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MicroRNAs and the target genes in early tumorigenesis of fallopian/ovarian carcinoma

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Introduction

- High-grade serous ovarian carcinomas (HGSOC) are one of the most deadly and common form of ovarian cancers (>70 % of ovarian cancer).

- Recent identification of its precursor lesion, serous tubal intraepithelial carcinoma (STIC), in the fallopian tubes provides a venue for study of early tumorigenesis of HGSOC.

- Characterization of the molecular and genetic alterations in early stage of HGSOC is compelling and a few oncogenic factors have been identified:
  - **P53** mutations are common in STIC (>90%). However, P53 mutations are neither sufficient to trigger a sequence of neoplasm nor rate-limiting.
  - **BRCA1/2** mutations are a hallmark of HGSOC. 10-20% of HGSOC have germline or somatic BRCA1/2 mutations. Women with have a 30%-70% chance of developing PSC by age 70.
  - **HMGA2** is a major oncogenic factor in HGSOC. Over 70% of STIC and HGSOC have HMGA2 overexpression. HMGA2 is defined as a key marker for ovarian cancer (The Cancer Genome Atlas Research Network).

Rationale and Hypothesis

- BRCA1 mutations account for 10%-20% of cases and 50-60% HGSOC have low or absence of BRCA1 expression.
  
  3. McMillen B et al. (2012). Mol Path (July online publication)

- P53 is a major regulator and many miRNAs are regulated by P53
  

- HMGA2 regulates microRNA expression and is also the major target of miRNAs
  

Hypothesis:

MicroRNA dysregulation is involved in early tumorigenesis of HGSOC
Experimental designs

• Examine global microRNA expression in FT, STIC and HGSOC
• Identify oncogenic miRNAs dysregulated in HGSOC
• Characterize the oncogenic functions of miRNAs *in vitro* and *in vivo*
• Investigate the specific target genes associated with HGSOC
microRNA dysregulation in early and advanced ovarian cancer

MicroRNA maturation and its functions

MicroRNA expression (Log)

miR-34c miR-375 miR-31 miR-10b miR-182 miR-345 miR-106a miR-15b miR-106b

PSC STIC FT

miR-34
miR-10b
miR-375
miR-31
miR-182
miR-345
miR-106

N=5

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE
**MIR182 expression** is validated by TaqMan RT-PCR and miRNA *in situ* hybridization in FT, STIC and HGSOC.

MIR182 *in situ* hybridization in high grade serous ovarian carcinoma (right), serous tubal intraepithelial carcinoma (mid) and fallopian tube (right). U6 as RNA loading control and TP53 IHC for mutant TP53.

Dot plot analysis of relative MIR182 expression in HGSOC, STIC and FT, normalized by U6.
Oncogenic properties of *MIR182* in benign and malignant ovarian cancer cell lines

- Stable *MIR182* overexpression was established by lentiviral transfections in 3 normal and 3 cancer cell lines.
  
  ![Image of Western blot](image1.png)

- Introducing *MIR182* overexpression results in increased anchorage independent growth in normal ovarian surface epithelial (T29, T80), fallopian tube secretory epithelial (FTE187) and ovarian cancer (HEY, OVCAR3 and SKOV3) cell lines.
  
  ![Image of colony formation assay](image2.png)

- Introducing *MIR182* overexpression enhances cell migration/invasion in Mitragel.
  
  ![Image of cell migration assay](image3.png)
HMGA2 is regulated by MIR182 through its negative regulation of BRCA1

- Two independent studies show:
- We confirmed that MIR182 enhances HMGA2 expression through double negative regulation and this regulation is dose-dependent in both benign and malignant ovarian cell lines
**MIR182 overexpression impairs DNA damage response (DDR) by IR exposure**

- Low dose IR (2Gy) exposure in FTE187 cells with MIR182 overexpression revealed significantly delayed DDR. This results can be repeated in T29 cell line.
- Delayed DDR maybe related to MIR182-mediated BRCA1 and HMGA2 dysregulation.
Characterizing miR-182 target gene MTSS1

- **MTSS1** (metastasis suppressor 1) is a tumor suppressor.
- Downregulation of **MTSS1** enhances the growth, invasion and mobility of ovarian and breast cancer cells and poor clinical outcome.
Tumor burden for miR-182

Pathology-IV: Histology and IHC

miR-182 (-)  miR-182 (+)
**MiR-182 and its target gene expression in high grade serous ovarian cancer**

<table>
<thead>
<tr>
<th>Markers</th>
<th>Fallopian Tube</th>
<th>High grade serous ovarian carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th P</td>
<td>min-max</td>
</tr>
<tr>
<td>No. cases</td>
<td>30</td>
<td>117</td>
</tr>
<tr>
<td><strong>MiR-182</strong></td>
<td>1</td>
<td>1.00-3.00</td>
</tr>
<tr>
<td>BRCA1</td>
<td>2</td>
<td>1.00-3.00</td>
</tr>
<tr>
<td>FOXO3a</td>
<td>3</td>
<td>0.00-3.00</td>
</tr>
<tr>
<td>MTSS1</td>
<td>1</td>
<td>0.00-2.00</td>
</tr>
<tr>
<td>HMGA2</td>
<td>1</td>
<td>0.00-3.00</td>
</tr>
</tbody>
</table>

![Image of gene expression and survival analysis](image-url)
HMGA2 and cancer

A
Non-random chromosomal translocation
- The loss of HMGA2 3'UTR
- The gain of promoter of the partner gene

HMGA2 overexpression
- Benign, mesenchymal tumors

B
- Senescence
- Malignant, epithelial tumors

Stress

Let-7s
- miR-365
- Gdf/BRCA1/BRCA3 complex
- β-catenin
- Rep/MEK/ERK pathway
- Nmi2-1
- miR-182

HMGA2
- Twist, Snail, Lumican, AXIN1, et al.
- PIT1, CCNB2, Mia/Cd-rap, E2F1, cyclin A, et al.
- ATR-CHK1, DNA-PKcs, ERCC1, et al.
- p16inh, p19inh, et al.
- Imp2, hTERT, IL-2, IL-15, NF-κB, et al.

EMT
- Proliferation
- DNA repair
- Differentiation
- Tumorigenesis
anti-miR-182 in vivo
Orthotopic mouse model of ovarian cancer
Therapeutic potential of *anti-miR-182 in vivo*

Pathology V: Experimental animal pathology
Anti-miR-182 inhibit tumor proliferation
Ovarian cancer invasion through intrabursa
Ovarian cancer metastasis in pancreas
Anti-miR-182 reduces metastasis
Anti-miR-182 blocks miR-182 expression and restores tumor suppressor genes in tumor xenograft.

Mouse serum
miR-106a expression in HGSOC

microRNA in situ hybridization

Real-time RT-PCR
Characterizing miR-106 target gene RBL2
miR-106 mediated tumor growth through stem cell regulation
miR-106 promotes tumor growth and dedifferentiation
Future directions

• The genetic mechanism(s) for MIR182 upregulation in early and late stages of HGSOC

• The relationship between MIR182-mediated DDR defects and P53 mutations in tumorigenesis of HGSOC

• Animal model of MIR182-mediated tumorigenesis in mice

• Therapeutic potential of anti-MIR182 to treat HGSOC
Acknowledgement

Wei’s Lab
• ZhaoJian Liu
• Xiaofei Xu
• Jingjing Wu
• Brian McMillen
• Elizabeth Gersbach

Collaborators
• Jinsong Liu
• Eva Hernando
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