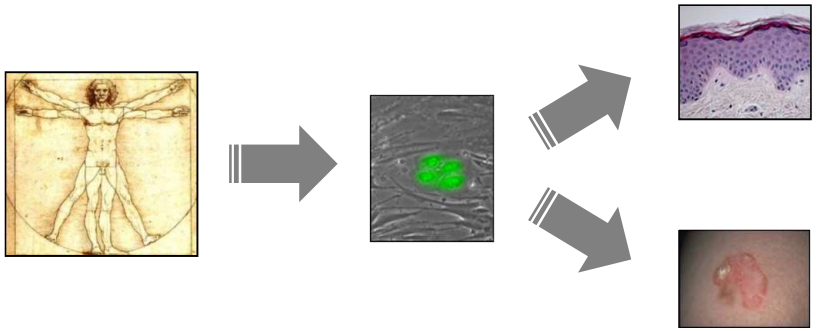
DE LA RECHERCHE À L'INDUSTRIE

Non coding RNAs: a new mechanism to regulate sensitivity to IR?



Michèle T MARTIN

Genomics and Radiobiology of Keratinopoiesis

CEA/DRF/IRCM – INSERM/ UMR 967, Evry, France

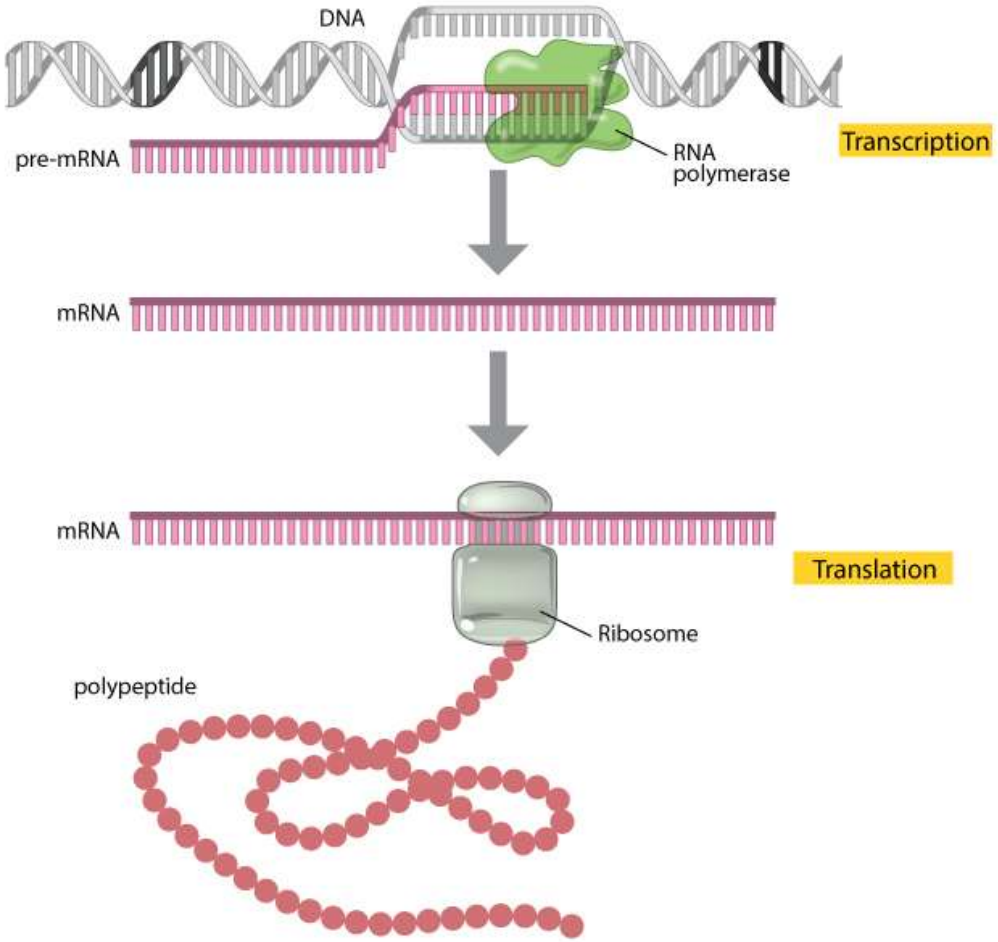
Genome activity: production of proteins

DNA
the source of information

messenger RNA

protein
the product

the functions



GWAS genome sequencing

- **2003: human genome sequencing**

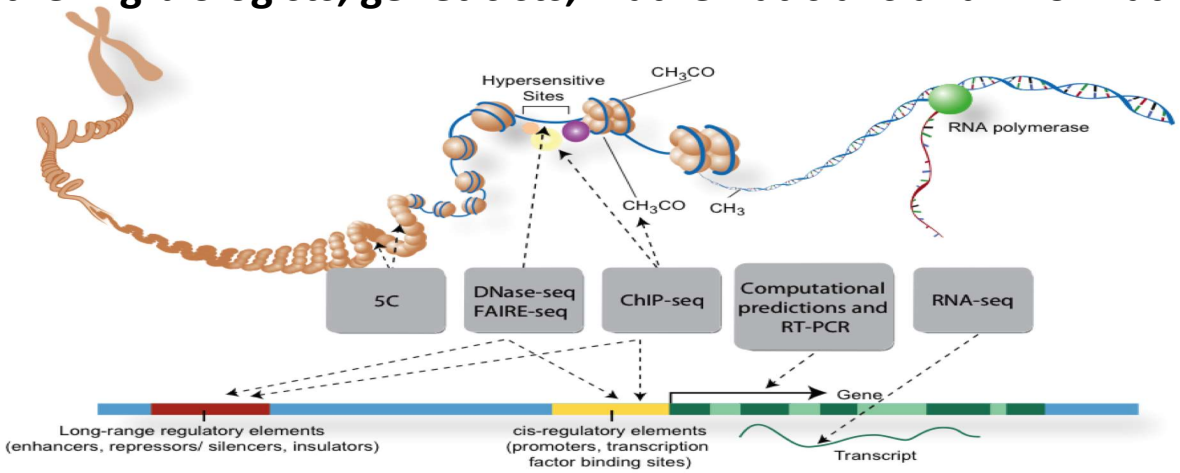
Only 2% is functional, coding genome: production of RNAs and proteins

- **Most non coding, JUNK DNA: not functional, no product ?**

	Yeast	Nematode	Drosophila	Human
Genome size in Megabases (Mb)	13	100	180	3 300
Number of genes	6 200	19 100	13 600	23 000
Coding fraction	**69%**	**25%**	**11%**	**1.2%**
Non coding fraction	**31%**	**75%**	**89%**	**98,8%**

