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NcRNAs as biomarkers for clinical outcome and toxicity in locally advanced NSCLC stage III

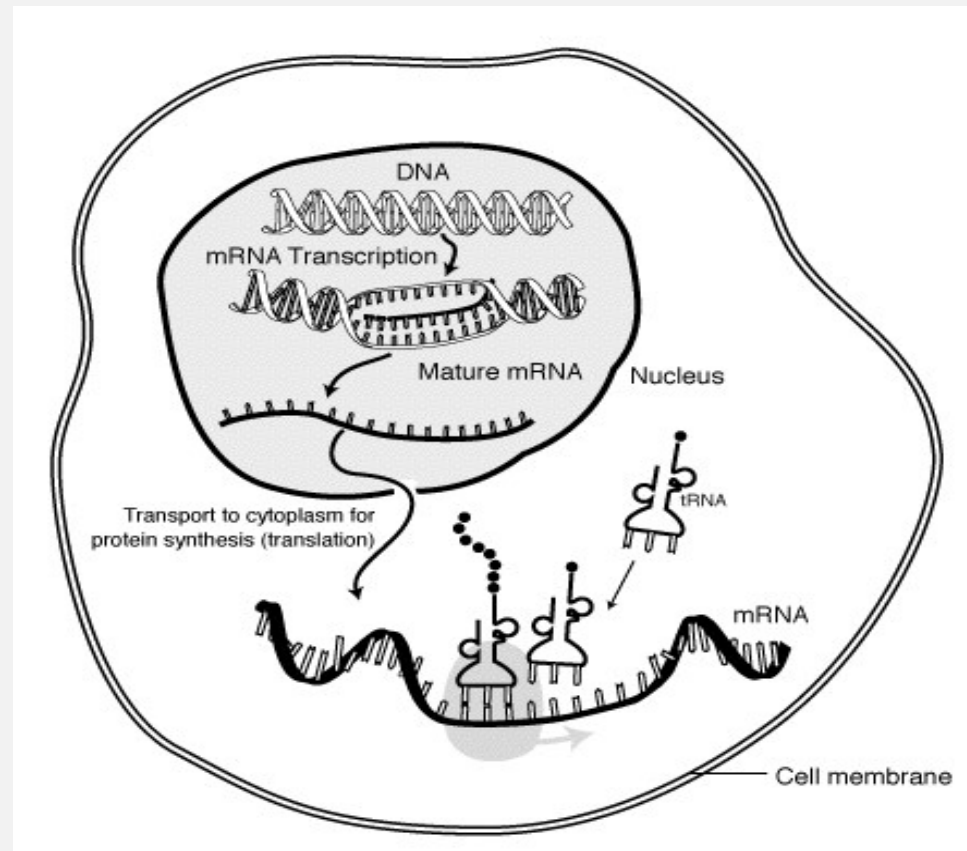
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Molecular Radiation Oncology

- > 300 000 hits on pubmed with search term “ncRNA”
- Guiding therapy decisions
 - Targeted drugs
 - Targeted radiotherapy

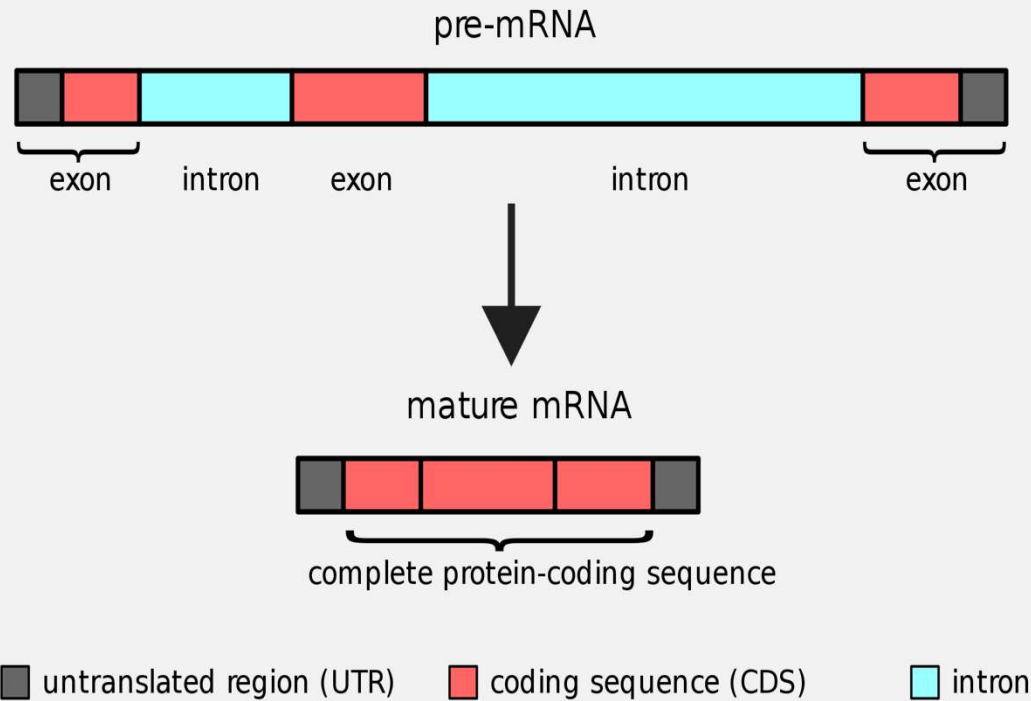
Gene expression



Reference:

