CANCER STEM CELL BIOLOGY and CANCER VACCINES
(6)

Assoc. Prof. Pınar BAYDIN

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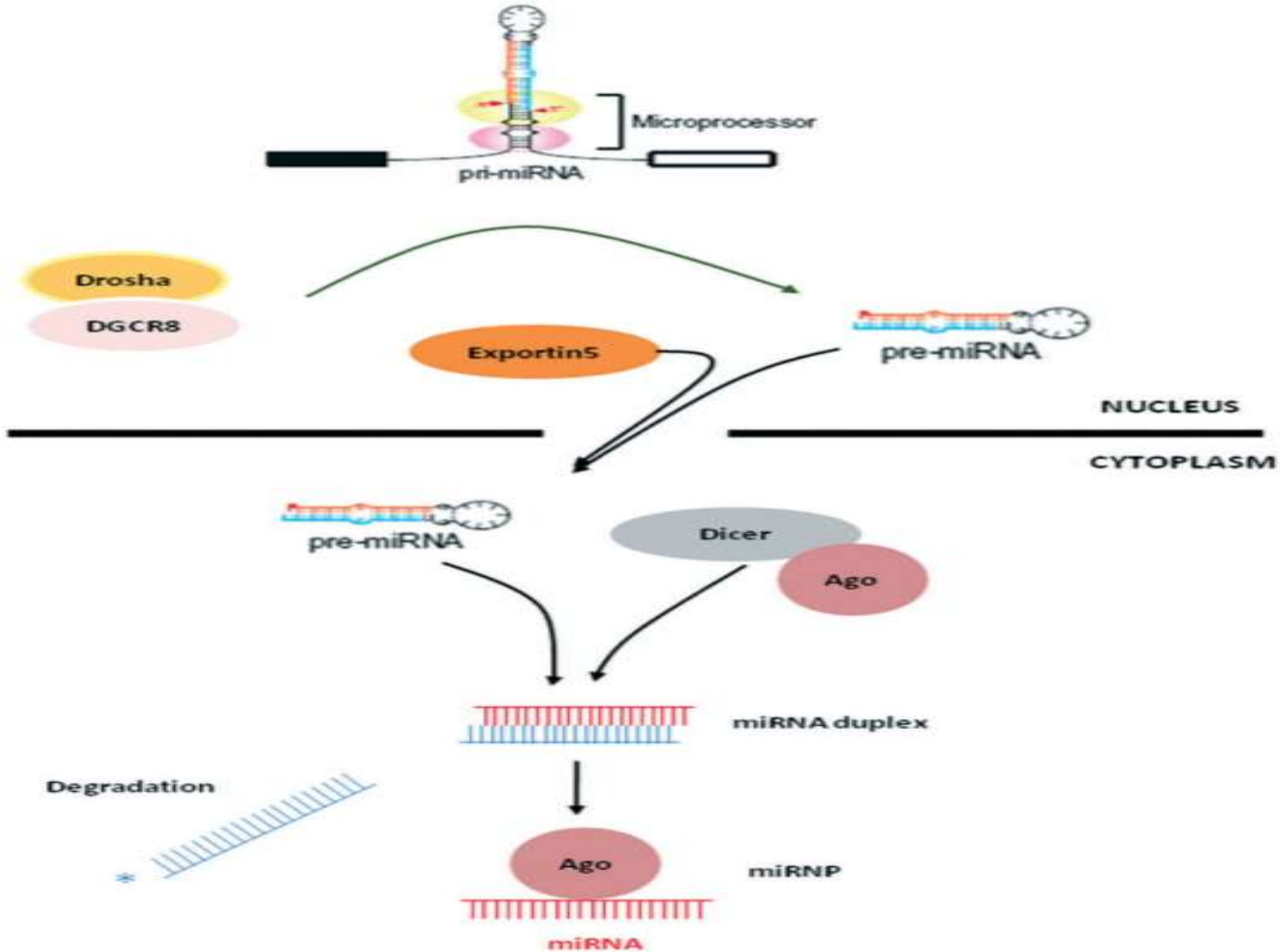
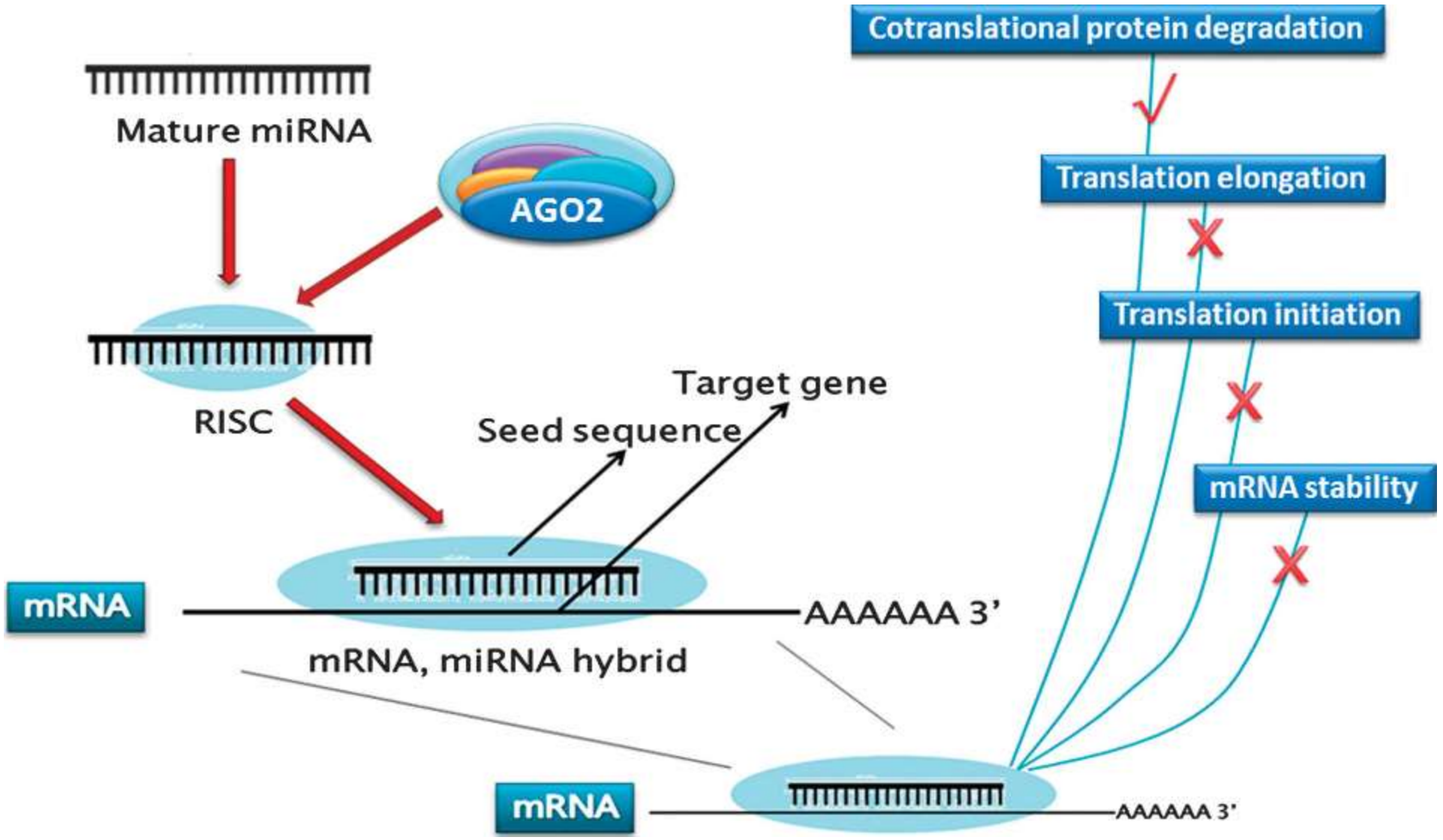
microRNAs
and
Cancer Stem Cell