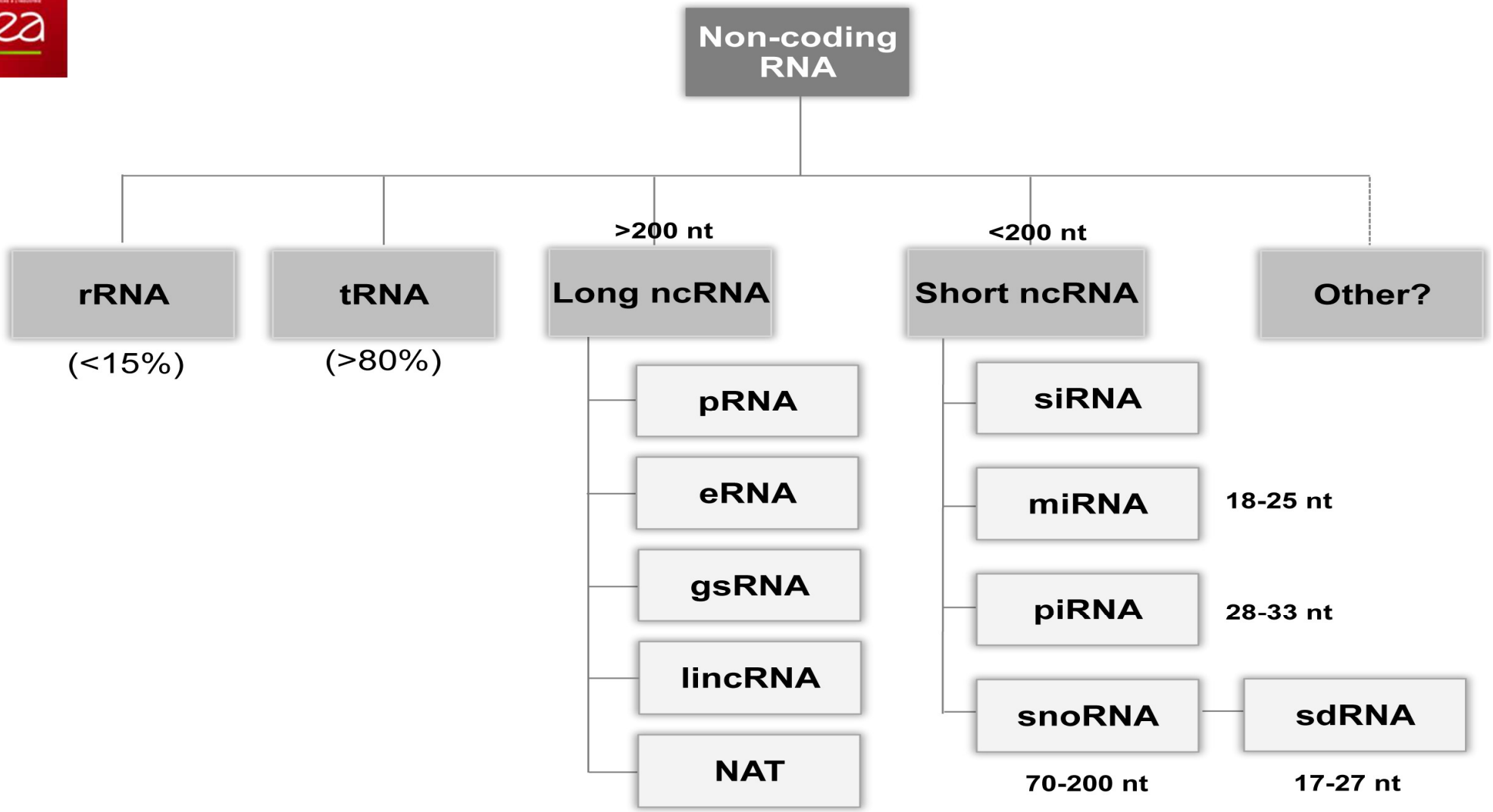
ENCODE revolution in 2012

International project on interactions with DNA , consortium of 32 laboratoires worldwide, gathering biologists, geneticists, mathematicians and informaticians

