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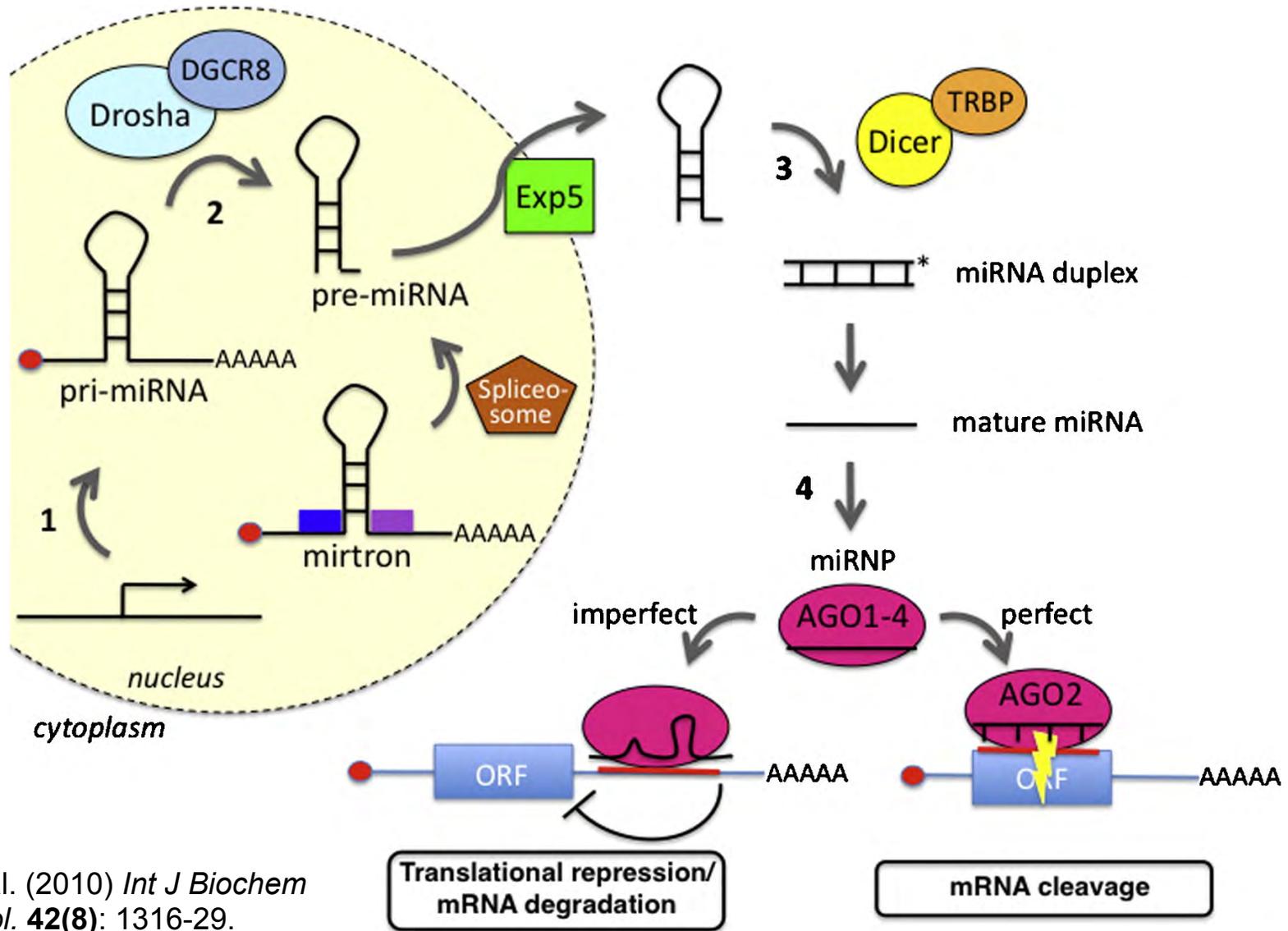
# Surrogate markers of radiation quality: microRNA

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New York, NY*

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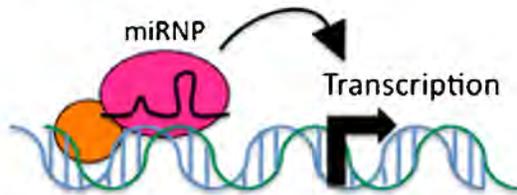
# Non-coding RNAs that regulate mRNA expression



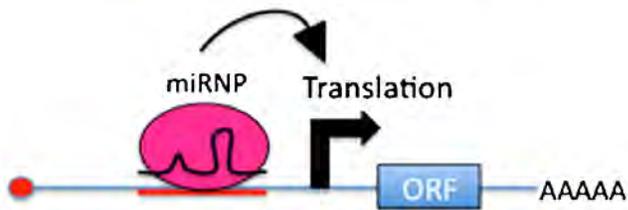
Breving et al. (2010) *Int J Biochem and Cell Biol.* **42(8)**: 1316-29.

