MicroRNAs in Glioblastoma: Insights and Implications Unveiling the Role of MicroRNAs in Brain Tumor Biology and Therapy

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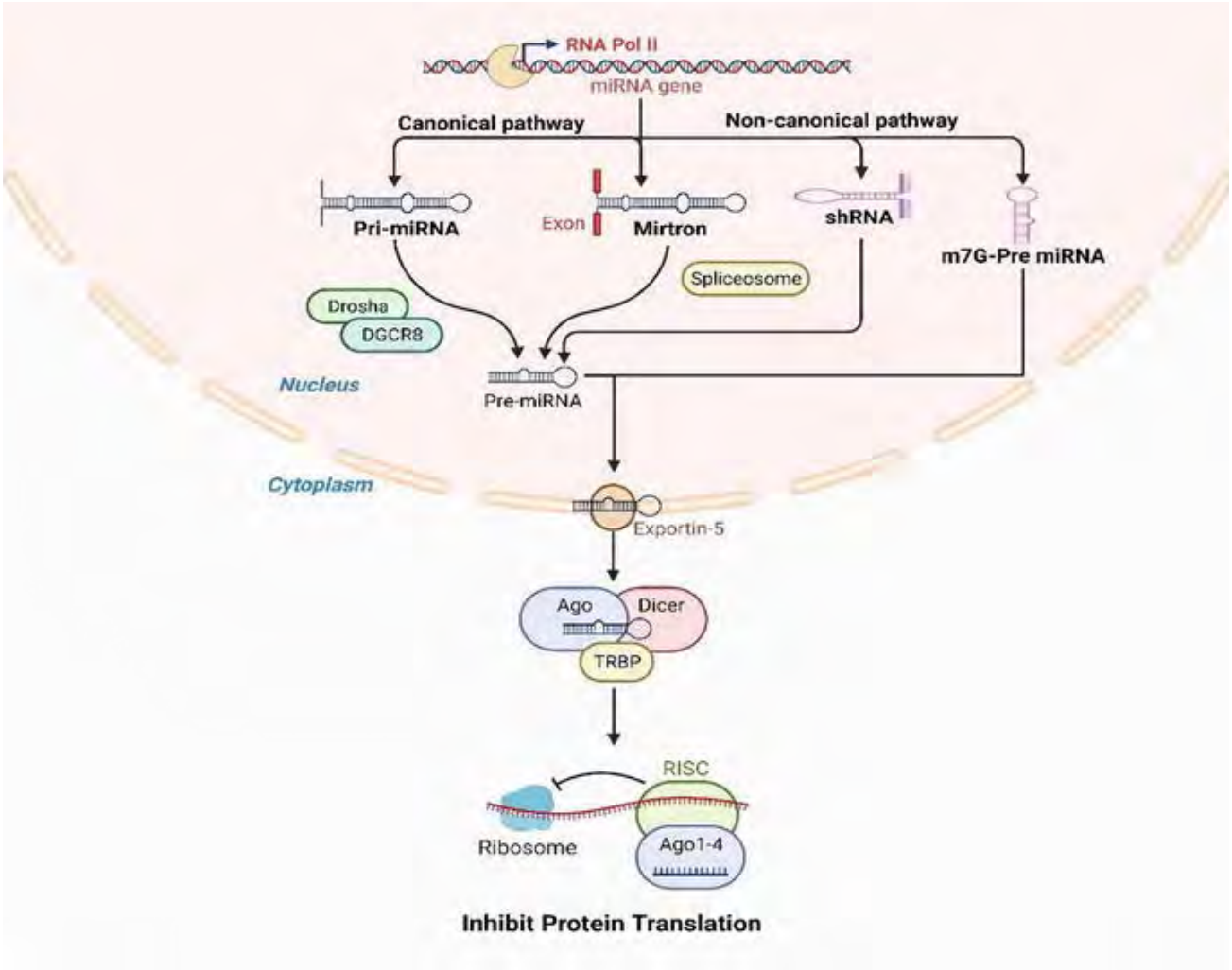
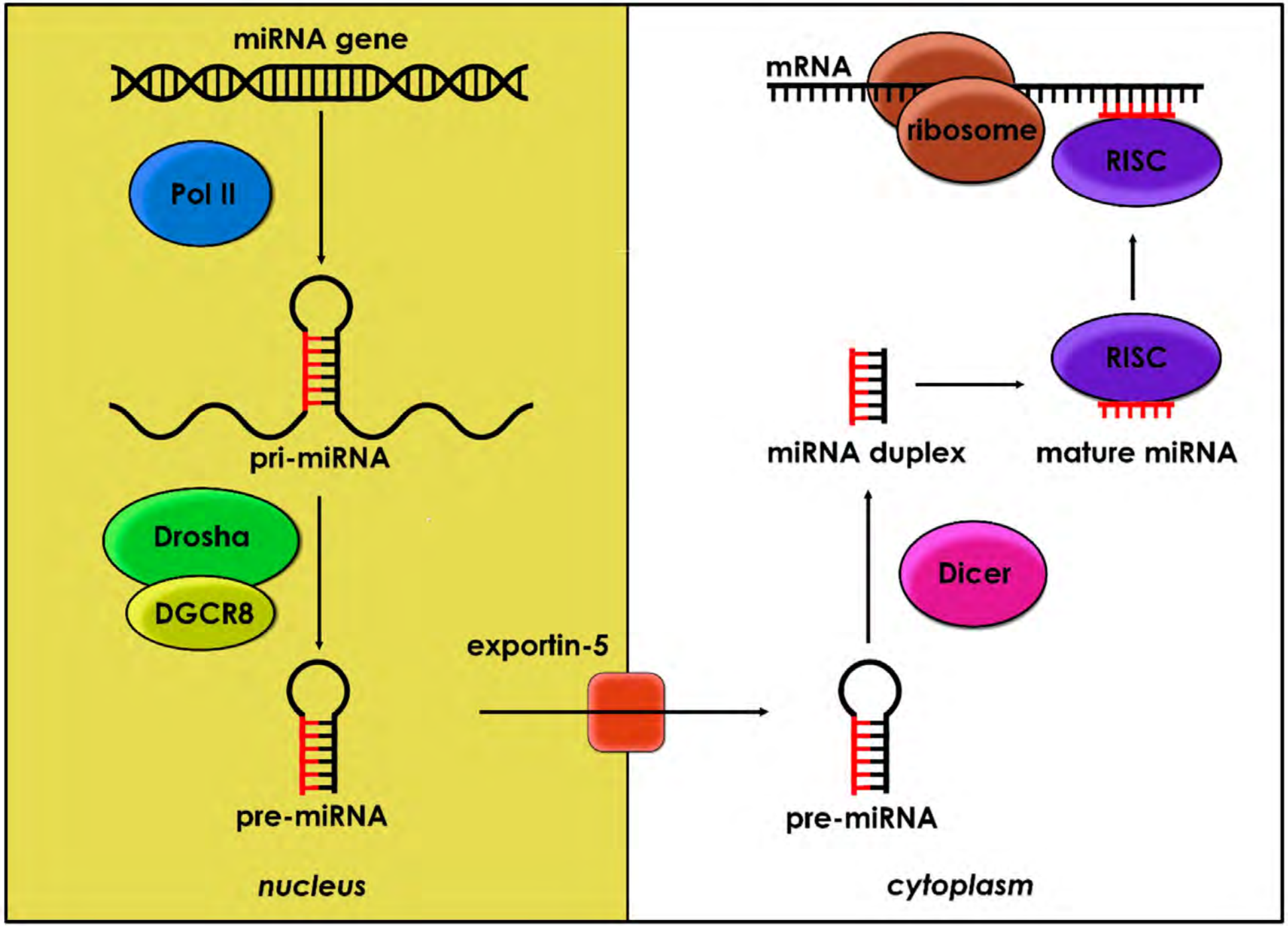
MicroRNAs and Cancer