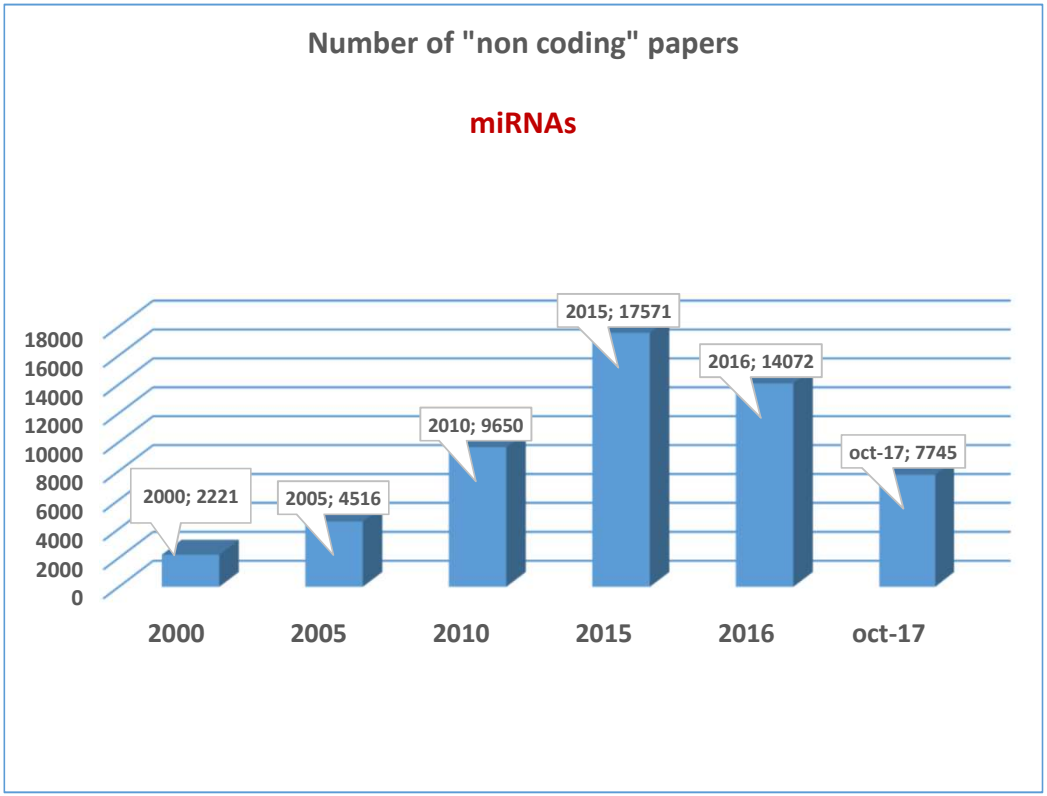


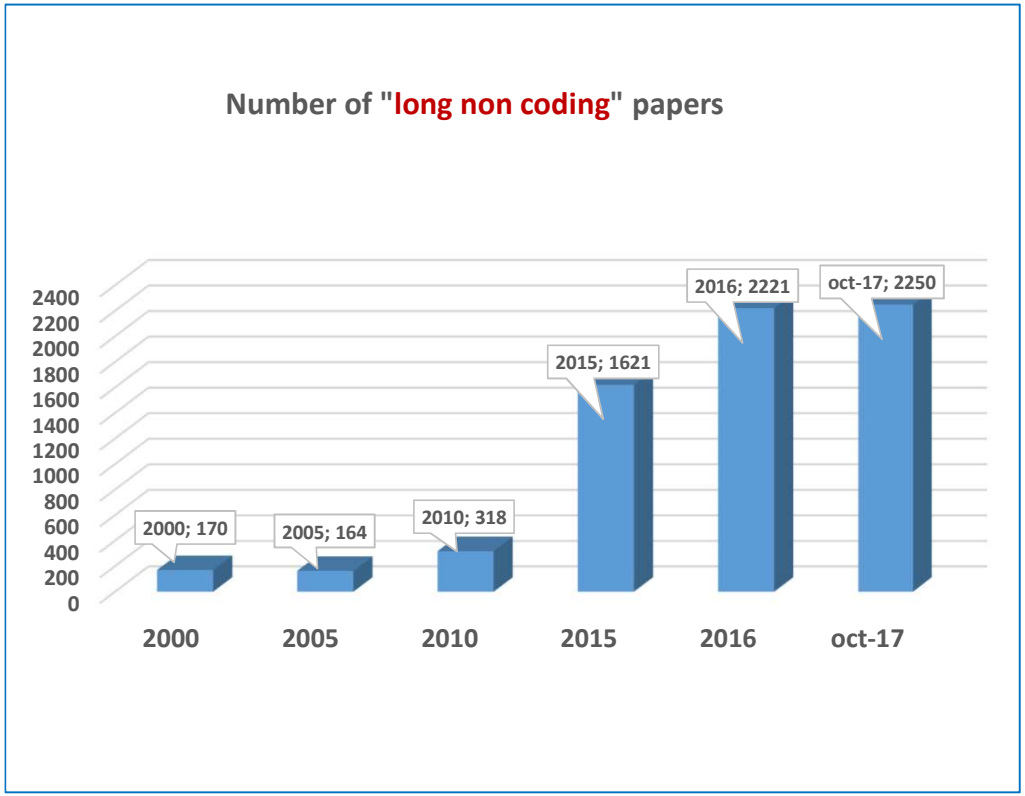
- **No Junk DNA : 80% useful, production of RNA molecules, but not coding for proteins !**
- **70% of genetic variants associated to human common diseases are found out of coding regions in the human genome !**

What are these RNA molecules and what are their functions?


Non-coding RNA
rRNA
(<15%)
tRNA
(>80%)
>200 nt
Long ncRNA
pRNA
eRNA
gsRNA
lincRNA
NAT
<200 nt
Short ncRNA
siRNA
miRNA
18-25 nt
piRNA
28-33 nt
snoRNA
70-200 nt
sdRNA
17-27 nt
Other?

The emerging role of long non-coding RNAs





Definition of long-non coding RNAs: lncRNA

Definition:

Transcripts > 200 nucleotides, similar to the mRNAs coding for proteins but lacking the structures necessary for traduction into proteins

Similar to messenger RNAs:

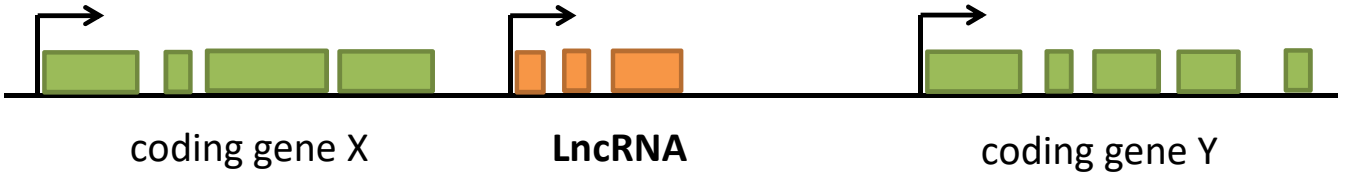
- may have exons and introns
- mean size 19 kb
- splicing and polyadenylation
- transcribed by RNA Polymerase II

Differences beeween lncRNAs and mRNAs:

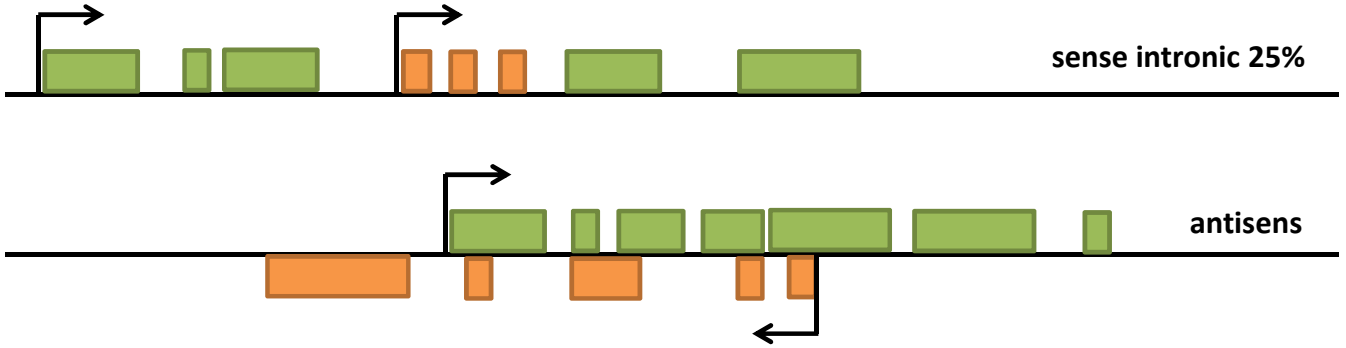
- lower conservation between species of their DNA sequences
- lower expression (10-fold less)
- lower stability
- high tissue specific expression