[Image 1: Image: mRNA interaction \(Wikipedia\), retrieved from MRNA-interaction.png - Wikipedia Commons, 2015](#)

Pre-mRNA to mRNA



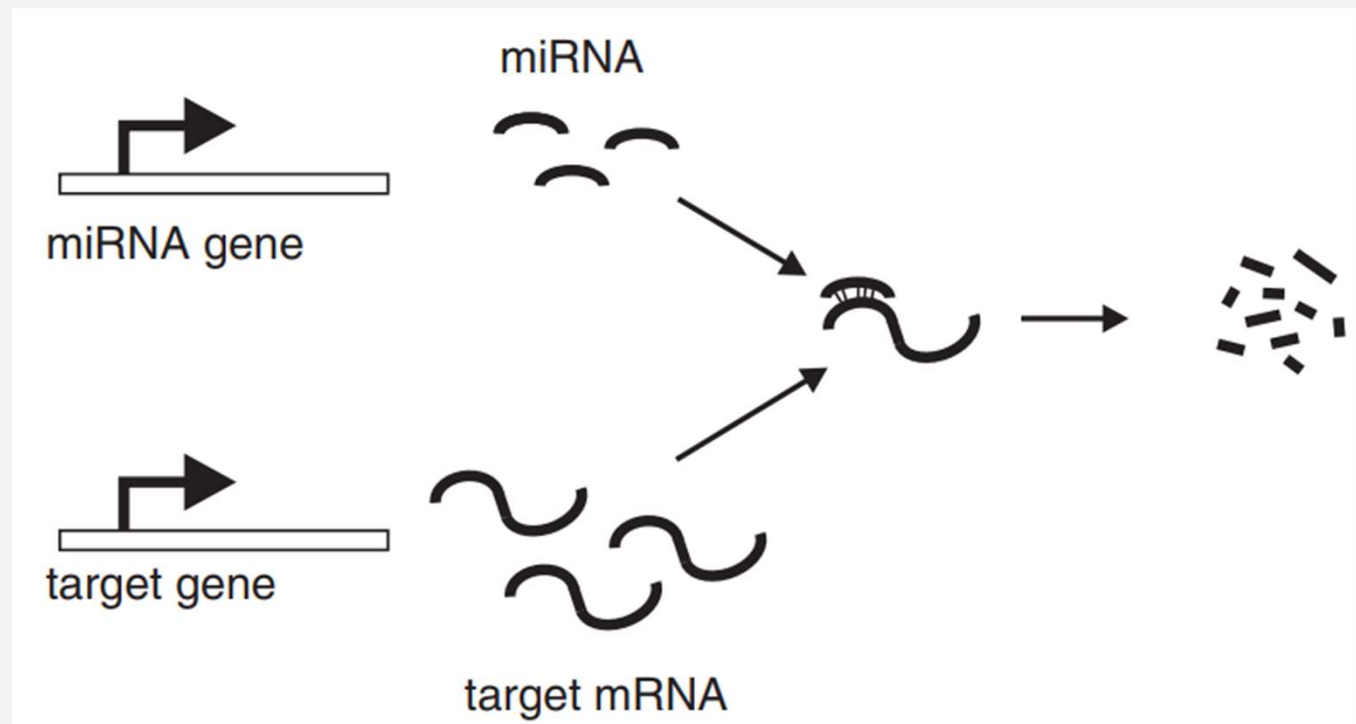
References:

[Image 1: pre mRNA to mature mRNA by Mutundis, retrieved from: File:Pre-mRNA to mRNA MH.svg - Wikimedia Commons, 2015.](#)

Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci U S A. 2002 Nov 26;99(24):15524-9. doi: 10.1073/pnas.242606799. Epub 2002 Nov 14. PMID: 12434020; PMCID: PMC137750.

RNA induced silencing complex (RISC)

- Gene knockout
 - Perfect base pair matching
- Gene knockdown
 - Base pair matching



References:

[Image 1: Numerical modelling of microRNA-mediated mRNA decay identifies novel mechanism of microRNA controlled mRNA downregulation - Scientific Figure on ResearchGate.](#)
McManus MT, Sharp PA. Gene silencing in mammals by small interfering RNAs. Nat Rev Genet. 2002 Oct;3(10):737-47. doi: 10.1038/nrg908. PMID: 12360232.