- MicroRNAs can act as oncogenes or tumor suppressors, influencing cancer initiation, progression, and metastasis.
- Dysregulation of miRNAs is a common feature in cancer, leading to abnormal cell growth and differentiation.
- Understanding the role of miRNAs in cancer can offer insights into disease mechanisms and identify new targets for therapy.



Introduction to Glioblastoma

- Glioblastoma is the most common and aggressive form of brain cancer in adults.
- Despite advances in treatment, the prognosis remains poor, with a median survival of about 15 months post-diagnosis.
- Treatment typically involves a combination of surgery, radiation therapy, and chemotherapy, aiming to prolong survival and improve quality of life.

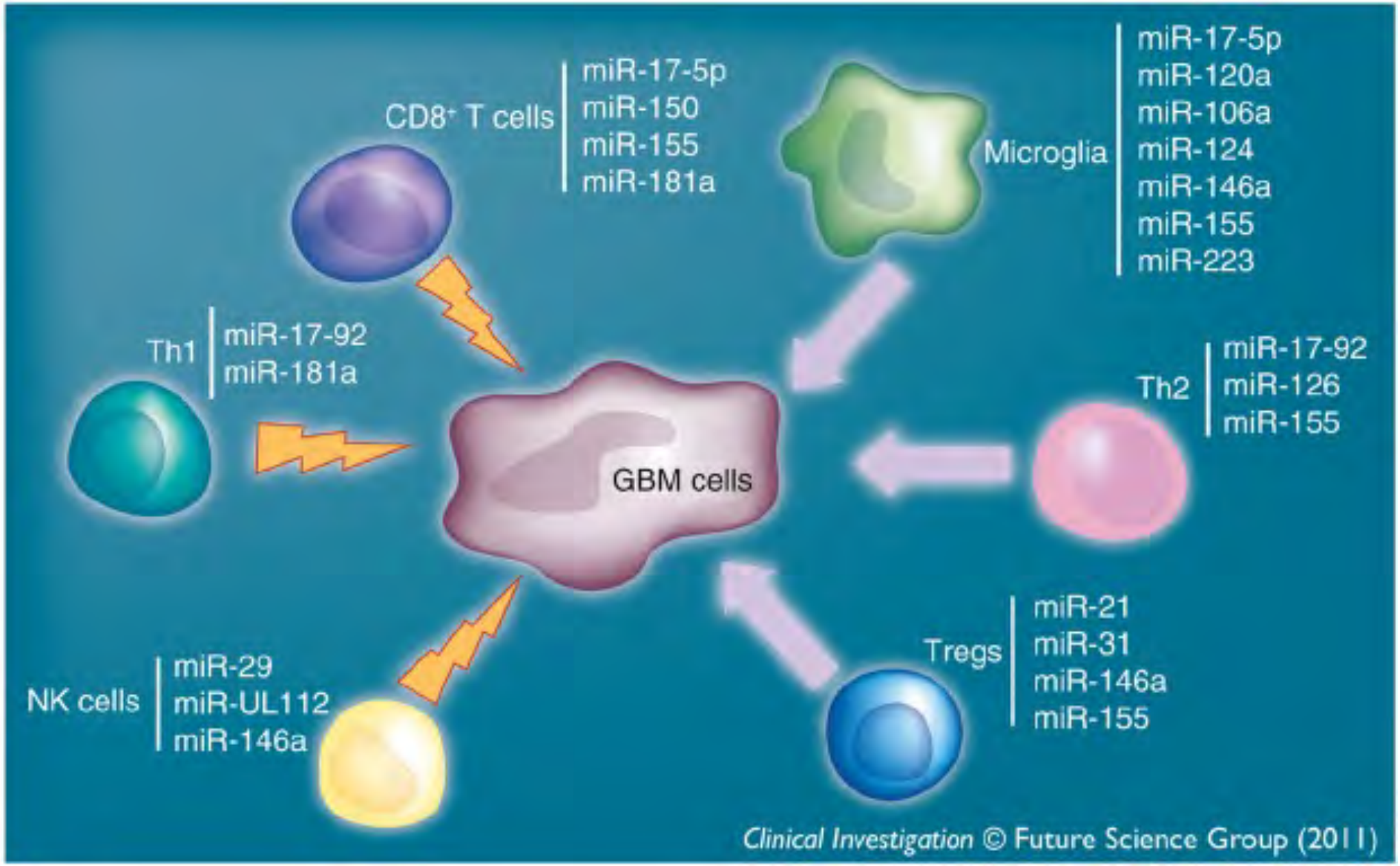

miRNA gene
Pol II
pri-miRNA
Drosha
DGCR8
pre-miRNA
nucleus
exportin-5
pre-miRNA
Dicer
miRNA duplex
RISC
mature miRNA
RISC
mRNA
ribosome
cytoplasm

MicroRNAs (miRNAs) are small, non-coding RNA molecules, about 22 nucleotides in length, that play a crucial role in regulating gene expression.

They bind to complementary sequences on target messenger RNAs (mRNAs), usually resulting in gene silencing.

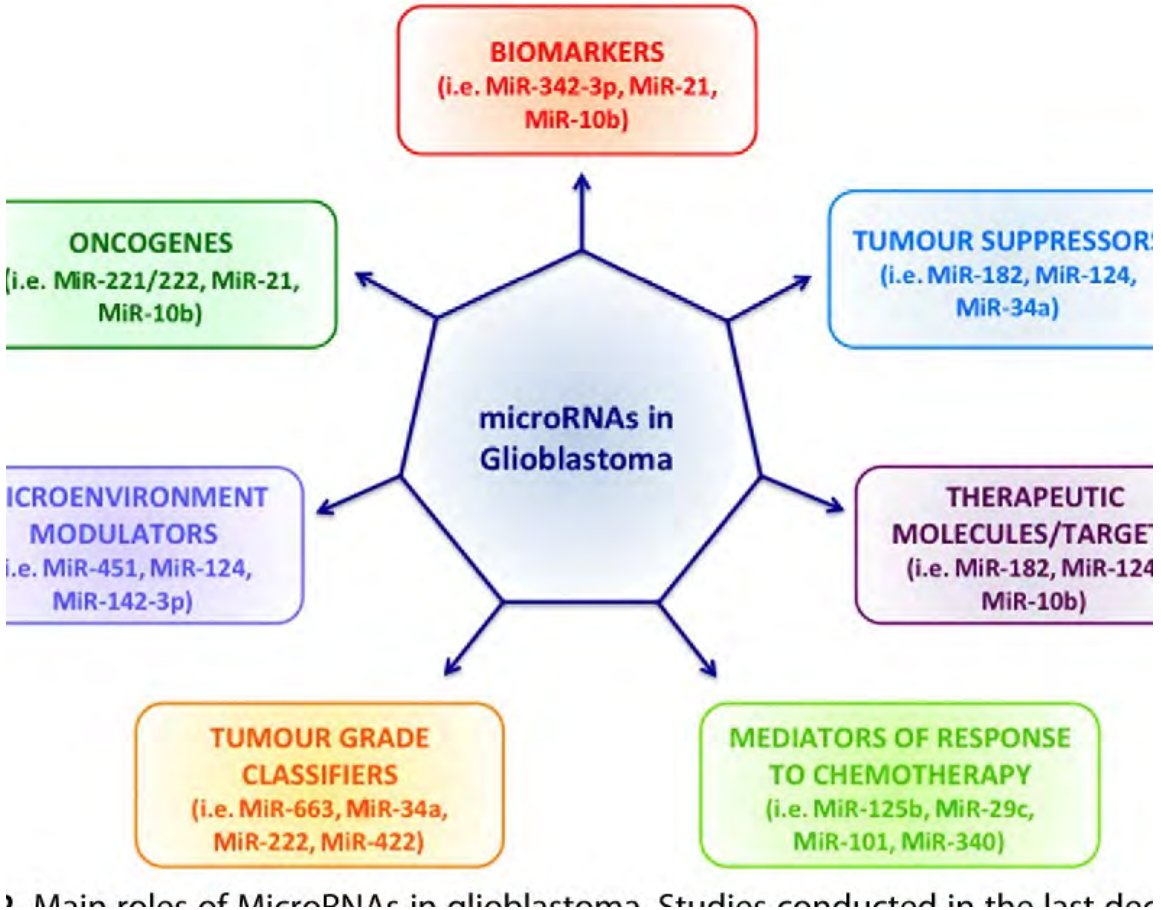
Their regulation of gene expression is essential for normal development and functioning, as well as in the pathology of various diseases, including cancer.