Two main categories: intergenic and intragenic lncRNAs

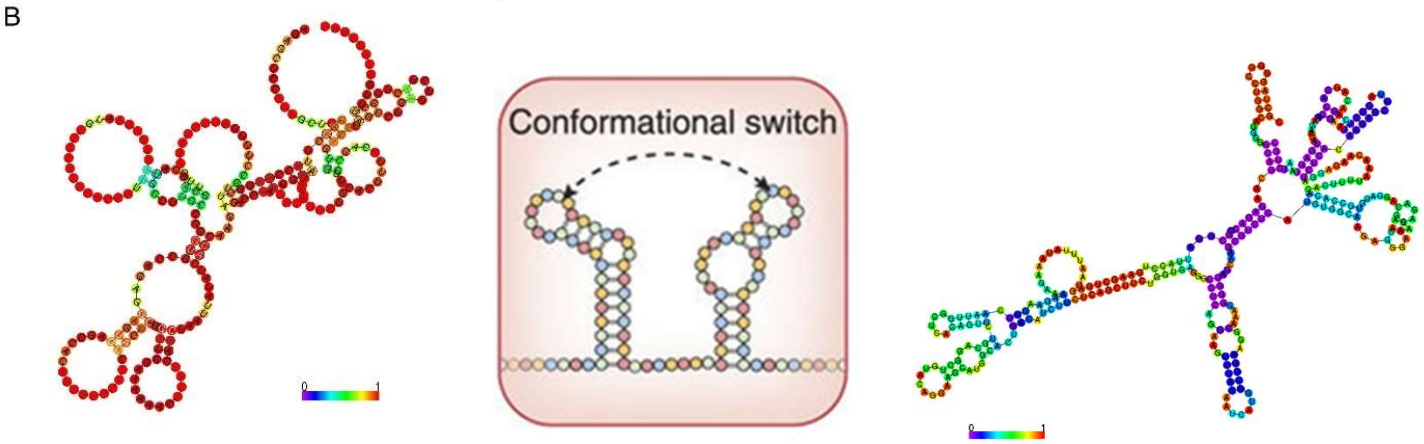
- intergenic lncRNAs : lincRNAs most abundant 60%

