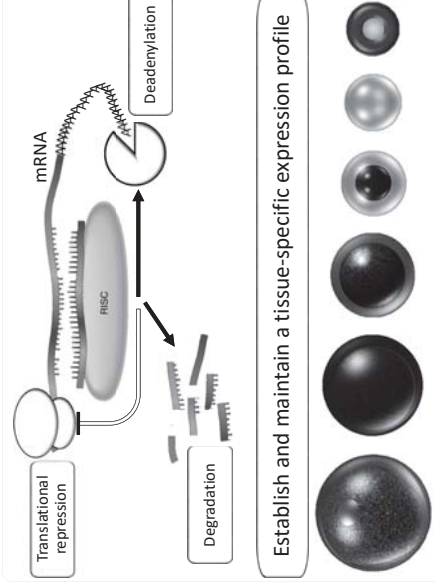


The Role of miRNAs in Hematological Malignancies



Kristin Landis-Piwowar PhD, MLS(ASCP)^{CM}

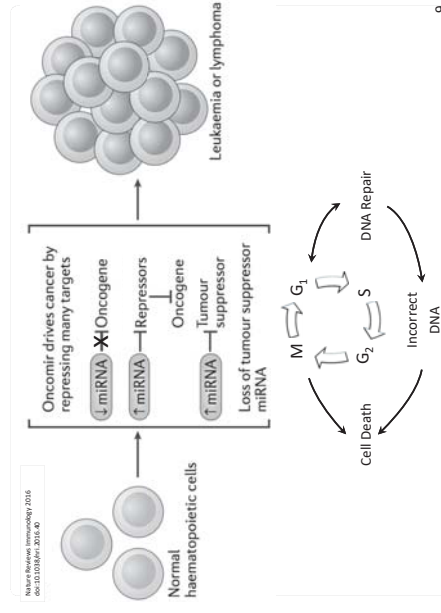
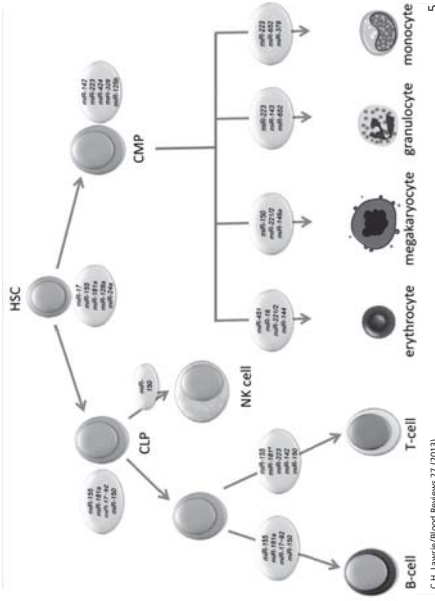
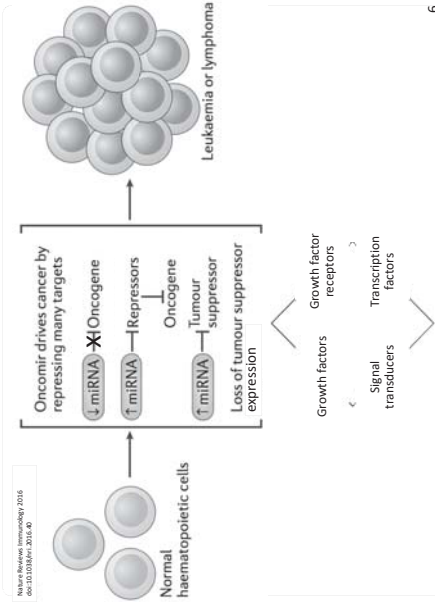
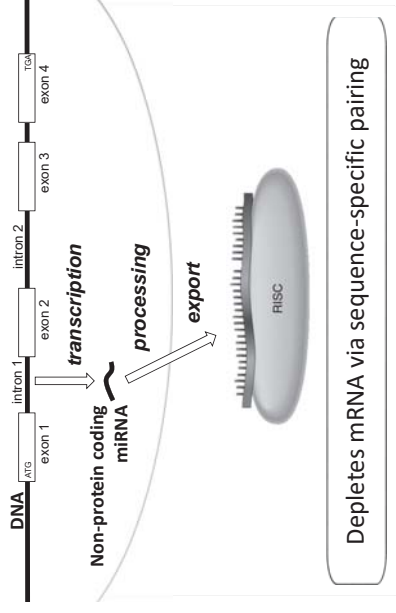
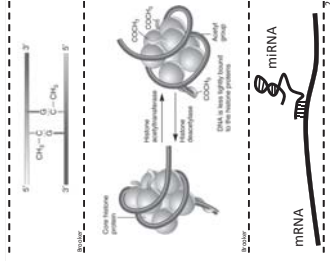