Overview of MicroRNAs


CD8+ T cells
miR-17-5p
miR-150
miR-155
miR-181a
Microglia
miR-17-5p
miR-120a
miR-106a
miR-124
miR-146a
miR-155
miR-223
Th1
miR-17-92
miR-181a
GBM cells
Th2
miR-17-92
miR-126
miR-155
NK cells
miR-29
miR-UL112
miR-146a
Tregs
miR-21
miR-31
miR-146a
miR-155
Clinical Investigation © Future Science Group (2011)

MicroRNAs in Glioblastoma

- **In glioblastoma, certain miRNAs are upregulated, contributing to tumor growth and survival, such as miR-21, which inhibits apoptosis and promotes proliferation.**
- **Conversely, some miRNAs are downregulated, like miR-34a, which normally functions as a tumor suppressor by targeting multiple oncogenes.**
- **These alterations in miRNA expression contribute to the aggressive nature of glioblastoma.**



Recent Research

- Recent studies have identified miR-124 and miR-128 as critical regulators of glioblastoma stem cell differentiation, offering new targets for therapy.
- Another study showed that inhibition of miR-10b suppresses tumor growth and extends survival in glioblastoma animal models.
- These findings highlight the potential of miRNA-targeted therapies to complement existing treatments.

miRNAs with both suppressor and oncogenic functions in glioblastoma multiforme.

S. No.	miRNA Name	Expression in Glioblastoma	Role in GBM
1.	miR-21	up-regulated [34]	oncomiR
2.	miR-93	up-regulated [35]	oncomiR
3.	miR-10b	up-regulated [35]	oncomiR
4.	miR-196a	up-regulated [36]	oncomiR
5.	miR-221/222	up-regulated [37]	oncomiR
6.	miR-182	up-regulated [38]	oncomiR
7.	miR-7	down-regulated [39]	tumor suppressor
8.	miR-128	down-regulated [40]	tumor suppressor
9.	miR-124/137	down-regulated [41]	tumor suppressor
10.	miR-101	down-regulated [42]	tumor suppressor
11.	miR-181	down-regulated [40,43]	tumor suppressor
12.	miR-146a	down-regulated [44]	tumor suppressor
13.	miR-137	down-regulated [45]	tumor suppressor
14.	miR-34a	down-regulated [43]	tumor suppressor

The correlation of microRNA-181a and target genes with poor prognosis of glioblastoma patients