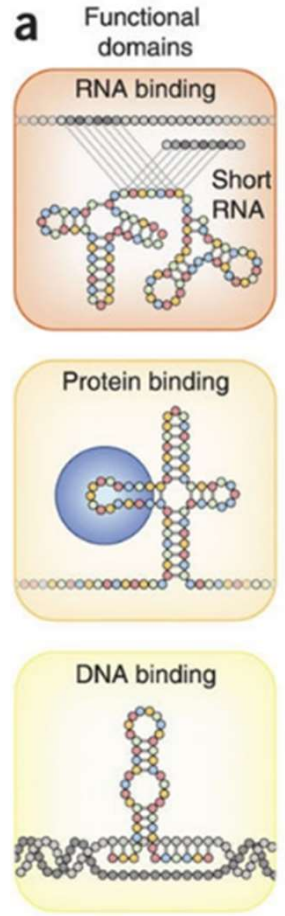


- intragenic lncRNAs



Flexible structure of lncRNAs





RNAS

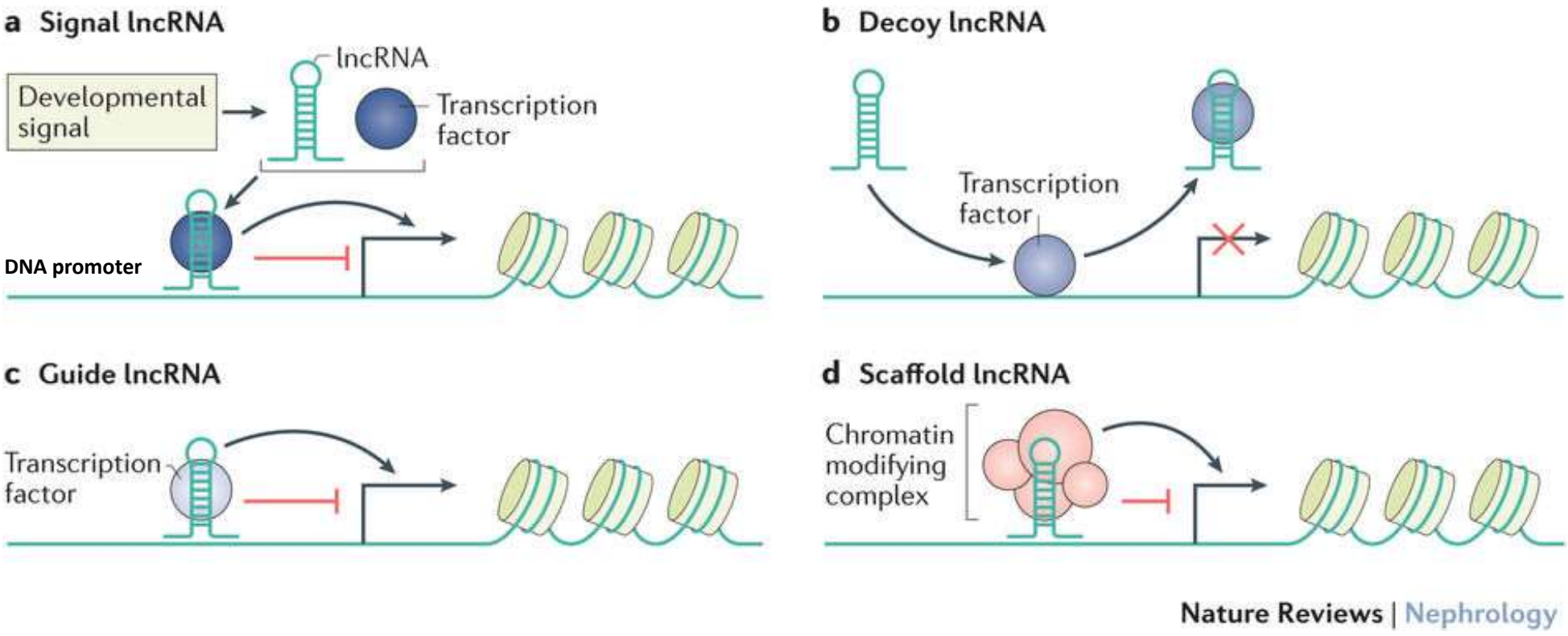
proteins

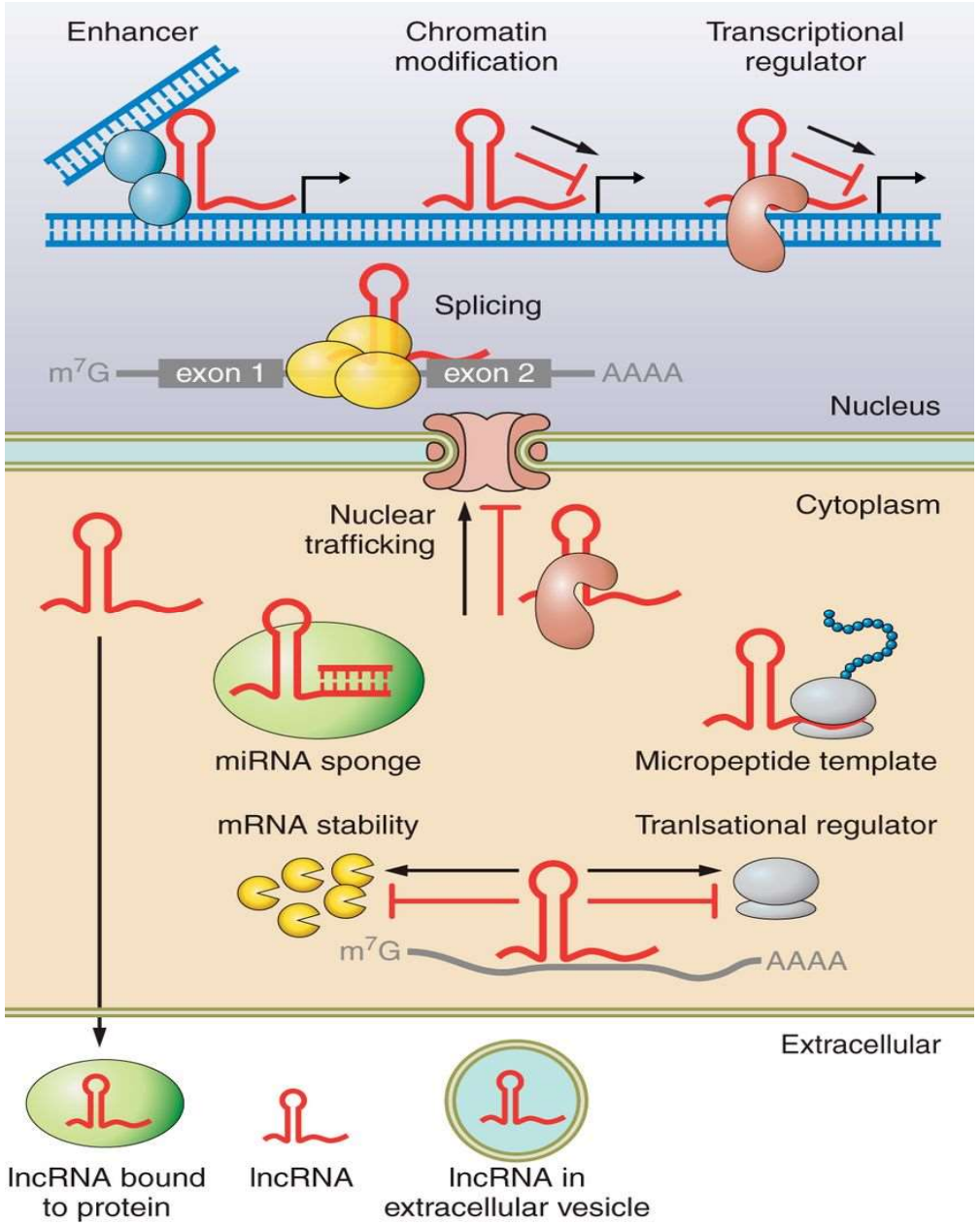
DNA

. RNAs possesses a unique ability to form complex secondary and tertiary folds

. This structural flexibility enables them to perform organizational, catalytic and regulatory functions

A main LncRNA function: to regulate transcription





NUCLEUS

CYTOPLASM

OUT of the CELLS

LncRNAs play a role in various human diseases

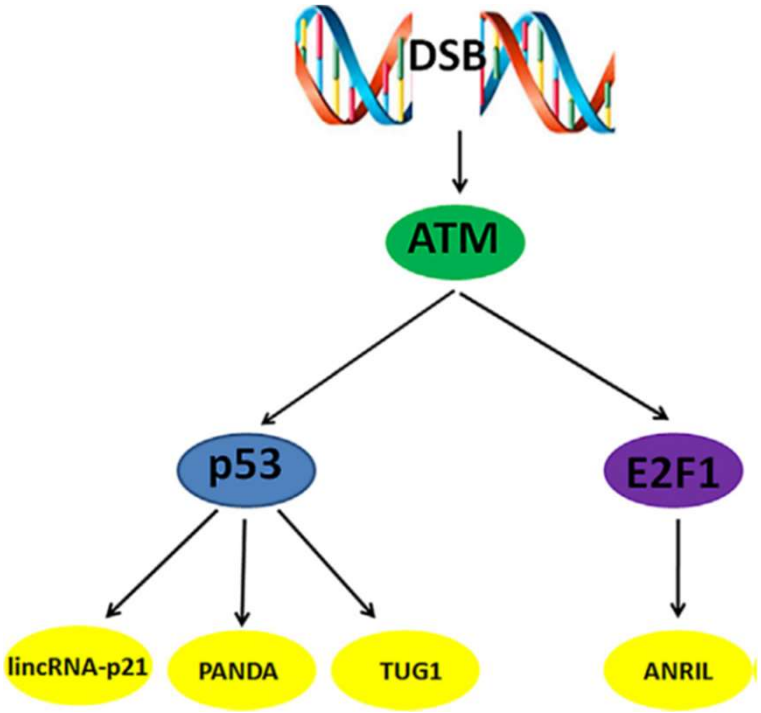
NAME	DISEASE
CDKN2B-as1	Vascular diseases, cancer
BACE1-as	Alzheimer
DBE-T	Muscular dystrophy
MVIH	Hepatic carcinoma
HOTAIR	Cancer, breast, colon
HULC	Cancer, liver
lncRNA HYMAI	Neonatal diabetis
PCA3	Cancer, prostate
lincRNA-p21	Sarcoma, lymphoma, colon cancer
MALAT1	Numerous epithelial cancers: poumon, utérus, sein, pancréas, rein , colon et prostate

What about ionizing radiation and LncRNAs ?

