Signature Role of miRNA in Cell and Therapeutic Value in the Treatment of Acute Myeloid Leukemia (AML)

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What is Cancer

- Cancer is characterized by the uncontrolled growth and spread of abnormal cells. If the spread remains unchecked, it may spread to other parts of the body.
- It may lead to death.
What is Acute Myeloid Leukemia (AML)

- Malignant clonal disorder of immature myeloid progenitor cells characterized by clonal proliferation of abnormal blast cells and impaired production of normal blood cells
- Leukemic blasts may express capabilities for maturation to a variable degree, that lead to morphological heterogeneity
Blood Cell Formation

LT-HSC

ST-HSC

MPP

CFU-GEMM

CMP

CFU-M

CFU-G

CFU-Eo

CFU-Base

CLP

Pro-B

Pro-T

Pre-B

B Cell

T Cell

NK Cell

Erythrocyte

Platelets

Megakaryocyte

Neutrophil

Eosinophil

Basophil

Macrophage

Osteoclast

Dendritic Cell

Stem Cell

Multipotent progenitor

Committed progenitor

Mature cells
AML with Minimal Differentiation
Acute Leukemia: Blasts with Auer Rods
Two-hit model of leukemogenesis

Loss of function of transcription factors needed for differentiation
eg. AML1-ETO
CBFβ-SMMHC
PML-RARα

Gain of function mutations of tyrosine kinases
eg. FLT3, c-KIT mutations
N- and K-RAS mutations
BCR-ABL
TEL-PDGFβR

differentiation block + enhanced proliferation → Acute Leukemia
AML Incidence Rate

- The incidence rate of AML in adults is found 80% while in child it is 20% as compared to ALL.
- The incidence rate of 60 years aged people increases up to 10/100000 population.
- The incidence rate of leukemia was found 6.30% at INMOL cancer registry (Pakistan) during 2004–2011 cancer patients

(Mehmood et al., 2014)
Death Rate Population per 100,000 in Pakistan per Year

- Breast
- Lungs
- Liver
- Cervical
- Lymphoma
- Leukemia
Importance of AML

• Approximately every 3 minutes one person in the United States (US) is diagnosed with a blood cancer.
• An estimated combined total of 162,020 people in the US are expected to be diagnosed with blood cancer in 2015.
• Hematological Malignancies (HM) comprise approximately 6.5% of all cancer incidences worldwide in 2012.
Conti....

- WHO predicts that the number of blood-related cancer cases would increase about 48% in less developed countries by 2030 as compared to 2012.
- It has been estimated that AML incidences are increasing persistently 4.0% per year.
What is Micro RNA

- The first micro RNA (abbreviated miRNA) was discovered in the early 1990s.
- miRNA is a small non-coding RNA molecule (containing about 19 to 25 nucleotides) found in plants, animals and some viruses (DNA).
- The human genome encodes more than 1,000 unique mature miRNAs,
- They are controlling approximately 60% of all human genes.
- Any abnormality in miRNA leads to cancer.
miRNA
MicroRNAs are produced from either their own genes or from introns.

As much as 40% of miRNA genes may lie in the introns of protein and non-protein coding genes or even in exons of long nonprotein-coding transcripts.
Picture of Interon
Lay out of miRNA Biogenesis

Nucleus

Polymerase II

Pri-miRNA

Drosha

Pre-miRNA

Expotin 5 Help in transportation from Nucleus to Cytoplasm

Dicer

miRNA maturation

Incorporation of RISC

Functional miRNA
Functional miRNA
## miRNA involved in Cell Cycle

<table>
<thead>
<tr>
<th>Function</th>
<th>Example miRNA</th>
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<tbody>
<tr>
<td>Development/Proliferation</td>
<td>miR-17, miR-18, miR-19, miR-20 miR-92, miR-185 and miR-223 etc.</td>
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<tr>
<td>Differentiation</td>
<td>miR-9, miR-124a and miR-133 etc.</td>
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<td>Tumor Suppression</td>
<td>miR15 and miR16 etc.</td>
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<tr>
<td>Apoptosis</td>
<td>miR-21, miR-34, miR-126 and miR-212 etc.</td>
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Pathways of Gene Silencing

- Cleavage of the mRNA strand into two pieces
- Destabilization of the mRNA through shortening of its poly(A) tail.
- Less efficient translation of the mRNA into proteins by ribosomes.
- The miRNA are also helpful in gene silencing in AML.
## miRNA and Targets in Gene Silencing in AML

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Targeting Genes</th>
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<tbody>
<tr>
<td>miR-26</td>
<td><em>MYC, EZH2, E2F7 and PTEN</em></td>
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<tr>
<td>miR-29</td>
<td><em>DNMT3A, DNMT3B, SP1 and MCL1.</em></td>
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<tr>
<td>miR-125</td>
<td><em>CBFB, ABTB1, BAK1, PTPN18 and PTPN7.</em></td>
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<tr>
<td>miR-223</td>
<td><em>E2F1, NFI-A and FBXW7.</em></td>
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Mode of Gene Silencing of miRNA-29b in AML

- Enforce expression of miRNA-29b
- Direct interaction of miR-29b with the 3 untranslated regions of genes
- Blocking of Translation and degrade the mRNA

- Reduce expression of DNA methyltransferases DNMT1, DNMT3A, and DNMT3B
- Re-expression of p15INK4b and ESR1 via promoter DNA hypomethylation
- Induce apoptosis
THANKS!