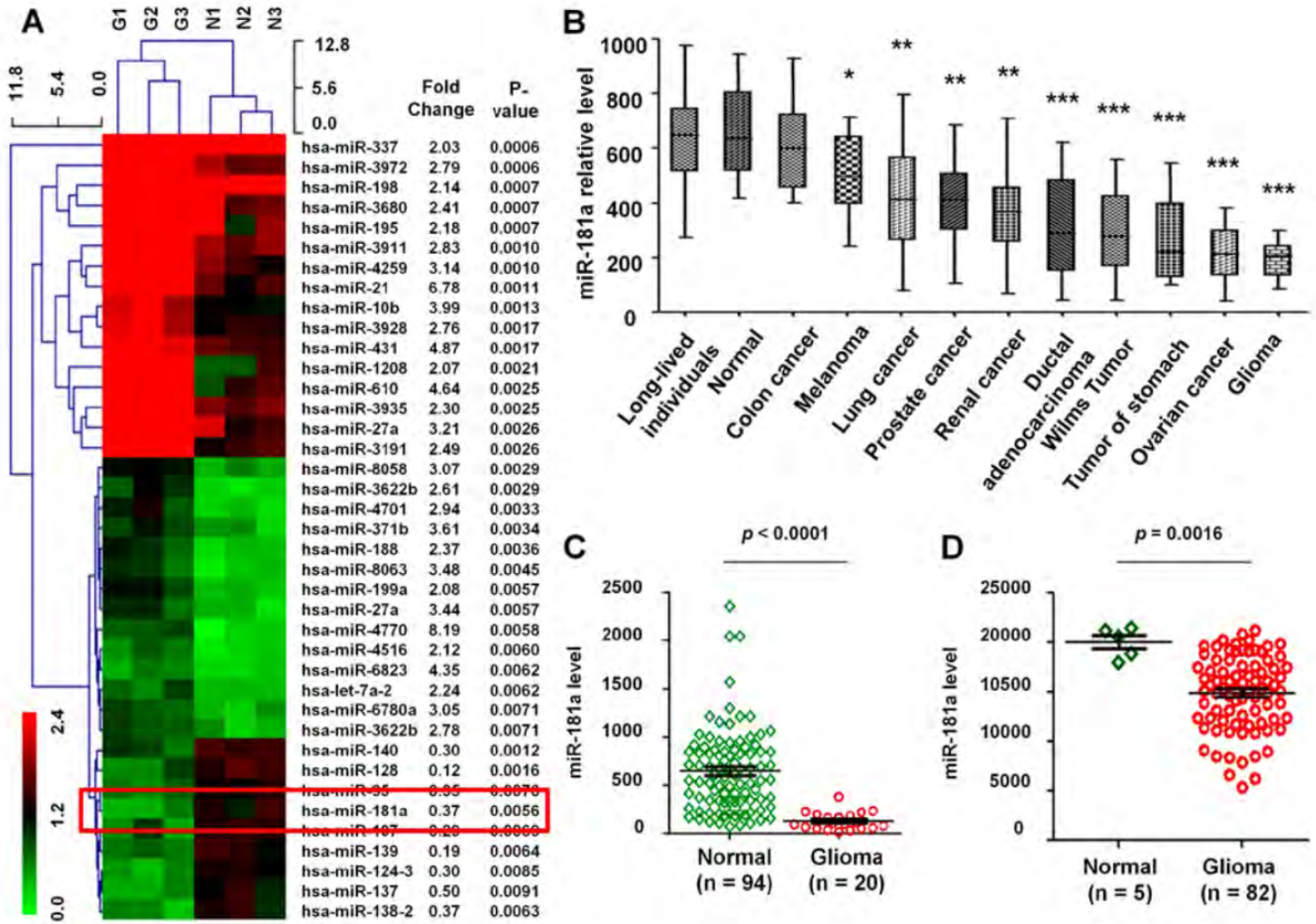


Figure 1. The expression of miR-181a in normal and GBM tissues. (A) Hierarchical clustering for differential miRNAs in 3 paired GBM tissues derived from GEO database (GSE65626-GPL19117). (B) Expression levels of miR-181a in long-lived individuals, normal tissues and various cancers derived from the GEO database (GSE61741). Expression levels of miR-181a in GBM vs. normal tissues derived from the (C) GEO dataset GSE61741 and (D) GSE25632-GPL8179.

miRNAs Expression Deregulation

miR-206 miR-4477a