LncRNAS regulate DDR

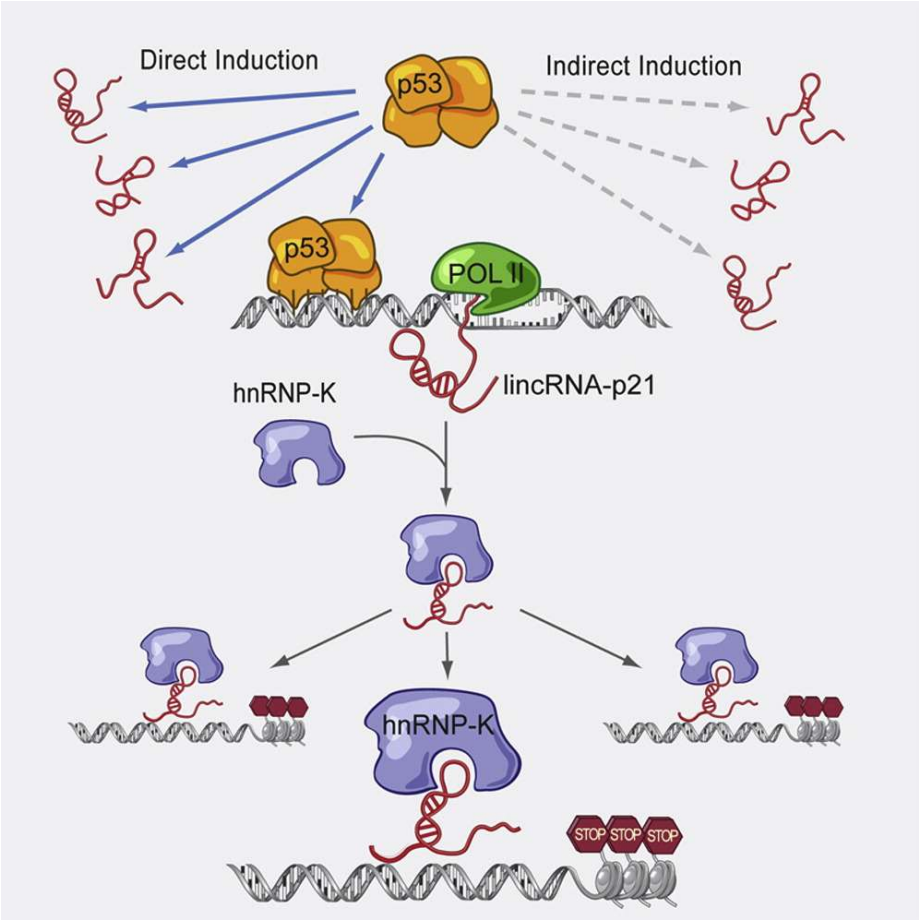
DNA Damage Response

- Rapid cellular processes involved in cell defense during the first 24 hours after IR
- LncRNA involved in most of these processes through the gatekeepers ATM, p53



Zhang, Mut Res 2015

p53 regulates LncRNAs and is regulated by them

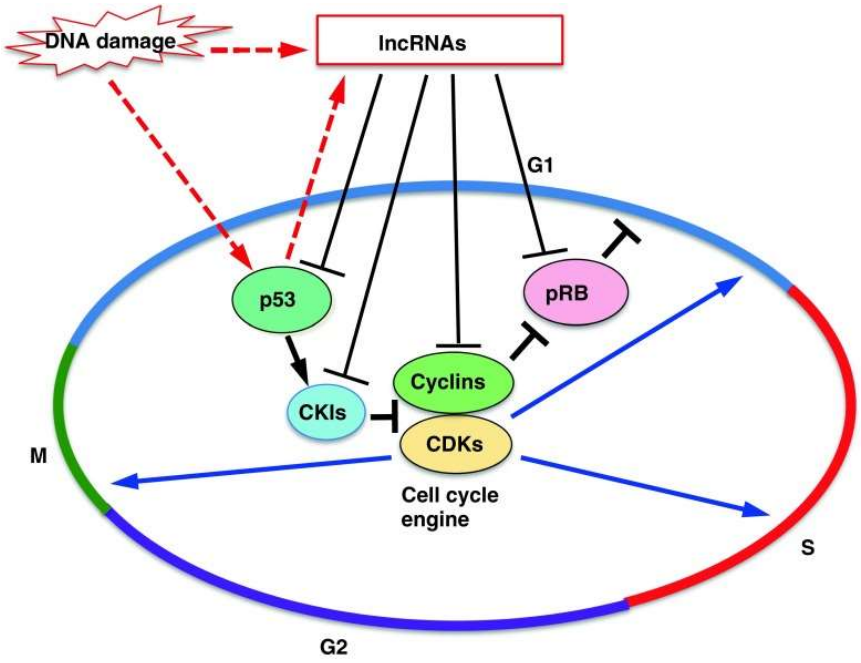


The Large Intergenic Noncoding RNA LincRNA-p21 Induced by p53 Mediates Global Gene Repression in the p53 Response

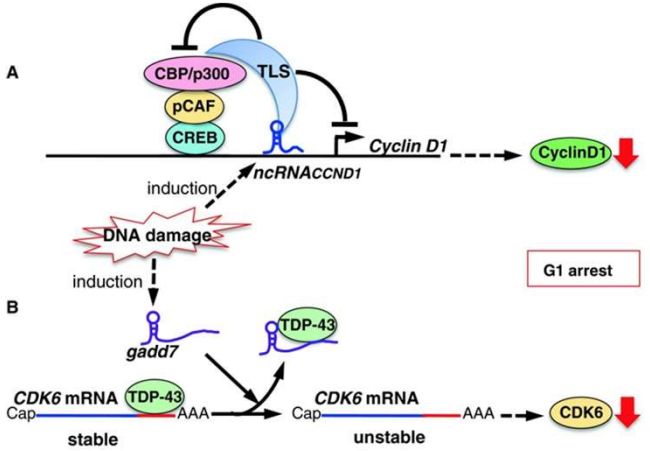
Huarte 2010

Cell **2010 142, 409-419DOI: (10.1016/j.cell.2010.06.040)**

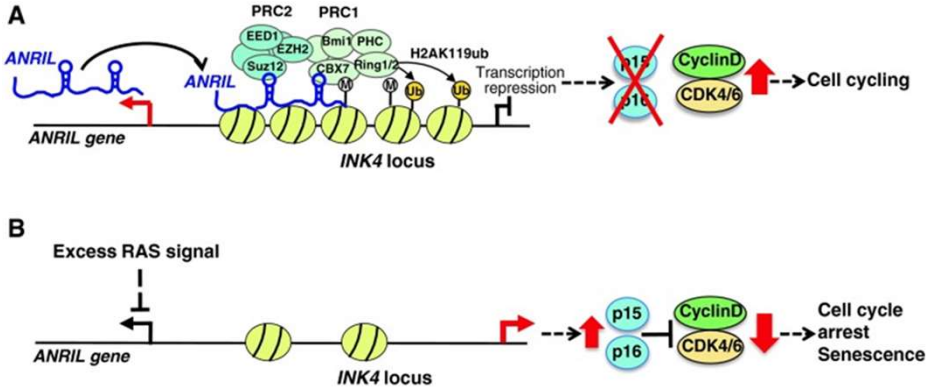
LncRNAs regulators of cell cycle arrests