miRNAs

- Micro RNAs are evolutionarily conserved, single stranded molecules of 21-25 nucleotides in length and function post-transcriptionally by partial binding to the mRNA of genes.
- Binding of a specific miRNA to its target on an mRNA can inhibit its expression by a variety of mechanisms.
- The most common mechanism is translational repression as a result of miRNA binding to the 3’UTR of an mRNA.
- Micro RNAs are currently considered as “master regulators” of gene expression.
- Since a single miRNA can bind and consequently regulate the expression of more than 100 different transcripts it has been estimated that miRNAs may be able to regulate up to 30% of the protein-coding genes in the human genome.
- As a result, miRNAs receive widespread attention on their potential role in complicated biological processes and multifactorial diseases.



Felekkis et al., 2010



Sun et al., 2014

miRNA Regulations of Stem Cells

- Non-coding RNAs (ncRNAs) were initially dubbed as “junk RNAs” because they are not translated into protein and seemed to have no further purpose .
- These “junk RNAs” play a central role in epigenetic, transcriptional, posttranscriptional, and translational regulation of gene expression in both physiological and pathological conditions.
- MicroRNAs (miRNAs) regulate cancer cell stemness, invasion and metastasis, tumor progression and EMT regulation.
- Similar to protein-coding genes, abnormal expression of miRNAs has been reported in various types of cancers.
- Additionally, some miRNAs are known to be related to the regulation of CSC properties, such as asymmetric cell division, tumorigenicity, and drug resistance.

- Oncogenic miRNAs and tumor suppressor miRNAs play pivotal roles in cancer initiation and progression.

- miRNAs may be:
  - CSC suppressors
  - CSC promoters
  - Heterogeneous expression in CSC depending on tissue type.

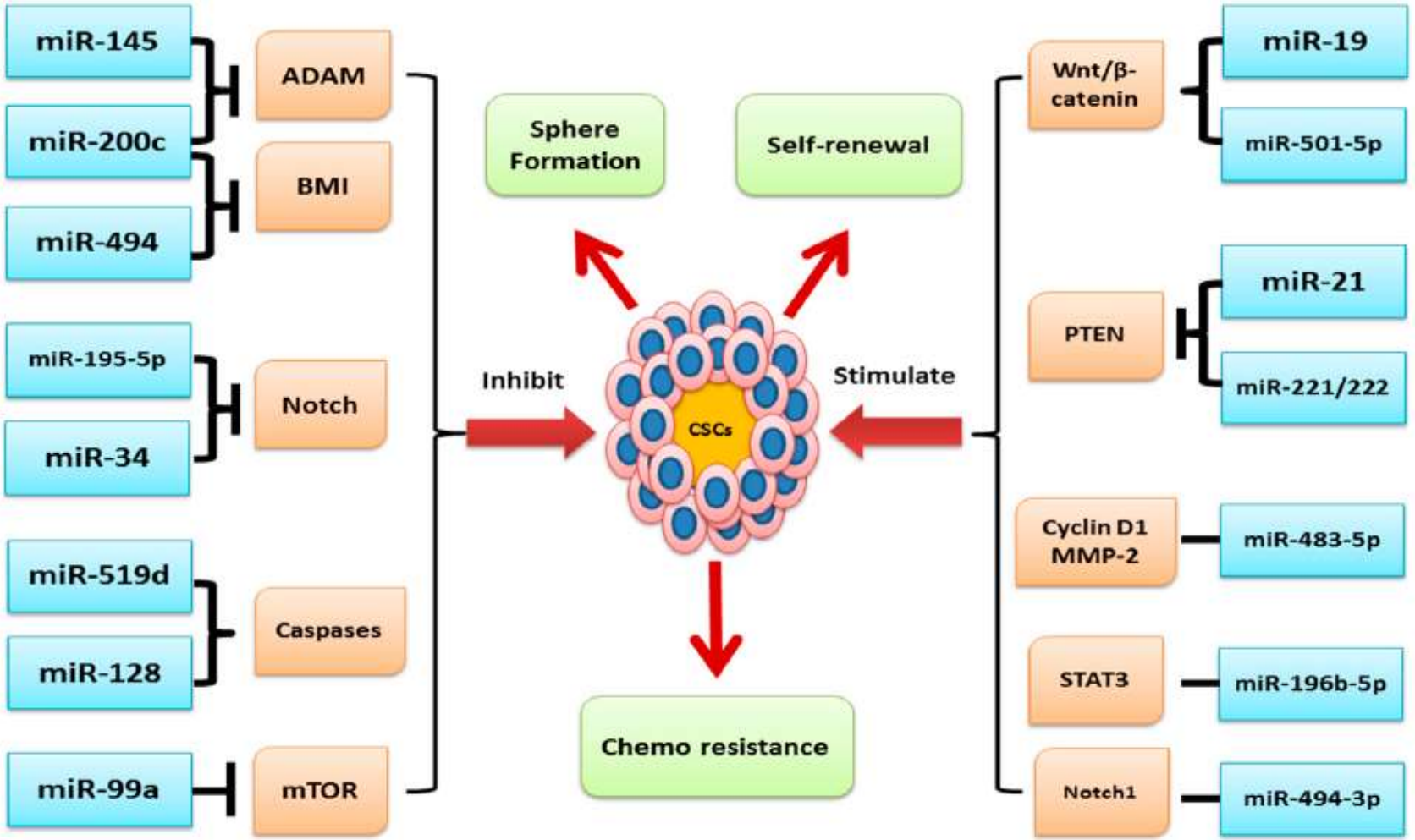
- One of the most famous oncogenic miRNAs is the miR-17e92 cluster. The miR-17-92 cluster is polycistronically expressed from the chromosome 13q31 locus, which is known to be **amplified** in lung cancer. The **expression levels of miR-17e92 are higher** in tumor tissues than in normal tissues, and increased miR-17e92 expression significantly promotes tumorigenesis in lymphoma.