miR-4795-5p miR-4311
miR-4796-3p

miR-451b

$p < 0.0001$
Significantly deregulation in brain tumor comapred to control

Diagnostic Biomarkers

microRNA	AUC	p-value
miR-206	1.00	<0.0001
miR-4477a	0.93	<0.0001
miR-451b	0.89	<0.0001
miR-4311	0.95	<0.0001
miR-4795-5p	0.91	<0.0001
miR-4796-3p	0.91	<0.0001

These microRNAs act as good diagnostic markers for glioma patients

Survival Analysis

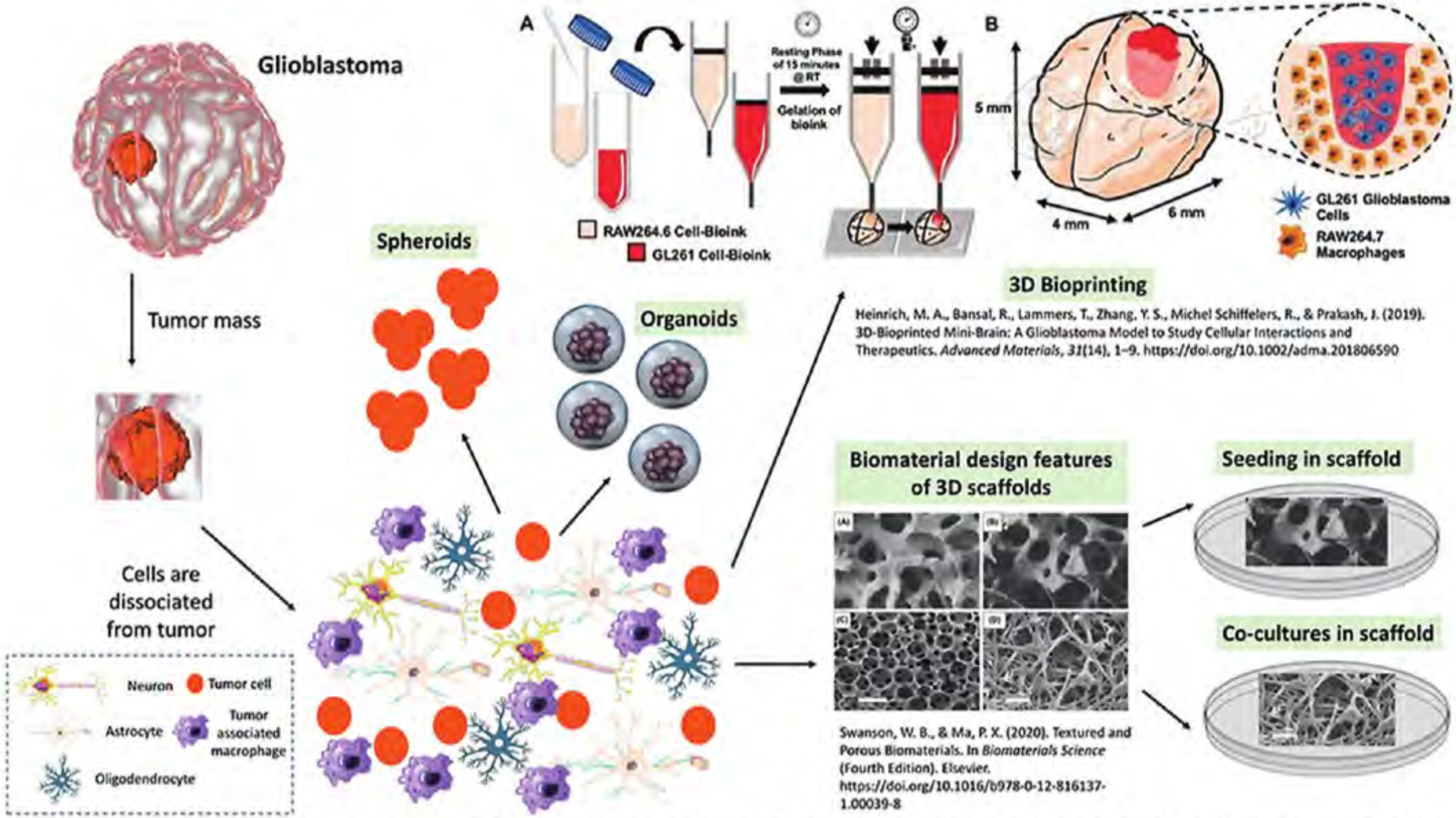
microRNA	p-value
miR-206	<0.01
miR-4477a	<0.04
miR-451b	<0.02
miR-4795-5p	0.004
miR-4796-3p	0.02