CCND1
GAD7

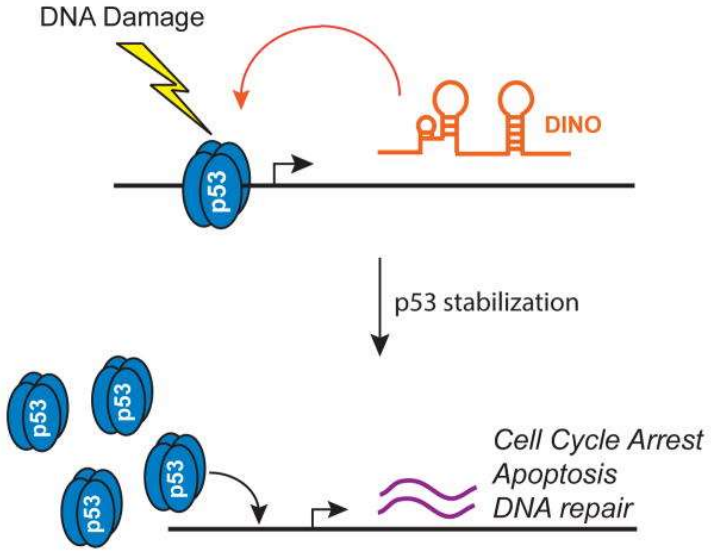


ANRIL



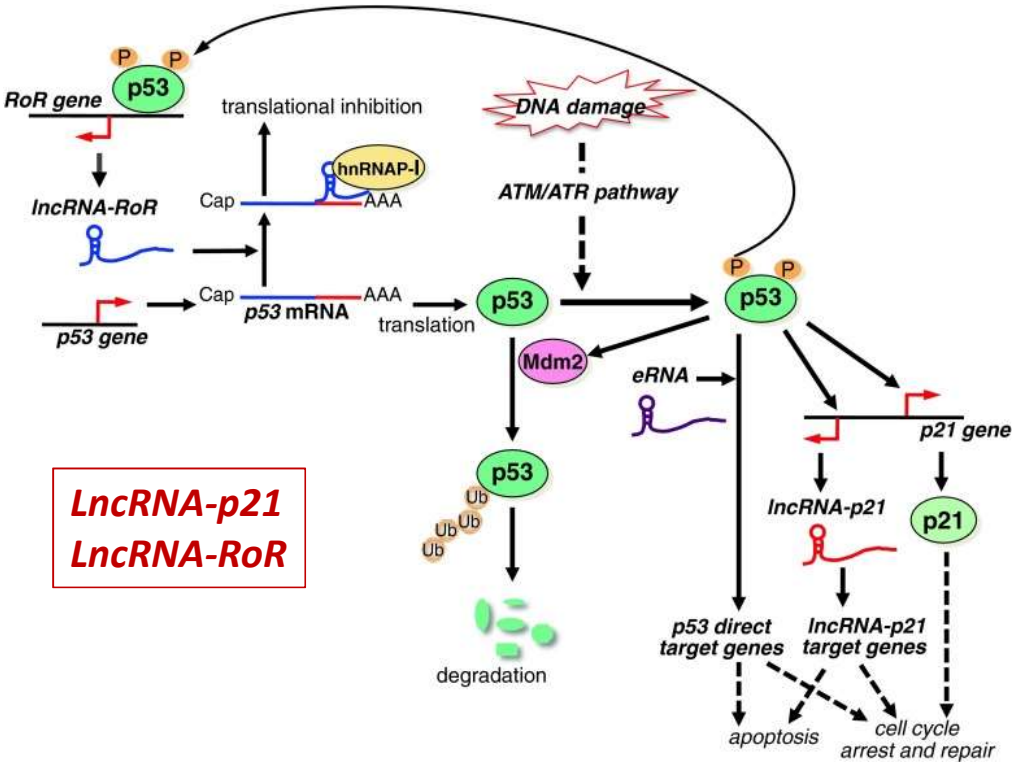
LncRNAs regulators of apoptosis

DINO



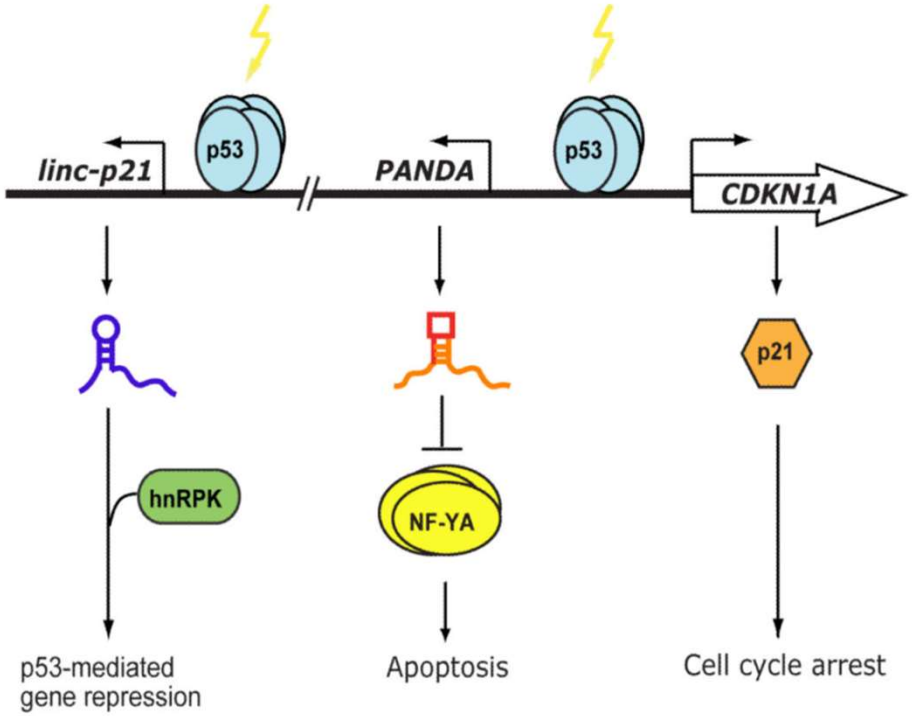
PANDA

Anti-apoptosis, decoy mechanism



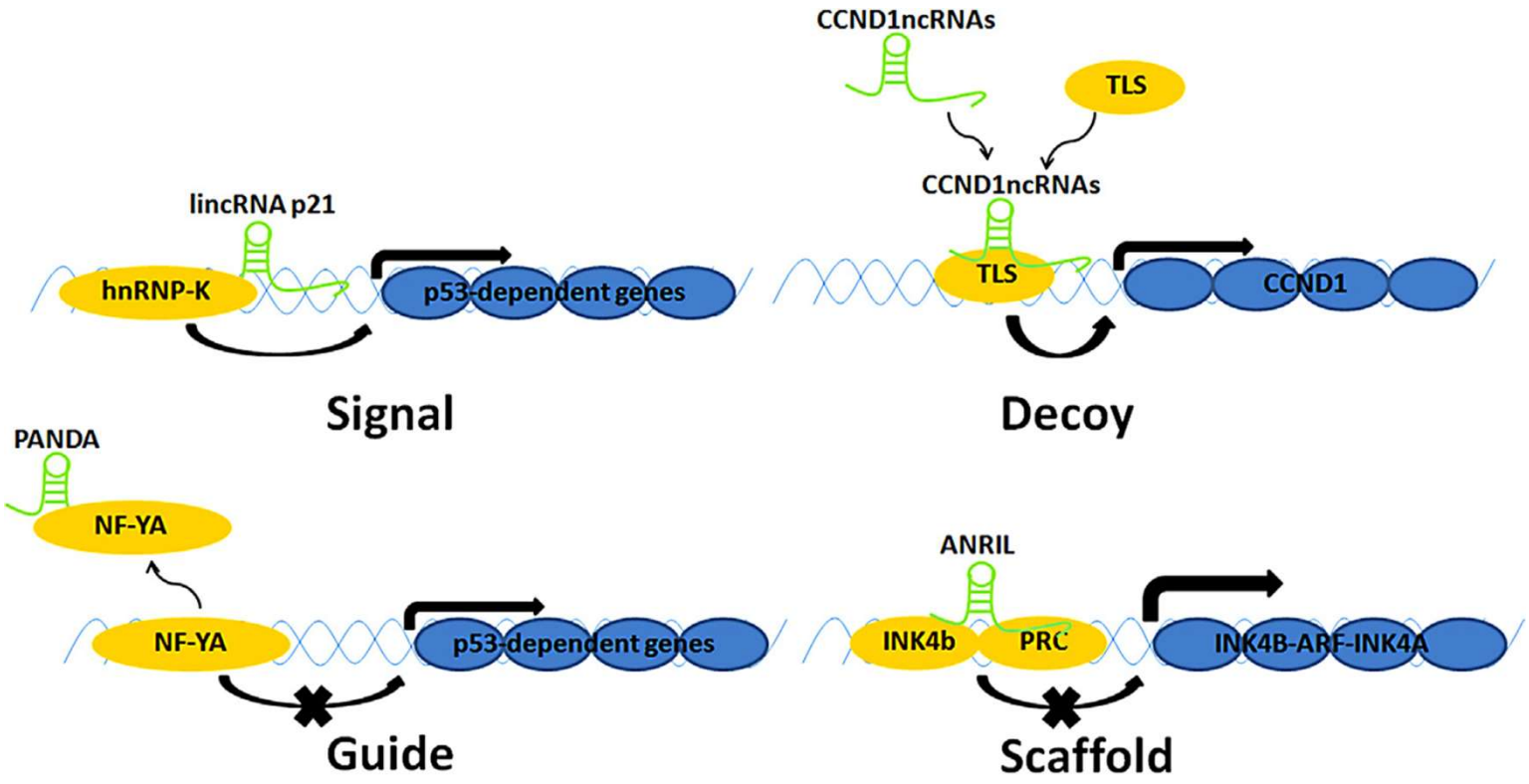
LncRNA-p21
LncRNA-RoR

New models of p53-regulated DDR



Upon DNA damage, p53 binding at the CDKN1A locus coordinately activates transcription of CDKN1A as well as LncRNA PANDA and linc-p21. CDKN1A mediates cell cycle arrest, PANDA regulates apoptosis through NF-YA, and linc-p21 mediates gene silencing through recruitment of hnRPK

All types of LncRNA activities targeted by DDR-involved species

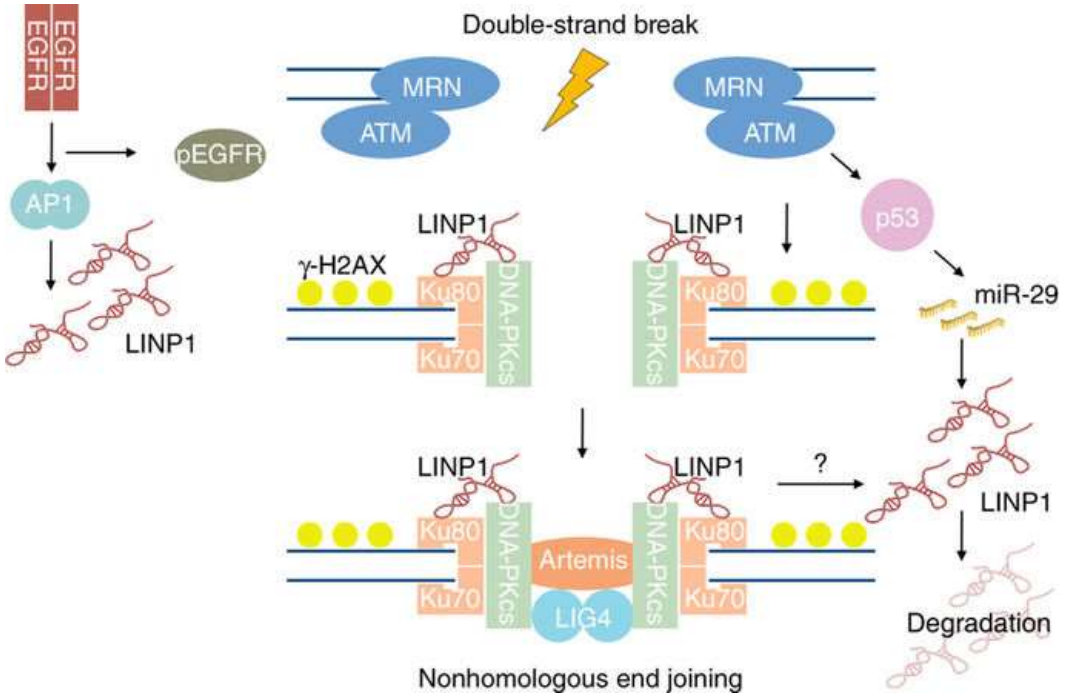


Main function: repression of gene transcription after DNA damage

LncRNA and DNA repair: still poorly explored

ANRIL, DDSR1 and SLC6A9-5:2:
Targets homologous recombination
Wan, Cell Sig 2013
Sharma Embo Rep 2015
Cheng Xiang, Oncotarget 2017

LINP1 upregulates NHEJ repair of DNA double-strand breaks in cancer cells
Zhang Nature Struct 2016



LINP1 providing a scaffold for Ku80 and DNA-PKcs

Increased DSB repair

Higher survival after IR

➢ Lncs and radiosensitivity