Project value:

- Progress in:
 - Molecular profiling of tumors with ncRNA-target patterns

- Contribution to:
 - cancer diagnosis
 - best patient/treatment selection
 - basic research for pipeline drugs that specifically target lung cancer pathways



Objectives:

- Next Generation Sequencing (NGS)
 - FFPE (cytology, histology)
- definition of differentially expressed ncRNAs and/or mRNAs
 - **Predictive Analytics:** Linear models (LIMMA); P-SVM (dyadic data based SVM);
- target relation detection between ncRNAs and mRNAs
 - Random Forest (MBSTar); TargetMiner, MiRanda (SVM); DeepTarget (RNN); DIANA, PITA
- cancer pathway analysis
 - Systems Biology (Bayesian Networks ...)
- correlation with clinical endpoints in lung cancer patients
 - **Predictive Analytics:** Correlation, Survival Analysis, Kaplan-Meier, Cox (Regression);



Research program overview

Lung cancer patients

Hypothesis generation phase (13 relapse vs 24 controls)

1st NGS run: Analysis of
differentially expressed
miRNAs

2nd NGS run: Analysis of
differentially expressed
targets

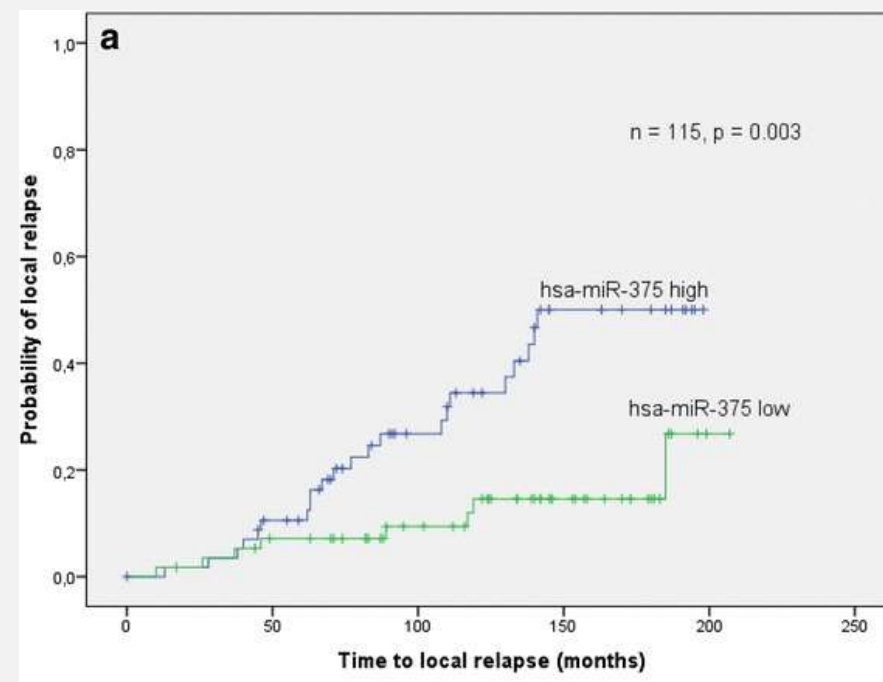
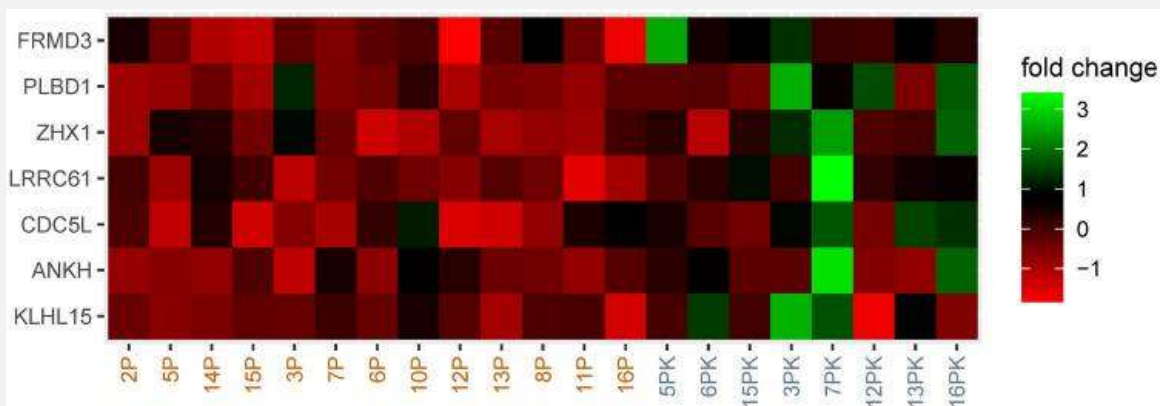
Implementation
of interfaces to target
databases (TargetScan,
PITA) and pathway
prediction tools
(TCGA, KEGG)

Validation phase

cBioPortal + TCGA data
miRNAs: n = 55 relapse vs 27 controls
targets: n = 54 relapse vs 28 controls

RT-qPCR, IHC
n = 57 relapse vs 57 controls

miRNA-375 predicts local relapse in breast cancer



Reference:

[Image 1: Zellinger et.al, Breast Cancer, 2022](#)

[Image 2: Zehentmayr et al., Clinical Epigenetics, 2016.](#)

Conclusion

- Molecular profiles predict patient outcome
- Big data analysis needs computer scientists and AI algorithms

Thank you!