MicroRNAs deregulation associated with poor survival of glioma patients

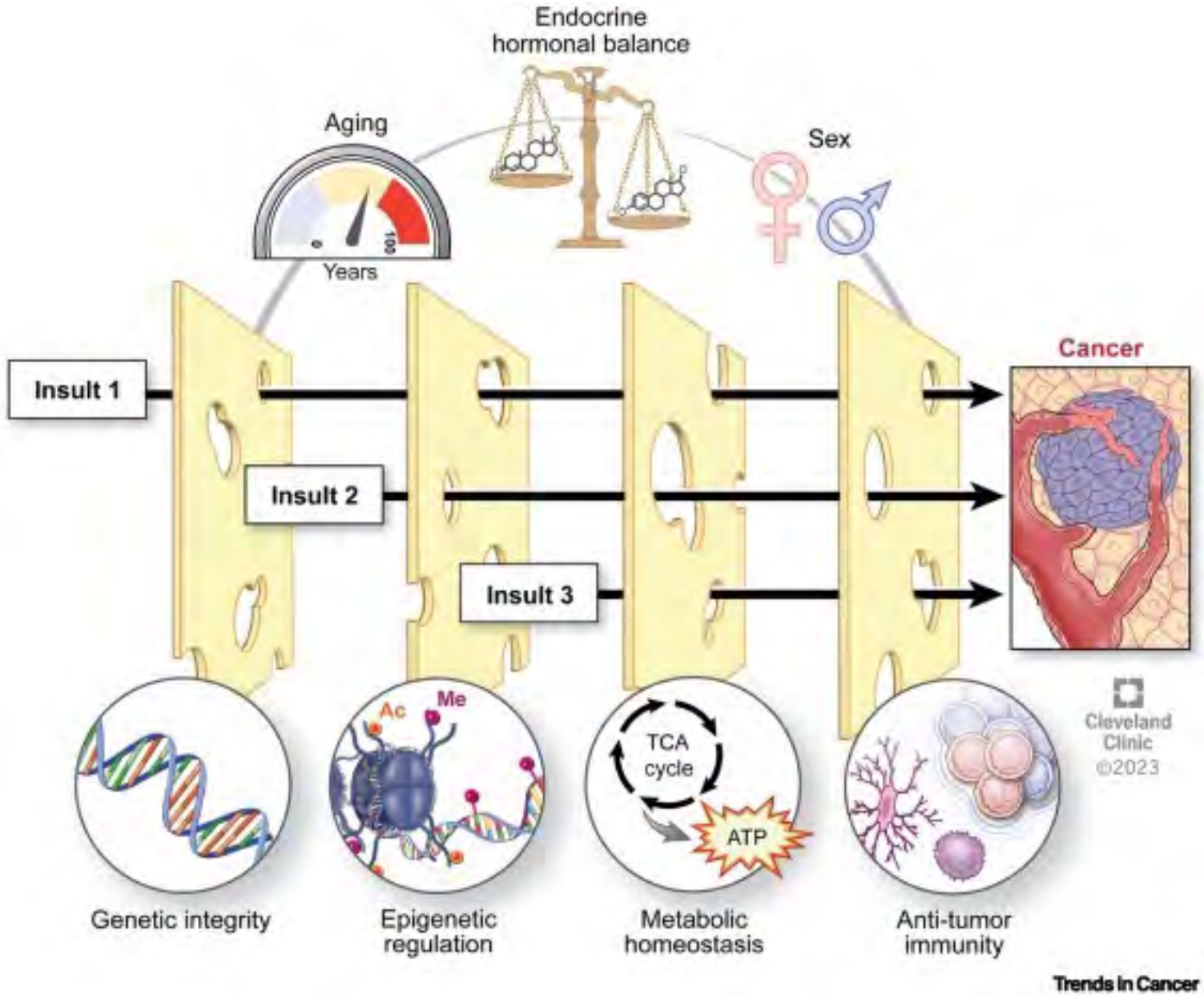
Prognostic Biomarkers

microRNA	wald	p-value
miR-206	4.6	0.03
miR-4477a	4.27	0.02
miR-451b	5.12	0.02
miR-4311	3.69	0.05
miR-4795-5p	9.41	0.0002
miR-4796-3p	7.12	0.02

These microRNAs act as worse/poor prognostic factors for glioma patients



3D *in vitro* modeling of glioblastoma multiforme (GBM) (reproduced with permission from [111]). The GBM tissues are derived from the tumor mass isolated from the patients. Then different kinds of cells are dissociated from the tumor mass. These are: neurons, astrocytes, oligodendrocytes, tumor cells, tumor associated macrophages. *In-vitro* modeling is done in several ways: spheroid formation, organoid formation, formation of 3D scaffolds with the use of engineered biomaterials (reprinted with permission from [216]) , 3D bioprinting etc. The bioprinting procedure and bioprinted mini brains are depicted using a schematic. A) Bioprinting procedure depicting the fabrication of cell-laden GelMA-gelatin bioinks and the subsequent two-step bioprinting of mini-brains. B) Close-up and cross-sectional view of the bioprinted mini-brains containing living cells (adapted with permission from [130]).