- Conversely, the **expression levels of some miRNAs are decreased** in tumorigenesis. Generally, this kind of miRNA is considered to work as a **tumor suppressor miRNA**. Tumor suppressor miRNAs negatively regulate oncogenes or oncogenic pathways and inhibit tumor development. The most classic and famous tumor suppressor miRNAs are the let-7 family.

Cancer type	Listed Suppressor miRNAs	Listed Promoter miRNAs
breast	let-7 [21,22], miR-30 [23], miR-140 [43], miR141 [33], miR-199a# [58], miR-200c [32], miR-205# [56], miR-600 [37]	miR-205# [57], miR-495 [5
lung	let-7 [17]	
ovarian	let-7 [18], miR-34c [30]	miR-134-3p [54]
prostate	miR-34 [26], miR-141 [34], miR-145 [52]	miR-302/miR-367 [55]
colorectal	miR-34 [27], tRF-miR-1280 [29]	miR-21 [47], miR-27a [51], [61]
brain	miR-34a [28], miR-128 [141], miR-136 [38]	miR-9/9* [50], miR-199b#
pancreatic	miR-200b-3p [31]	miR-181 [46]
liver	miR-589 [40]	miR-130b [47]
bladder	miR-139 [42]	
skin	miR-S8 [44]	miR-142 [48]
renal	miR-145 [52]	
leukemia		miR-99 [49]

List only encompasses miRNAs discussed in article. # - miRNA can act as a suppressor or promoter depending on cancer type and local factors.

Yan et al., 2018



Khan et al., 2019

miRNA Strategies

1- Self-renewal

- There are six major factors that are required for pluripotency maintenance, Nanog, Sox2, Oct4, KLF4, Lin28, and c-Myc.

- miRNA-296, miRNA-470, miRNA-134, and miRNA181a were postulated to be potential targets for these factors and to inhibit stem cells self-renewal.

- Regulates self renewal and differentiation by targeting oncogenic genes such as Myc, Ras ect.

miRNA Strategies

2- EMT

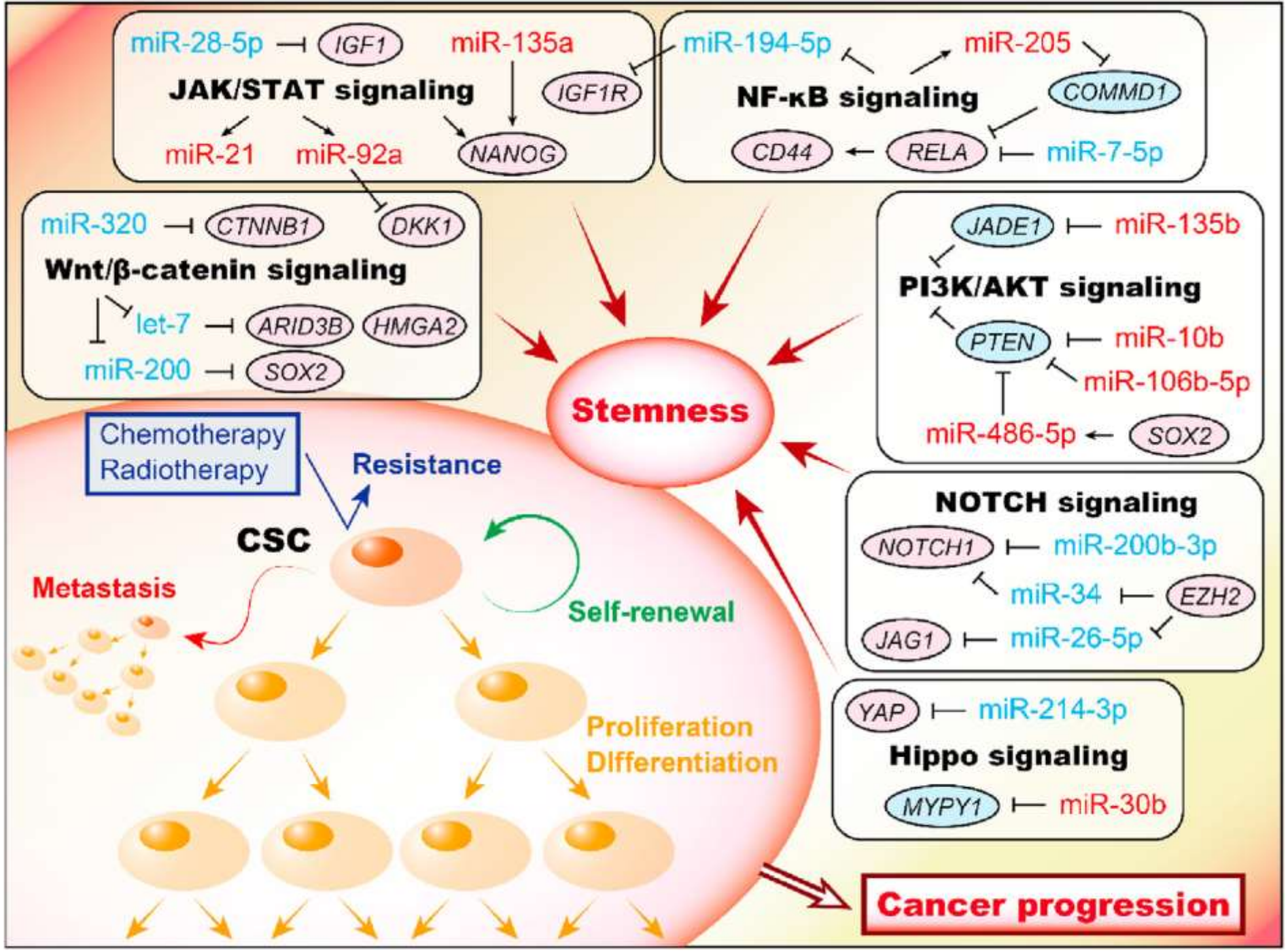
- EMT is a complex process that is regulated by several signaling pathways in which miRNAs could potentially regulate directly by binding and suppressing EMT transcription factors, or indirectly by binding to an inhibitor of EMT.