# miRNA can activate as well as repress expression

## (B) Activation

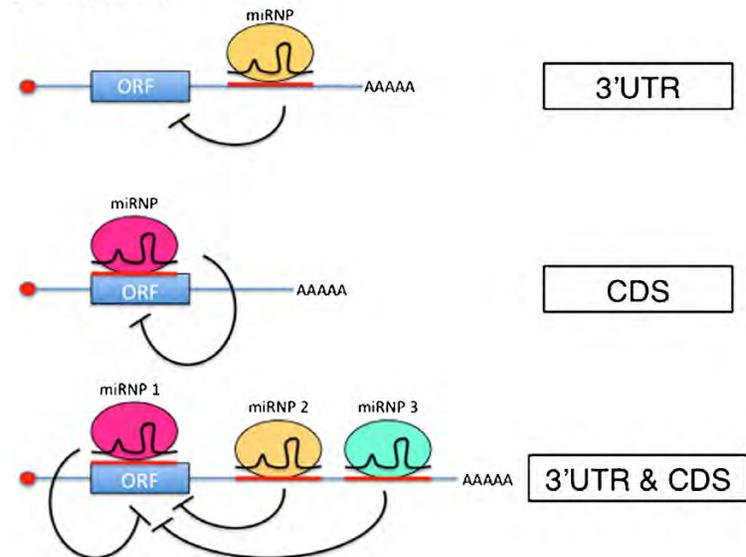


RNA activation



Induce translation

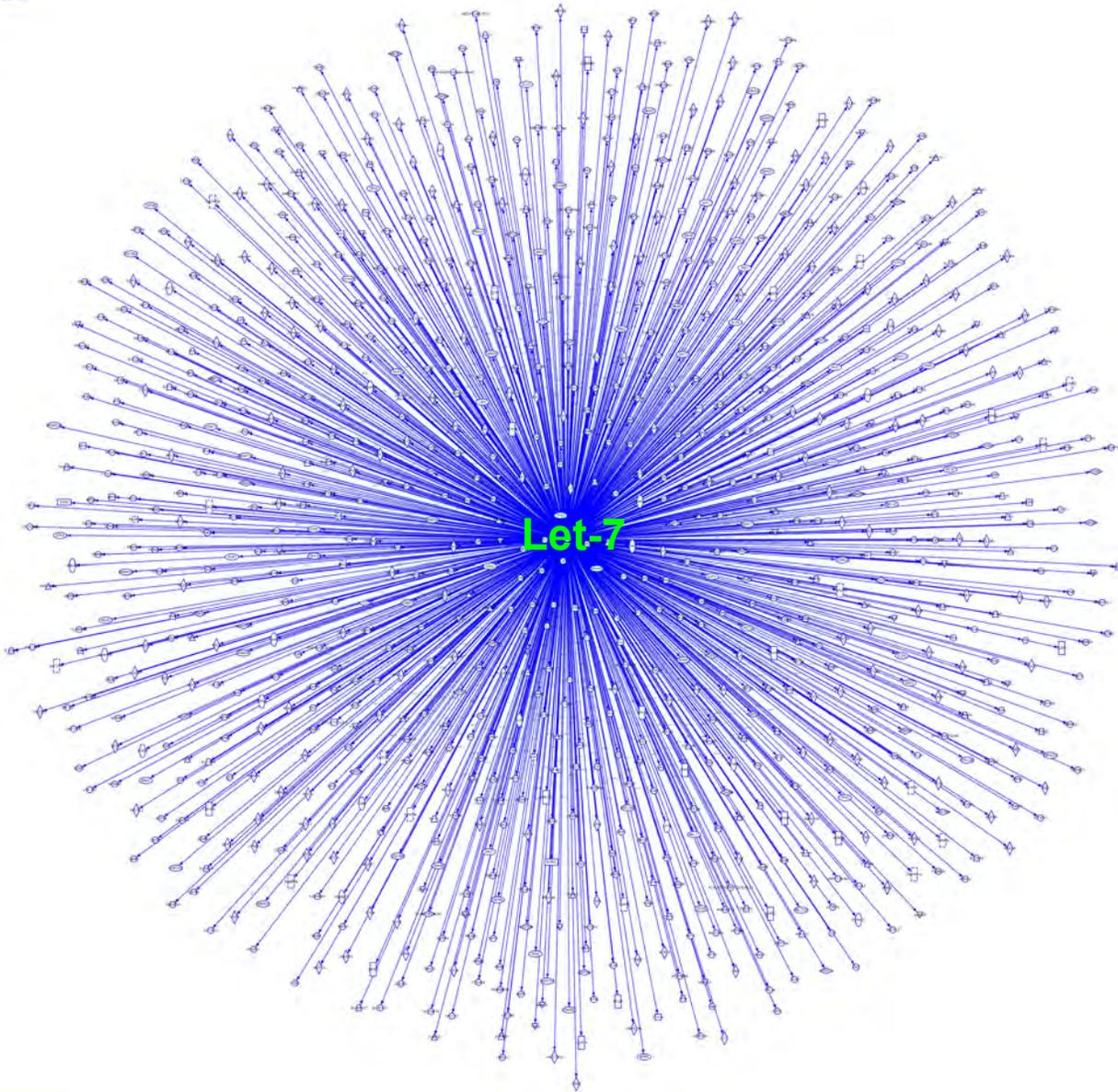
## (A) Repression



Brevig et al. (2010) *Int J Biochem and Cell Biol.* **42(8)**: 1316-29.

# Each miRNA has hundreds of potential targets

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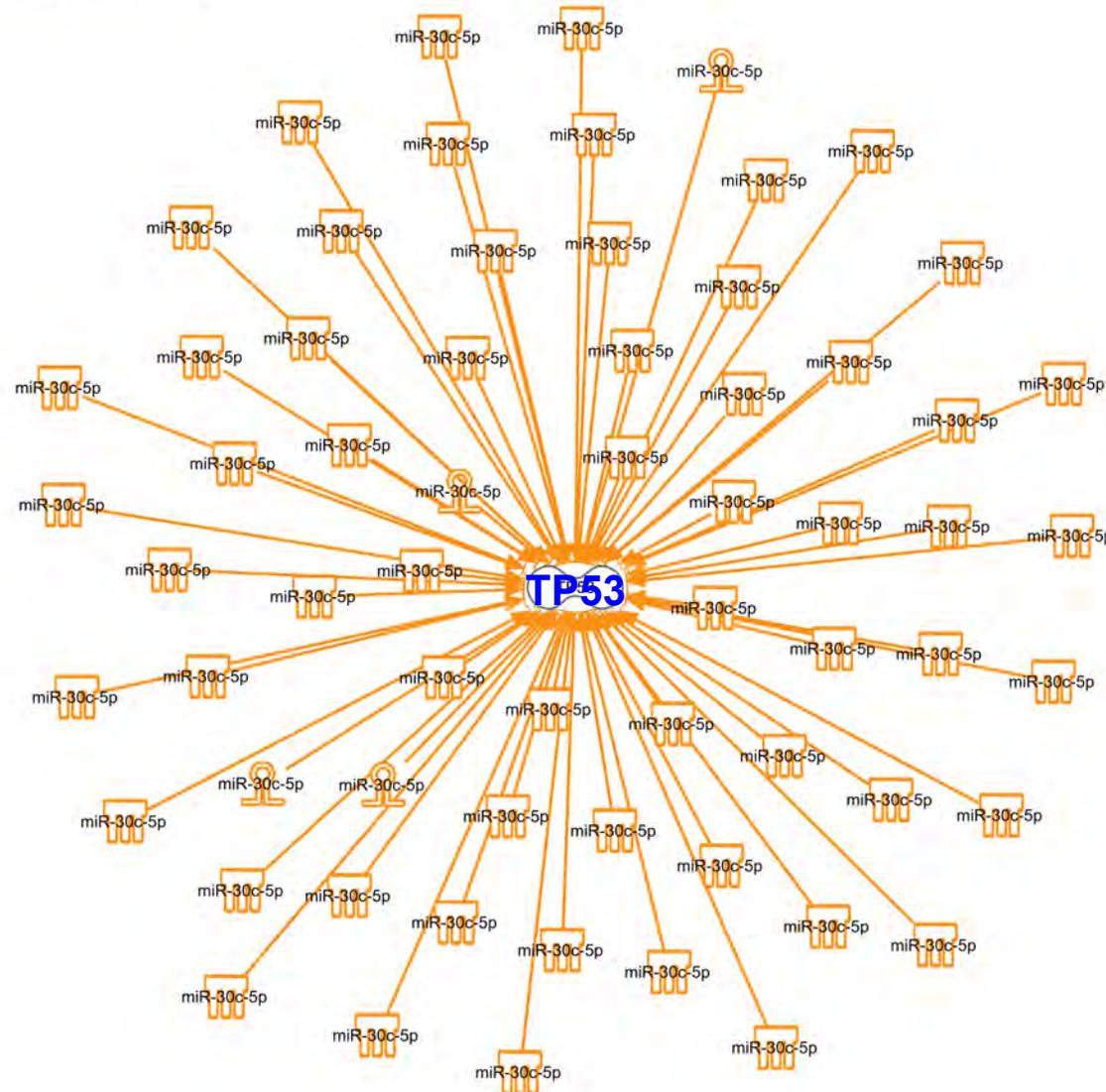