Endocrine
hormonal balance
Aging
0
100
Years
Sex
Insult 1
Insult 2
Insult 3
Cancer
Ac
Me
TCA
cycle
ATP
Genetic integrity
Epigenetic
regulation
Metabolic
homeostasis
Anti-tumor
immunity
Cleveland
Clinic
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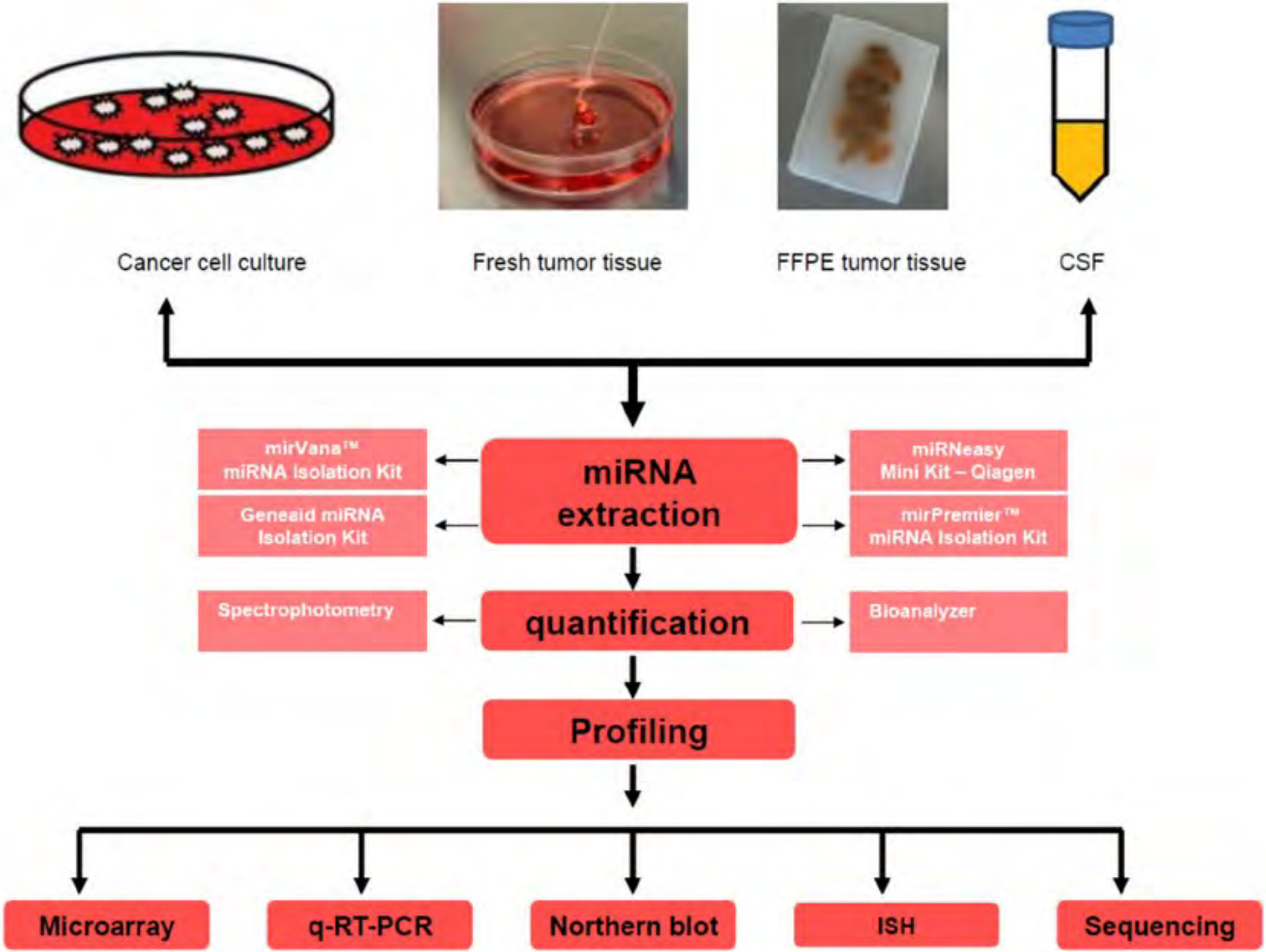
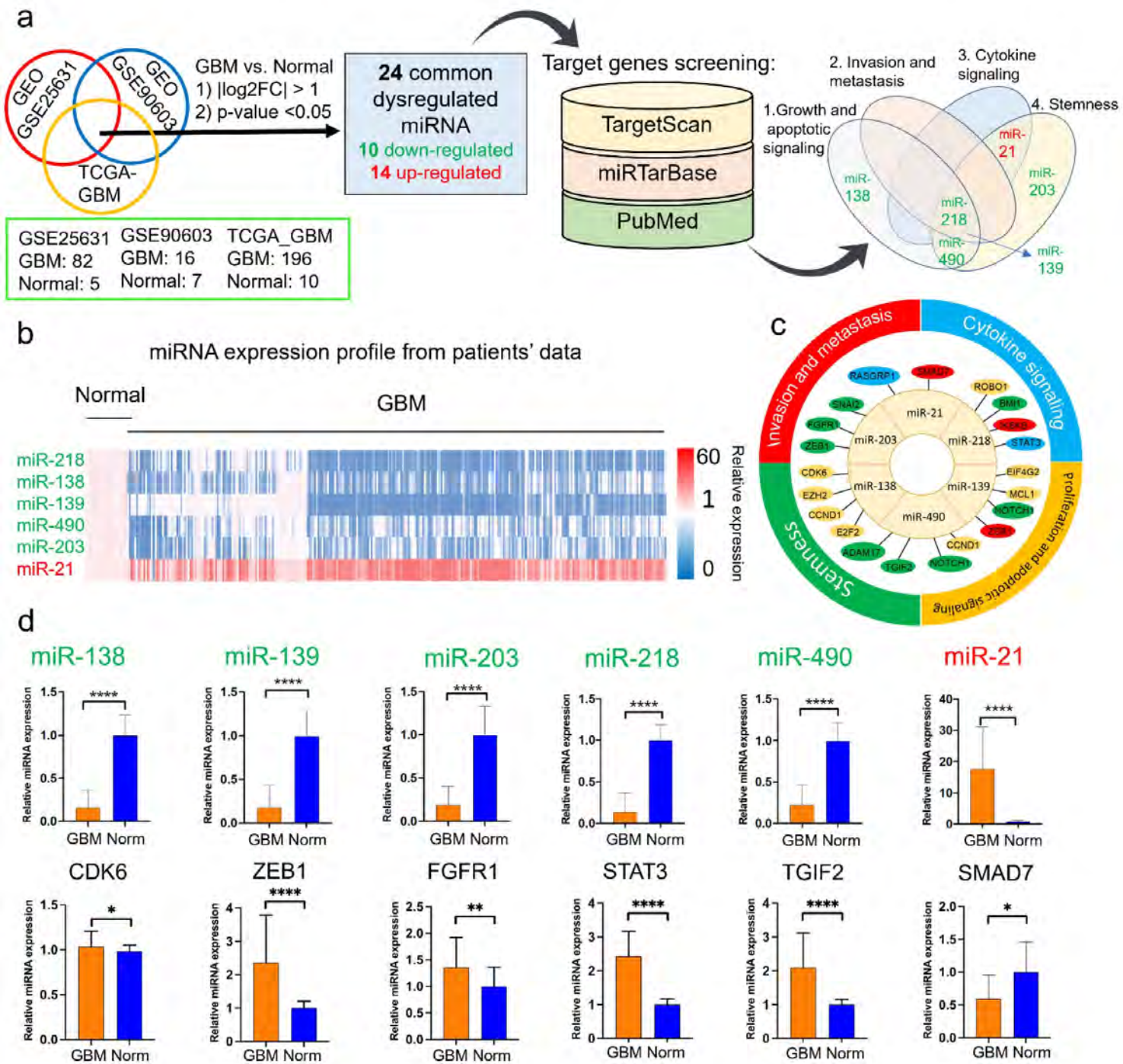
Trends in Cancer