Oncomirs

Regulating miRNA	Target gene	Leukemia	Regulating miRNA	Target gene	Leukemia
miR15b/16	BCL2, MCL1, CCND1, WNT3A, NFKB, VEGF	DLBCL, CLL, PCM	miR-181	TLR4, CARD8, CASP1, IL1B, KRAS, MAPK1	AML
miR-17-92	BCL2	PCM	miR-126	PLK2	AML
miR181-b	CYLD	CLL	miR-223	E2F	AML
miR-590	Rb, p21, STAT3	T-ALL	miR-195a	ERG	AML, T-ALL
miR17/92	Rb, p21, STAT3	DLBCL, CLL, MLL, etc.	miR-193a	AML1/Eto, HDAC3, KIT	AML
miR-31	CBL	GML		CCDN1	
miR-130a	RECK	CML		MDM2	
miR-564	E2F, AKT	CML		PTEN	
miR-130b	PTEN	APL	miR-221	p27	AML
miR-15-5p	STAT5b	JMML	miR155	SHIP1, CBL	AML, DLBCL, CLL
				CCDN1	

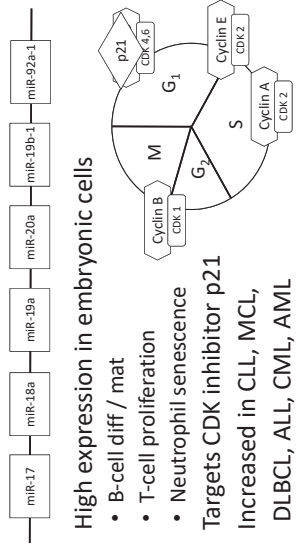
Epigenetics: Modification of gene expression without changing genetic code

- DNA provides the genetic plan
- Other factors affect how that plan will be expressed
- DNA methylation
- Histone modifications
- Non-coding RNA (miRNA)



miR 17/92

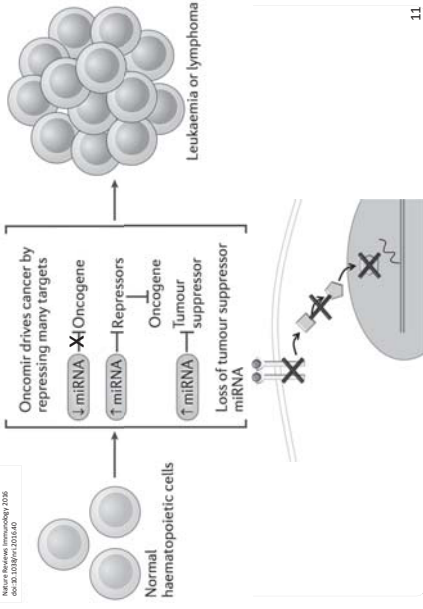
p21 mRNA 5' AGAAGUAAACAGAUUGGCUUUUG 3'
miR-17/92 3' GAUGGACGGACAUUCGGGAAAC 5'