## Let-7 family

- Commonly stress responsive
- Regulated by radiation
- IPA database has 1396 predicted targets
- Only a subset will actually be affected

# A single gene may be targeted by multiple miRNAs

miRNAs predicted in IPA to target the TP53 transcript



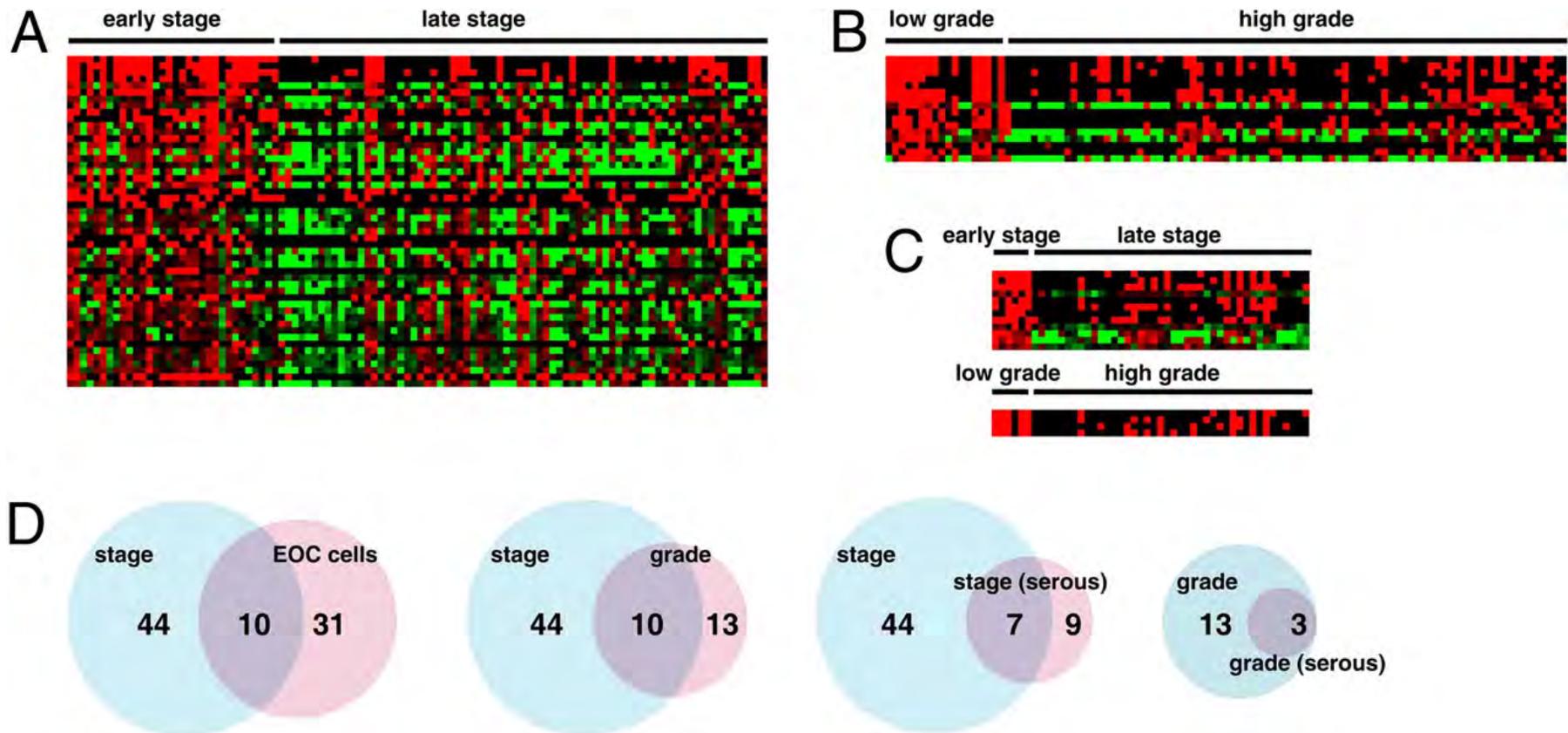
# Attractive as surrogate markers?

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- Altered miRNA expression patterns have been associated with many pathological states, including:
  - Cancers
  - Cardiovascular diseases
  - Viral infections
  - Diabetes
  - Injury to specific organ systems
- There has been some suggestion that miRNA profiles are more robust than mRNA profiles in defining disease states.
- Small size means they are generally more stable than mRNA.