- For example, miRNA-200 family, including miRNA-200b, miRNA200c, and miRNA-141, are some of the most important regulators of EMT.

miRNA Strategies

3- Signaling pathways

- Downregulation of the microRNA miR-199b-5p is associated with metastatic spread of medulloblastoma cells.
- Notch signaling plays a major role in maintaining glioma stem cell proliferation.
- This microRNA suppresses Notch signaling, which reduces the number of medulloblastoma stem cells.
- Based on the literatures, Wnt/b-catenin signaling, JAK/STAT signaling, NF-kB signaling, PI3K/AKT signaling, NOTCH signaling and Hippo signaling were illustrated to interacted with miRNAs.



Yoshida et al., 2021

miRNA Strategies

4- Tumorigenesis and progression

- The miRNAs targeting mRNAs were often discovered at translocation breakpoints, deletions and amplification sites, accounting for 50% of all fragile regions or cancer-associated sites.

- Oncogenic miRNAs are located mainly in the amplified regions, and tumor suppressive miRNAs are located mainly in the deleted regions in human cancer.

- Upregulation of oncogenic miRNAs in carcinoma may inhibit the tumor suppressors by amplifying the miRNA encoding locus. Downregulation of tumor suppressive miRNAs by deletion or methylation of the miRNA locus may result in oncogenes overexpression.