Cancer cell culture
Fresh tumor tissue
FFPE tumor tissue
CSF
mirVana™ miRNA Isolation Kit
Geneaid miRNA Isolation Kit
miRNA extraction
miRNeasy Mini Kit – Qiagen
mirPremier™ miRNA Isolation Kit
Spectrophotometry
quantification
Bioanalyzer
Profiling
Microarray
q-RT-PCR
Northern blot
ISH
Sequencing


a
GEO GSE25631
GEO GSE90603
TCGA-GBM
GBM vs. Normal
1) |log2FC| > 1
2) p-value <0.05
24 common dysregulated miRNA
10 down-regulated
14 up-regulated
Target genes screening:
TargetScan
miRTarBase
PubMed
1.Growth and apoptotic signaling
2. Invasion and metastasis
3. Cytokine signaling
4. Stemness
miR-138
miR-218
miR-21
miR-203
miR-490
miR-139
GSE25631 GBM: 82 Normal: 5
GSE90603 GBM: 16 Normal: 7
TCGA_GBM GBM: 196 Normal: 10
b
miRNA expression profile from patients' data
Normal
GBM
miR-218
miR-138
miR-139
miR-490
miR-203
miR-21
60
1
0
Relative expression
c
Invasion and metastasis
Cytokine signaling
Proliferation and apoptotic signaling
Stemness
RASGRP1
SMAD7
ROBO1
SNAI2
BMI1
FGFR1
KRAS
ZEB1
STAT3
CDK6
EIF4G2
EZH2
MCL1
CCND1
NOTCH1
E2F2
ZEB1
ADAM17
CCND1
TGIF2
NOTCH1
miR-21
miR-203
miR-218
miR-138
miR-139
miR-490
d
miR-138
miR-139
miR-203
miR-218
miR-490
miR-21
CDK6
ZEB1
FGFR1
STAT3
TGIF2
SMAD7
Relative miRNA expression
GBM Norm