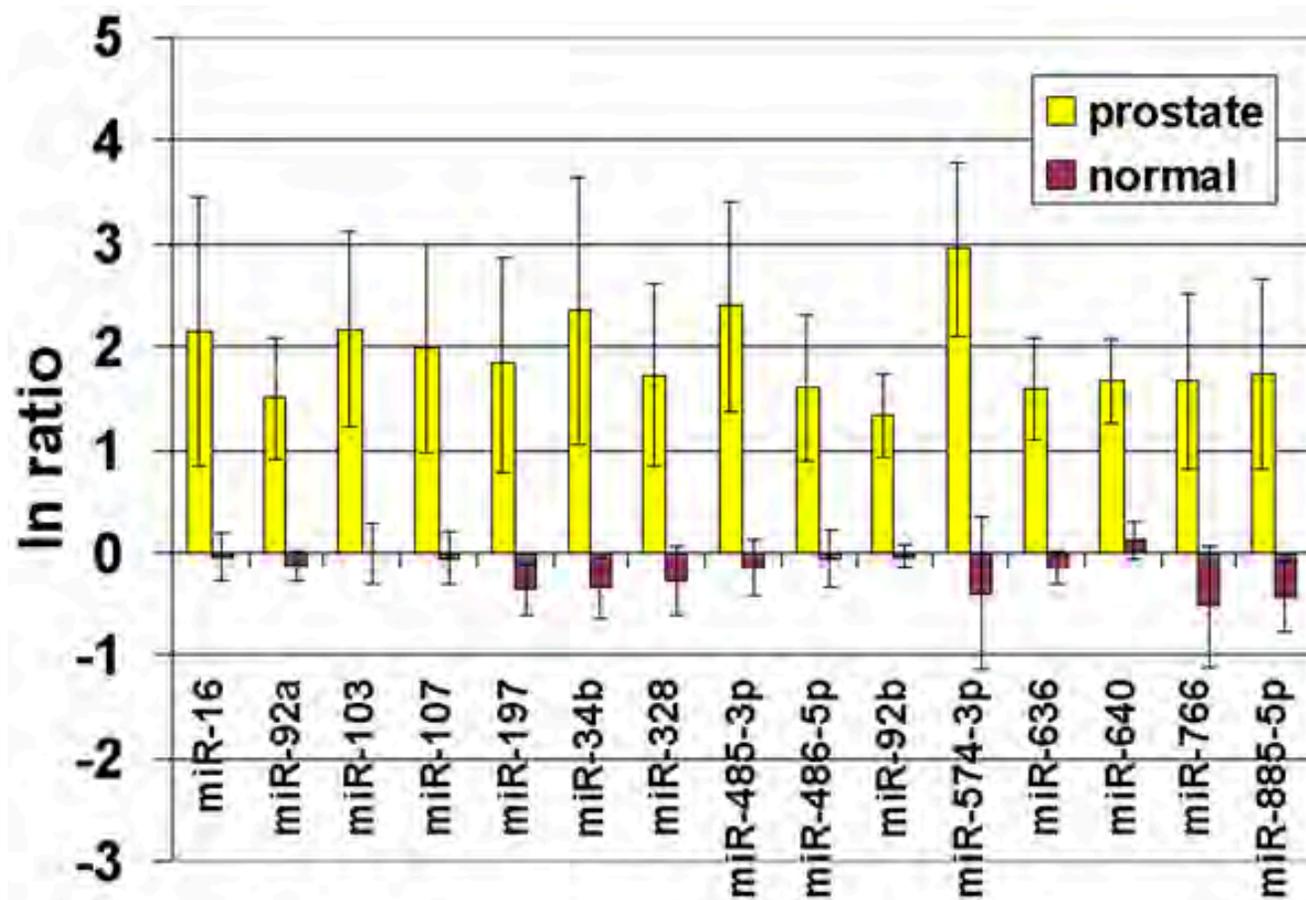
# miRNA expression may predict cancer type or stage

Numerous miRNAs are down-regulated in late-stage or high-grade ovarian cancer.



# miRNA in blood serum may detect disease

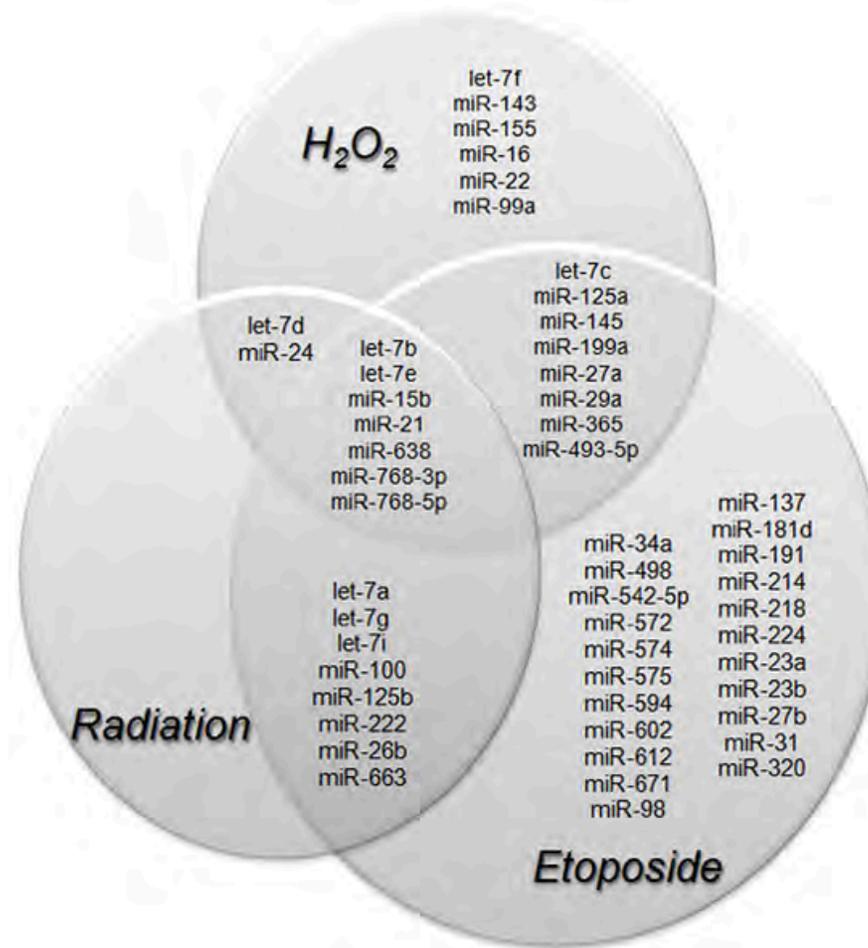
microRNA differentially expressed in normal and prostate cancer sera.