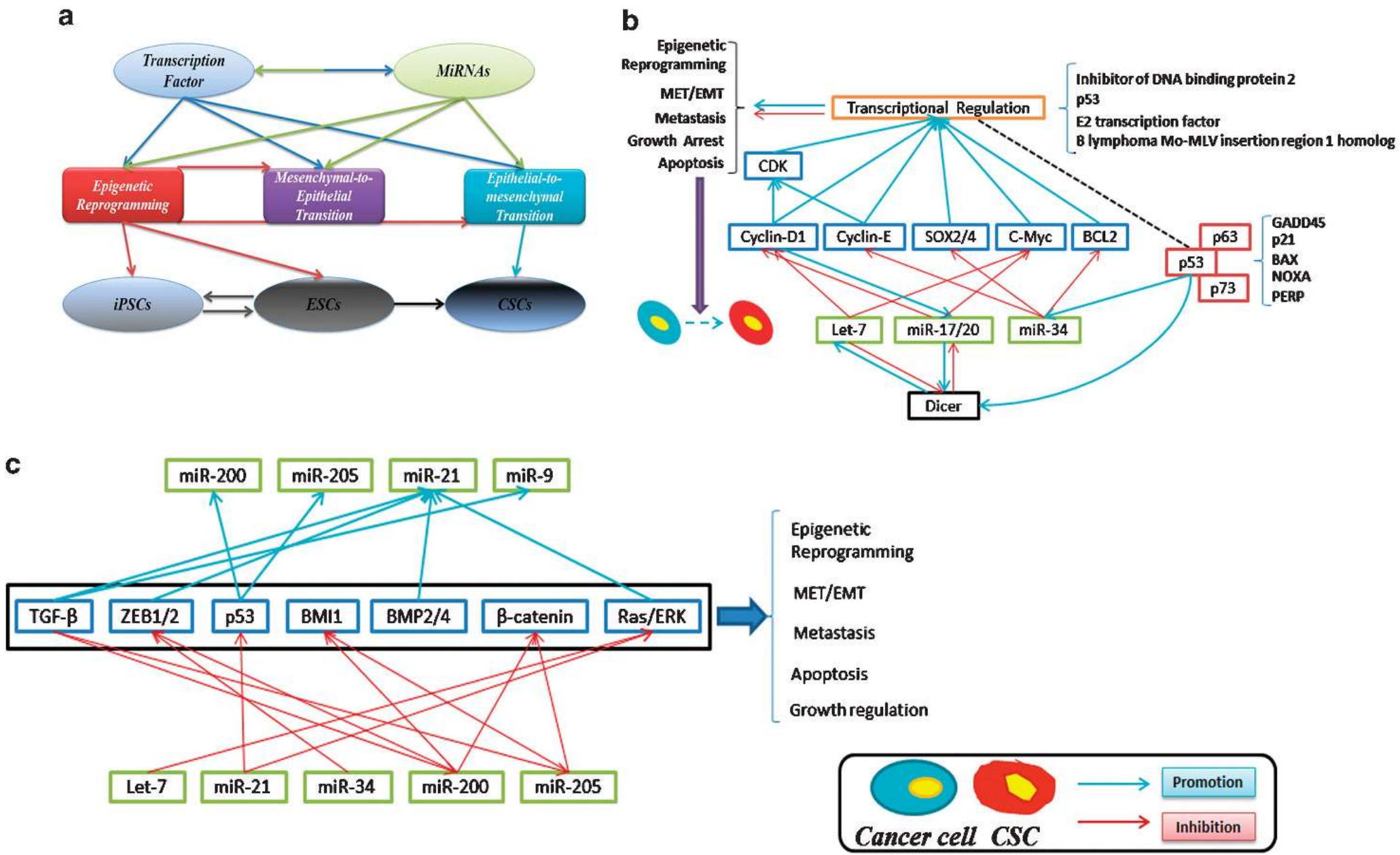
miRNA Strategies

5- Epigenetic reprogramming

- However, reprogramming process governed and mediated by transcription factors (TFs), noncoding RNAs and epigenetic modifiers were continually discovered, which could override the cellular identity and induce reprogramming of cellular fates.

- miRNAs were correlated with epigenetic reprogramming by epithelial mesenchymal transition (EMT) more often.

- The TFs implicated in epigenetic reprogramming were often targeted genes of miRNAs and, reversely, these miRNAs could be regulated directly by TFs.



Sun et al., 2014

miRNA Strategies

6- Therapy resistance

- Membrane transporters exclude anticancer drugs from the cytoplasm, inducing detoxification and insensitivity to drug-induced apoptosis, contributing to multidrug resistance (MDR).
- The ATP-binding cassette (ABC) transporters (ABCG2/BCRP1, ABCB1/MDR1 and ABCA3), COX-2, Ras, Cyclin-D1, Bcl-2 and Survivin were proved to play critical roles in drug resistance.
- The well-known cancer-related signal pathways, such as the epidermal growth factor receptor, extracellular signal regulated kinase, mitogen activated protein kinase and nuclear factor-kappa B also contributed.
- Chemoradiotherapy resistance could be regulated by post-transcriptional regulators: miRNAs.
- Discoveries of miRNAs made anticancer therapy promising, for nearly all proteins and signal pathways referring to therapy resistance have been identified as target genes of miRNAs, which could adjust cellular response to anticancer therapy via affecting signaling pathways, apoptotic responses and DNA repair systems.

