupta et al., 2010; Li et al., 2016b
THOR	lncRNA	lung, melanoma	CRISPR-Cas9 knockdown, overexpression in mouse xenografts; transgenic knockout, overexpression in zebrafish	binds IGF2BP1 to stabilize interactions with oncogenic target mRNAs, in turn stabilizing those transcripts and promoting proliferation	Hosono et al., 2017
BRAFP1	pseudogene	B cell lymphoma	transgenic overexpression mouse model	acts as a ceRNA for miRNAs that target the BRAF transcript, leading to increased BRAF expression, MAPK signaling, and proliferation	Karreth et al., 2015
circCCDC66	circRNA	colorectal	siRNA knockdown in mouse xenografts	sponges several miRNAs that target oncogenic transcripts (e.g., MYC), promoting proliferation, migration, and invasion	Hsiao et al., 2017

Slack & Chinnaiyan 2019 Cell

60

Oncogenic ncRNAs and cancer-promoting mechanisms

miR-155 directly targets and decreases expression of SHIP1



miR-155 can promote abnormal B cell proliferation

tsRNA (leucine tRNA) directly binds and enhances translation of RPS15 and RPS28 transcripts by the unfolding of their secondary structures

anti-miRs targeting miR-155 can inhibit tumor growth

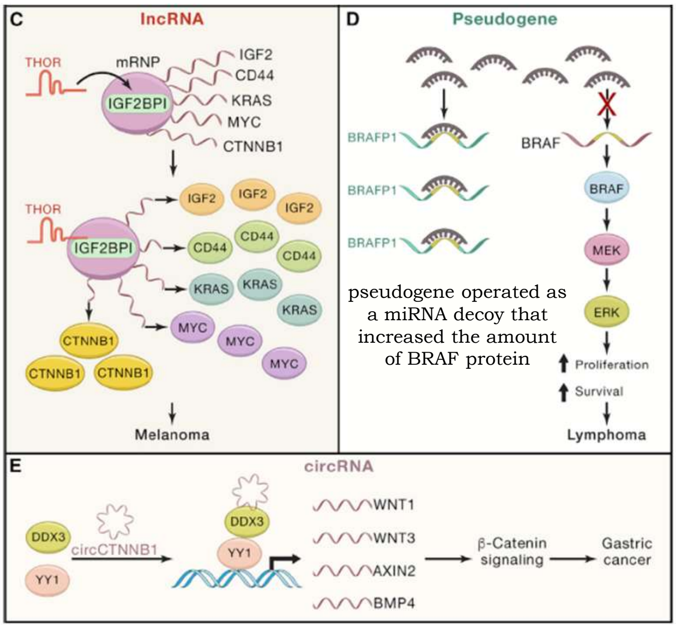
increase the levels of small ribosomal proteins and biogenesis of ribosomes, promoting proliferation of hepatocellular carcinoma cells

Slack & Chinnaiyan 2019 Cell

61

Oncogenic ncRNAs and cancer-promoting mechanisms

lncRNA THOR oncogene stabilize the binding and increase translation of IGF2BP1 target mRNAs



pseudogene operated as a miRNA decoy that increased the amount of BRAF protein

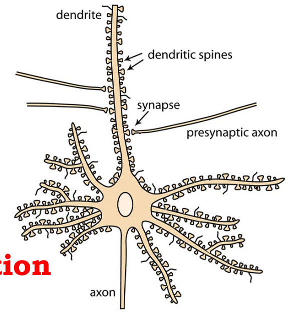
circRNAs prime candidates for novel cancer biomarkers

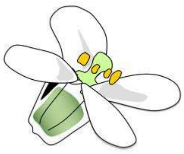
circCTNNB1 binds to DDX3 and increases its interaction with YY1 transcription factors, resulting in enhanced transactivation of YY1 target promoters

Slack & Chinnaiyan 2019 Cell

62

Summary



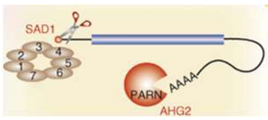


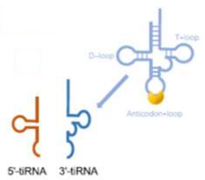
Chromatin and transcription

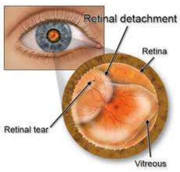
RNA processing

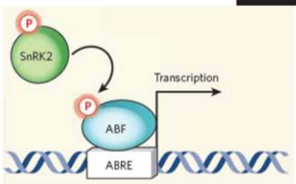
mRNA stability

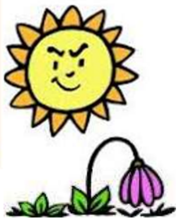
miRNA and lncRNA











63