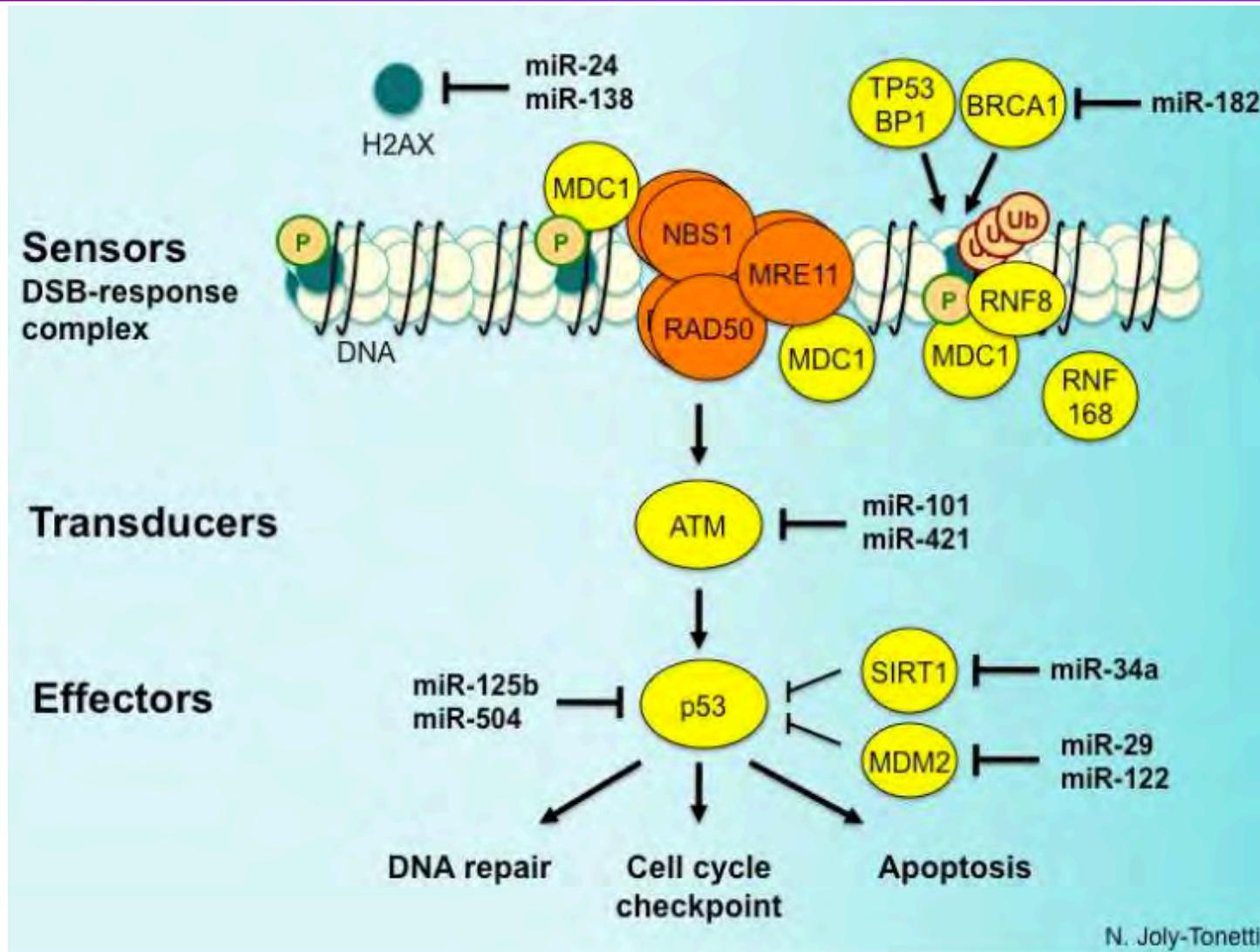
Lodes et al. (2009) PLoS ONE 4(7): e6229. doi:10.1371/journal.pone.0006229

# miRNA are induced by stress

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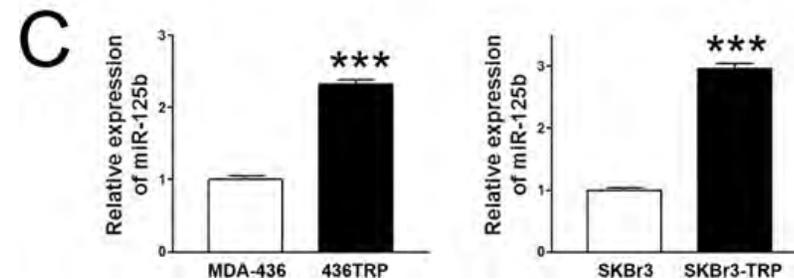
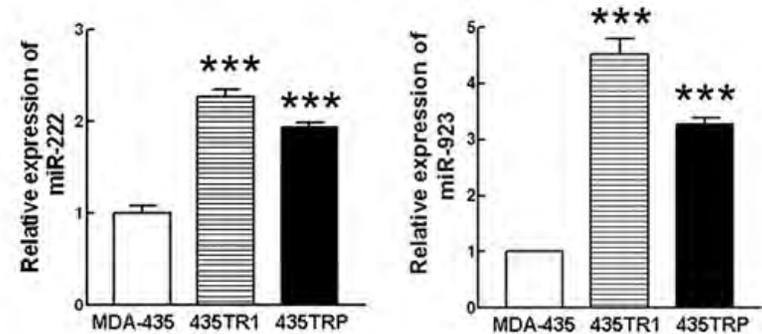
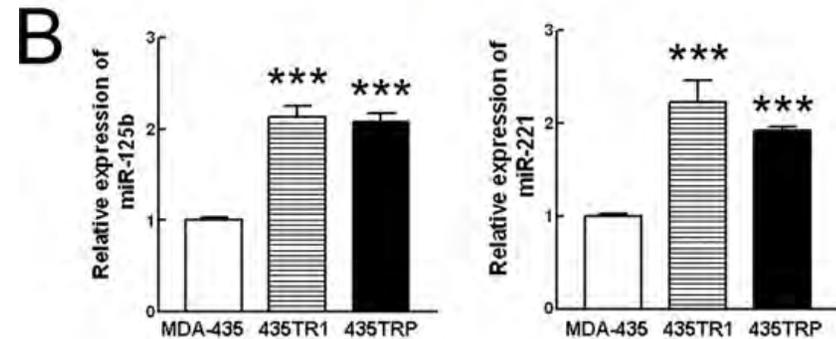
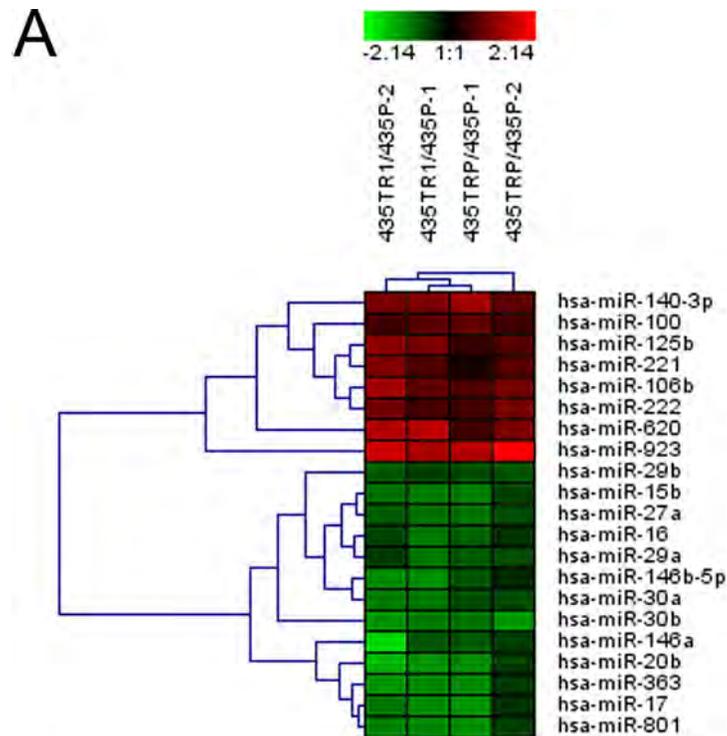
# miRNA can affect expression of key players in radiation response