In summary,

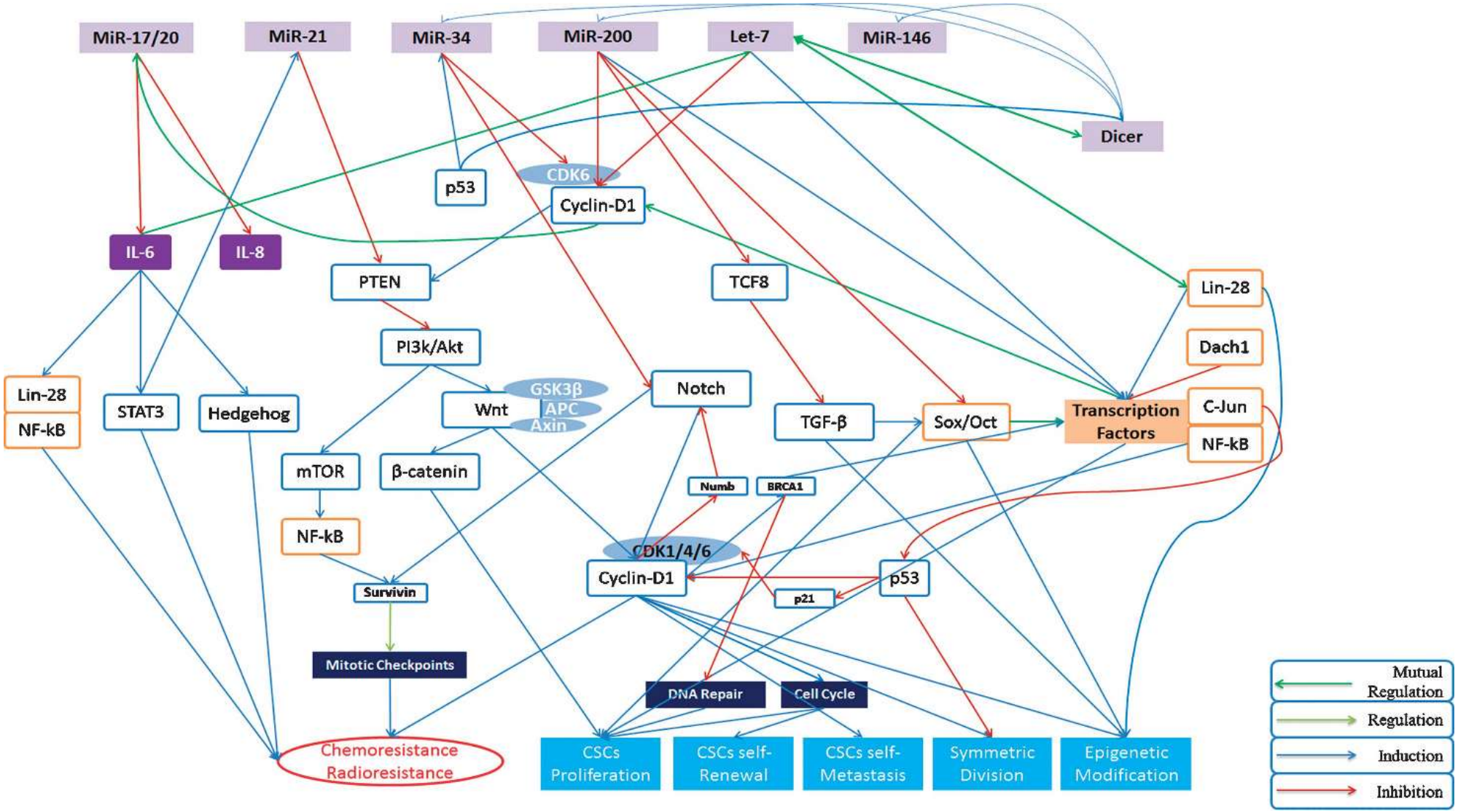
- miRNAs were proved to be involved in tumor development of multiple processes by critically regulating CSCs and were also proved to be crucial regulators in CSCs self-renewal and differentiation by influencing implicated signal pathways and protein-coding genes.

- miRNAs played crucial roles in establishing and ensuring CSCs identity by maintaining core networks of TFs and RNA-binding proteins.