High expression in embryonic cells

- B-cell diff / mat
- T-cell proliferation
- Neutrophil senescence
- Targets CDK inhibitor p21
- Increased in CLL, MCL, DLBCL, ALL, CML, AML

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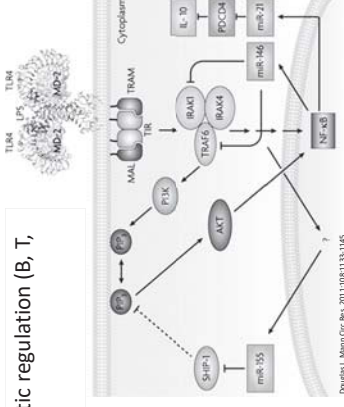
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miR-155

SHIP1 mRNA 5' UGGAGGGGUG---AAAGCAUUA 3'
miR-155 3' UGGGGAUGGUCUAUCGUAUUU 5'

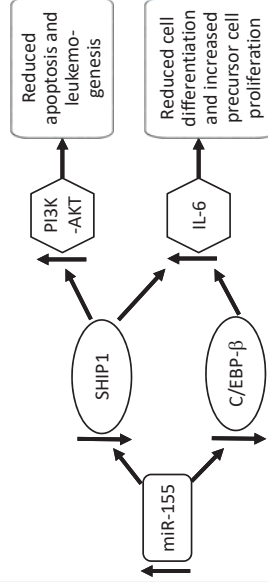
Hematopoietic regulation (B, T, gran)

- Targets ~140 genes
 - ↓ SHIP1, C/EBPβ
- Increased in DLBCL, HL, FL, CLL, ALL, AML



Douglas L. Mann *Cell* 2011;130:1133-1145

AML and miR-155



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Clinical Detection of miRNAs

- WBCs
 - Circulating (serum/plasma)
 - Body fluids (urine, amniotic, pleural, peritoneal, CSF, etc.)
 - Frozen tissues
 - FFPE, formalin-fixed paraffin-embedded
- qRT-PCR
 - \$\$\$-efficient
 - Inner reference gene for data normalization is controversial
 - Microarrays
 - High throughput
 - Array of miRNAs
 - Next-gen sequencing
 - In situ hybridization
 - Enzymatic luminescence

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Summary of miRNAs with functional evidence for an involvement in both normal hematopoiesis and hematological malignancy

miRNA	Hematopoiesis	Malignancy	Target
miR-155	B/T-cell development	DLBCL, B-ALL	IRAK1, IRK4, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-17-92	B-cell development	B-cell lymphoma, CLL, ALL, MCL, MFL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-34c	B-cell development	B-cell lymphoma	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-125	Myelopoiesis	DLBCL, ALL, MDS, AML	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-223	Myelopoiesis, megakaryopoiesis, granulopoiesis, B-cell development	MDS, ALL, MDS, AML	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-182	Myelopoiesis, megakaryopoiesis, granulopoiesis, B-cell development	MDS, MCL, NKT cell lymphoma	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-381	B/T-cell development, NK cell development	AML, CLL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-27(2/22)	Myelopoiesis	AML, CLL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-150(1/5)	Myelopoiesis, B-cell development, hematopoietic cells	CLL, ALL, MCL, MFL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-21	Unknown (probably apoptosis of hematopoietic cells)	B-cell lymphoma, NKT lymphoma, MDS, ALL, MDS, AML	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-29b	Myelopoiesis	AML, CLL, MCL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21
miR-129a	Myelopoiesis	AML, ALL	SHIP1, TRAF6, MYD88, NF-κB, SHIP1, C/EBPβ, IL-6, PDCD4, miR-146, miR-21

C.H. Lawley *Blood Reviews* 27 (2013)

- Involved in normal hematopoiesis
- Aberrantly expressed in neoplasms/malignancies
- Biomarkers of diagnosis, prognosis, predict tx response
- Expression can distinguish cancers; better accuracy than traditional gene expression analysis

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