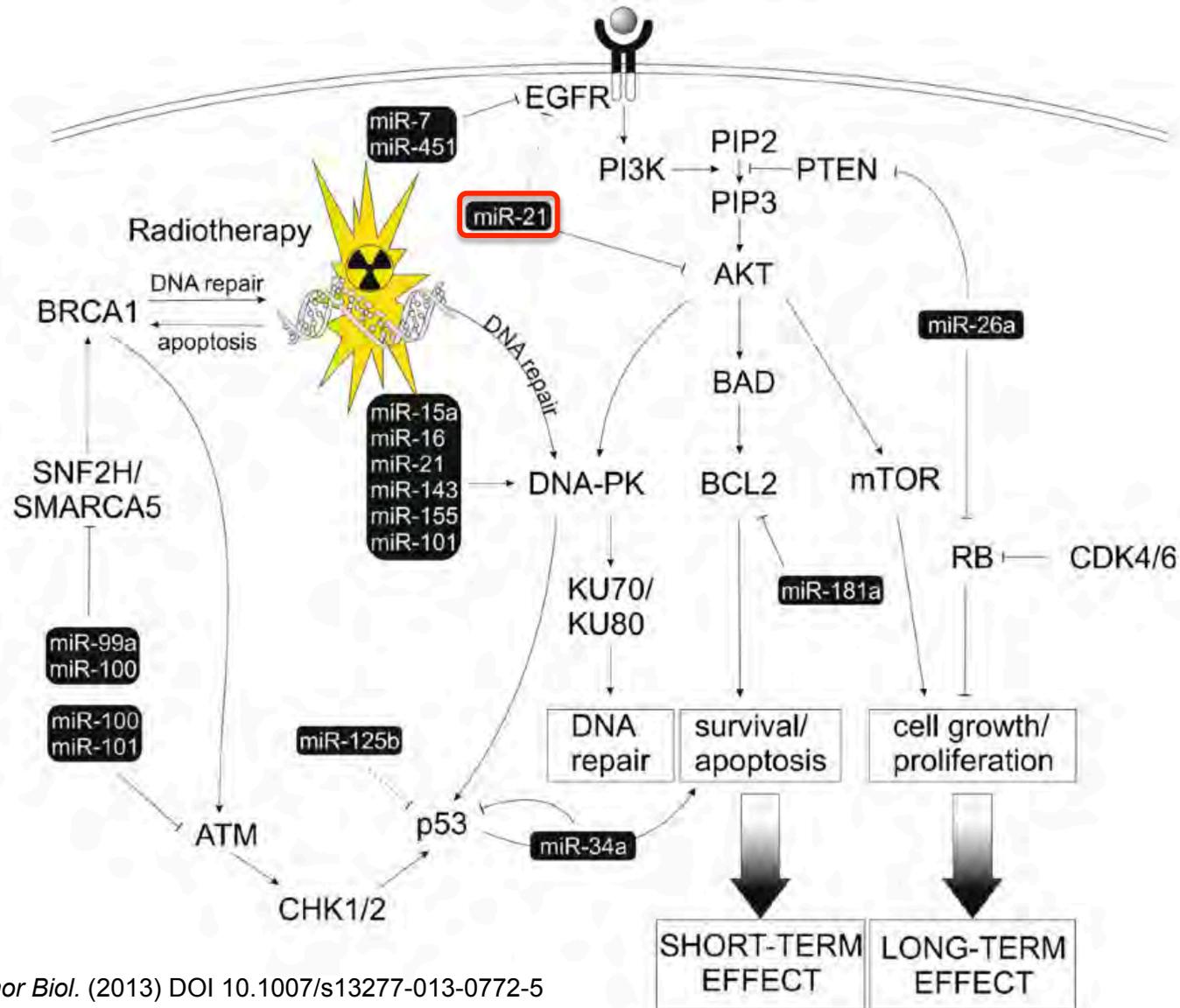
Joly-Tonetti and Lamartine (2012) in "Current Topics in Radiation Research,"  
M. Neno, ed.

# miRNA expression may predict sensitivity to treatment

Profiles of miRNAs in Taxol-sensitive and -resistant cancer cells.



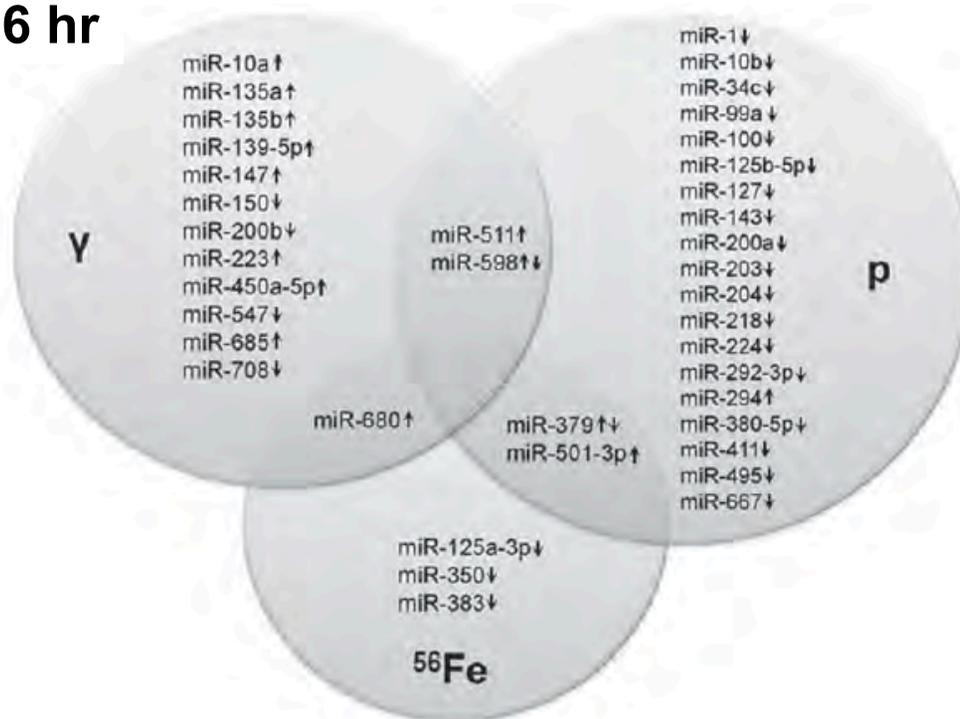
# miRNAs involved in radioresistance of gliomas