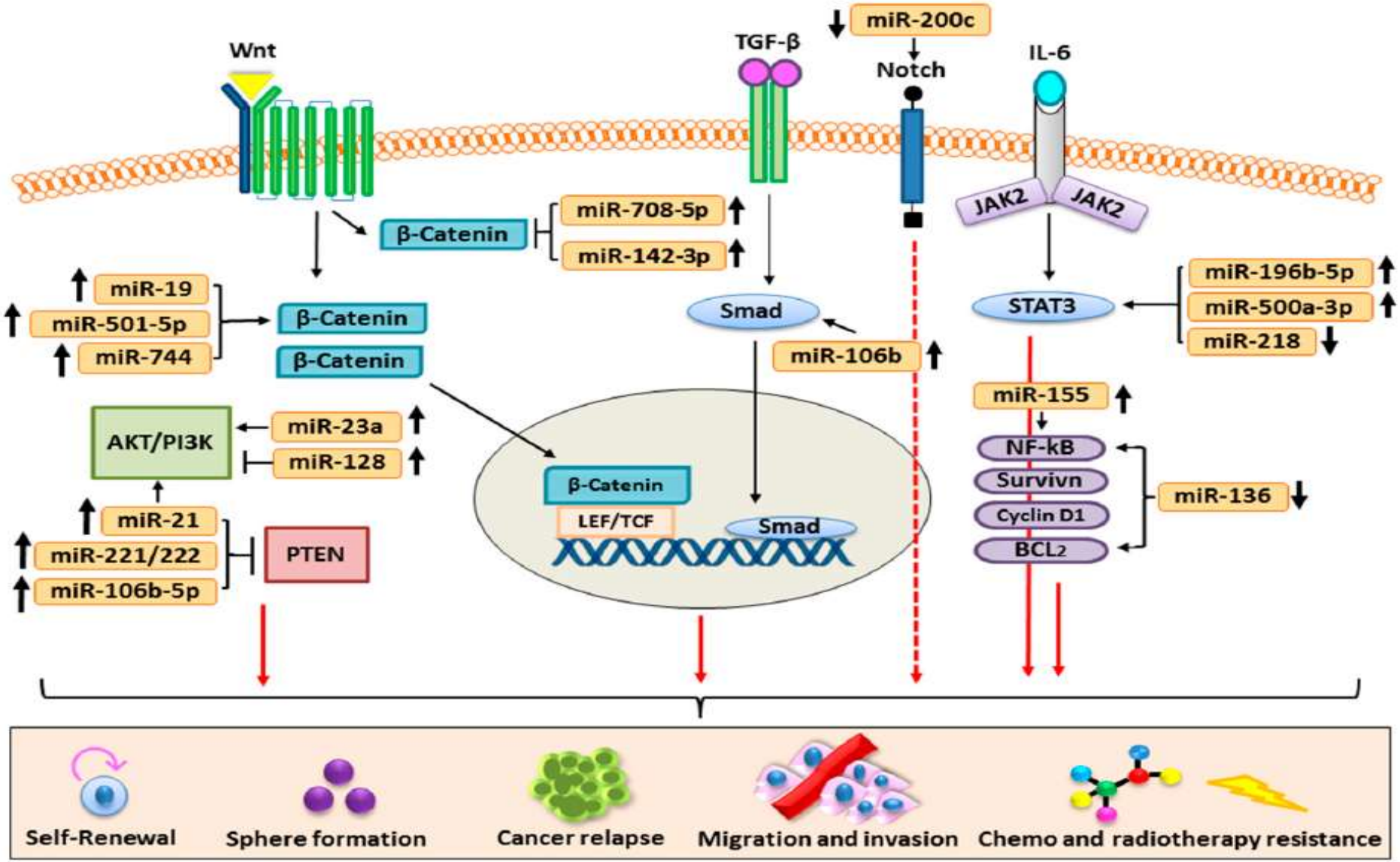
- Serving as the earliest-found and best-understood one, let-7 miRNAs family was testified to inhibit the malignancy of CSCs by targeting and repressing stemness factors and target genes, such as HMGA2, c-Myc, RAS, mitogen activated protein kinase, Notch.

- miRNAs affect diverse functions in the regulation of EMT and metastasis and could also be regulated by different signaling pathways related to EMT and metastasis.

- miRNAs also involved in epigenetic reprogramming, growth regulation and apoptosis.



Sun et al., 2014



Khan et al., 2019

- Exploration and understanding of the functions of miRNAs provides us new insights into cancer diagnoses and prognosis evaluation.

- A better and more complete understanding of miRNAs will undoubtedly yield diagnostic and therapeutic advances for anticancer treatment. Irregularly expressed miRNAs in CSCs were correlated with CSCs characteristics via multiple molecular mechanisms, while the critical questions are how could miRNAs be used and how do they work in a real clinical therapy?

- Cancer-specific miRNA expression signature is very informative for diagnostic, therapeutic and prognostic purposes. Let-7 deregulation has been identified as a diagnostic and prognostic feature in clinical studies, as let-7a and let-7g were correlated with lung cancer survival.

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