CCND guide		Hypoacetylation transcrption Radioprotector	TLS protein CCND1	Song, 2012
DDSR1 Intergenic no intron	ATM P53 NF kB	Proliferation survival DDR Dna repair	BRCA1 HR dna repair	Sharma Embo Rep 2015
DINO	P53	DDR Apoptosis Cell cycle	P53	Schmitt Nat Genet 2016
FAS-A1	ATM	Up regulated IR Linear induction Apoptosis protection	FAS	Kabacik, RadRes 2015
lincRNA-p21	P53	Signaling, Gene rep DDR, apoptosis, cell cycle Radioprotector	hnRNP-K protein P21	Huarte, Cell , 2010 Dimitrova 2014
LINP1		NHEJ Dna repair radioresistance	Ku DNA-PKcs	Zhang Nature Struc 2016
PANDA Decoy	P53, p21 DDR	Gene rep Cell cycle arrest, survival anti-apoptosis	NF-YA protein	Hung Nature Genet, 2011

- **Currently mostly investigated in cancer cells**
- **A series of LNCs involved in radioresistance**
- **New possible targets to improve radiotherapy**

Opened questions

- Low-dose responses ?
- Effects of IR on structure/functions of LncRNAs
- Tissue/cell type specificities?
- Coordination with other epigenetic regulations, miRNAs?
- Role on radiation-related pathologies
- Acute effects?
- Radiation-related cancer?
- Induced-tissue reactions?
- Markers of individual radiosensitivity ?

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