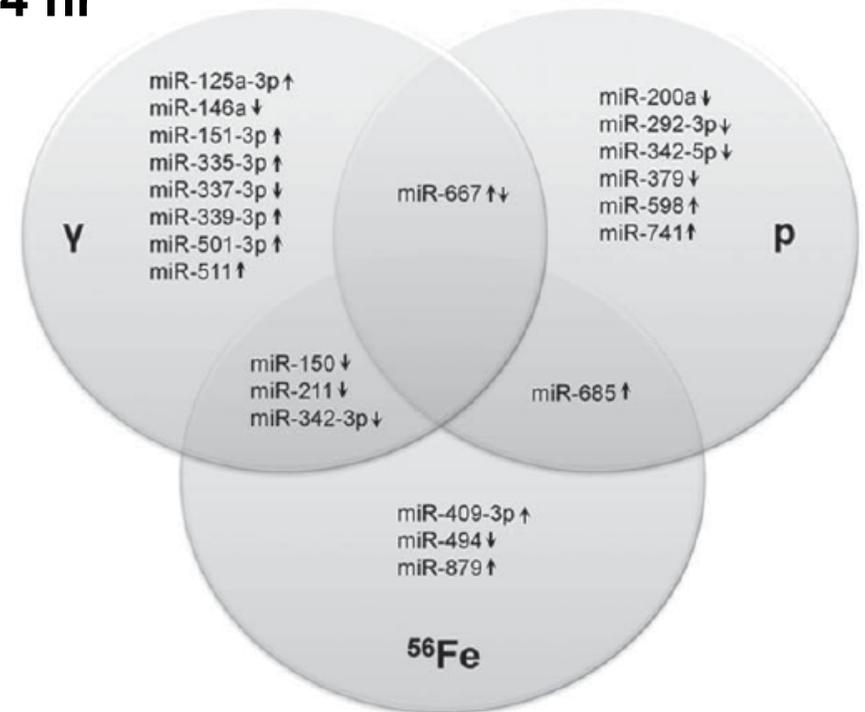
# Common miRNA regulation in mouse blood after exposure to different qualities of radiation

Little overlap in responding miRNA species was seen after exposure to gamma-rays, 600 MeV protons or 1 GeV/n iron ions

6 hr

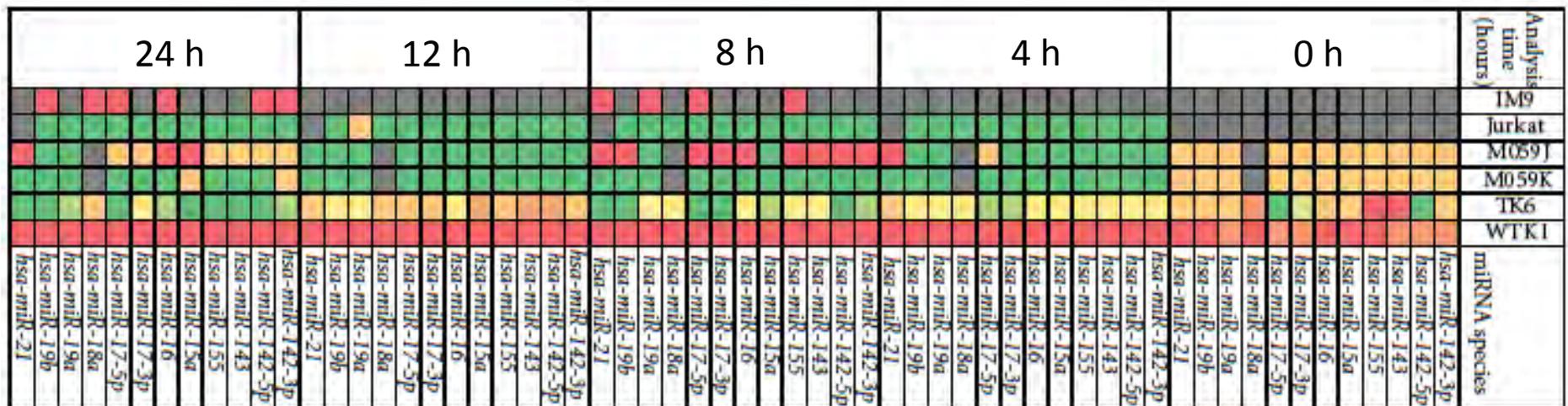


24 hr



Templin et al. (2012) *Int J Radiat Biol*  
**88:** 531-539.

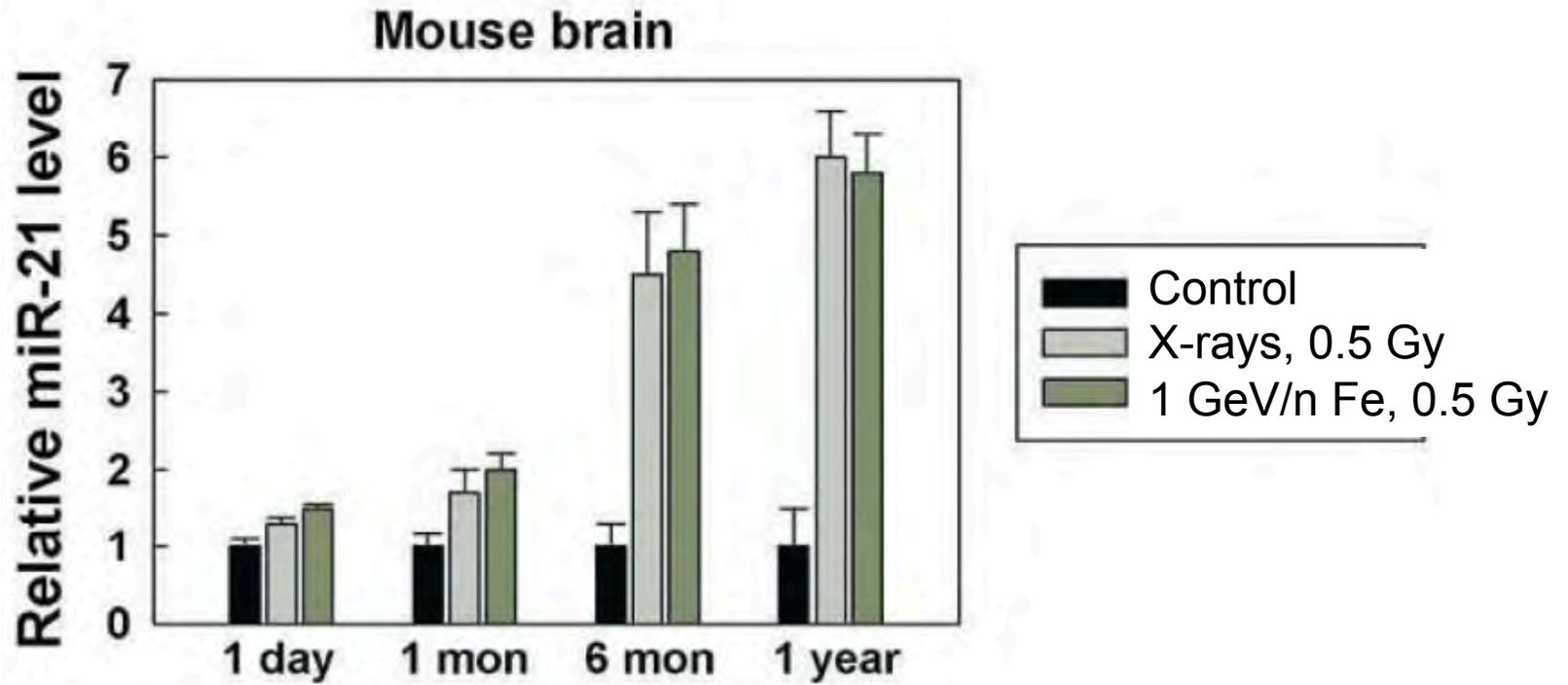
# Radiation response varies with time and in different cell lines or tissues



Red = low expression  
 Green = high expression  
 Grey = not measured

Lhaxhang and Chaudhry (2012) Comparative and Functional Genomics, Article ID 569731.

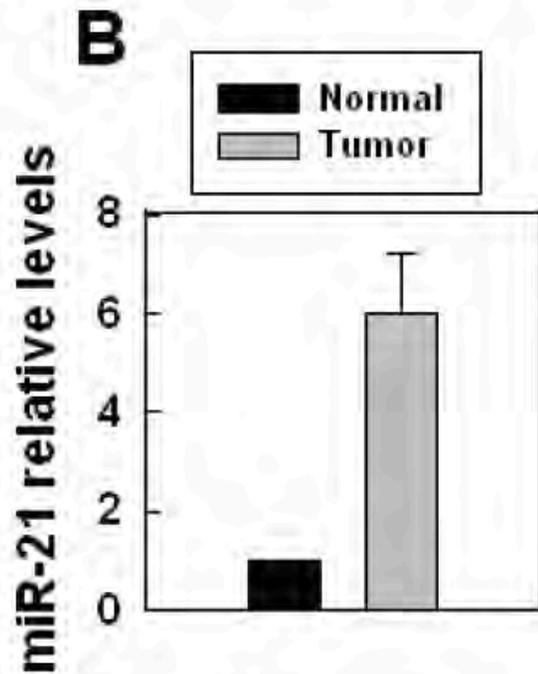
# miR-21 is elevated long-term after irradiation



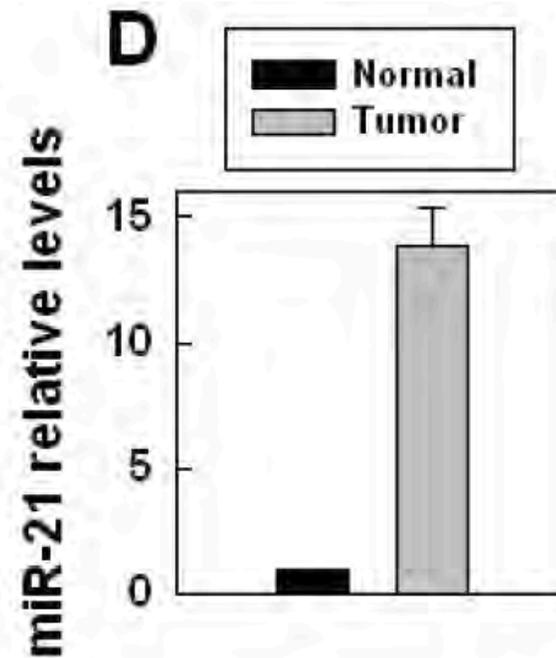
# miR-21 is elevated in liver tumors in irradiated mice

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1 Gy iron

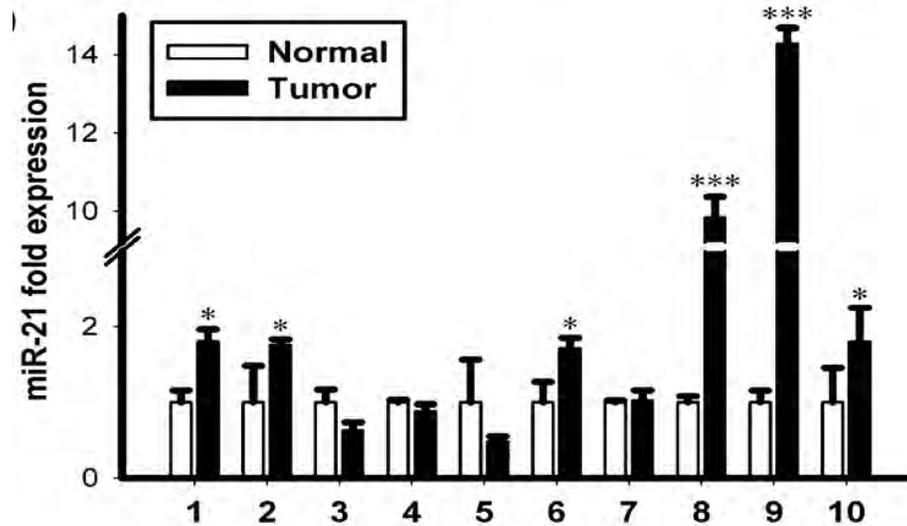


0.5 Gy neutron



# miR-21 is elevated in many non-irradiated tumors

## miR-21 expression and regulation in CaP.



Ribas J et al. *Cancer Res* 2009;69:7165-7169

©2009 by American Association for Cancer Research

# Conclusions

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Insufficient data to claim surrogates for LET-specific or even radiation-specific responses.

To date studies have looked at limited

- Different LETs
- Doses
- Times after exposure
- Cell types or animal models

Disturbed pathways or networks can't be reconstructed with only miRNA data, but these data can be an important piece of integromic studies.