DNA damage repair in GI tumors

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Receipt of speakers bureau: Abbvie
Outline

- Introduction to DNA damage repair (DDR)
- How do we characterize DDR deficiency in cancer?
- Examples of the most common DDR deficiency in GI cancer
  - Genomic alterations in genes in DDR pathway
    - Microsatellite instability (MSI)
    - Homologous recombination deficiency (HRD)
- Prevalence of DDR deficiency in GI cancer?
- What are the current therapeutic approaches for targeting DDR deficient GI tumors?
  - Checkpoint inhibitors
  - Poly (ADP-ribose) polymerase (PARP) inhibitors
- DDR drugs in development
Types of DNA damage

➤ Cancer cells can use DDR pathways to corrupt signaling pathways for its own gain (proliferation & differentiation)

➤ Cancer cells navigate the DDR pathways during the progression of the disease.

➤ Overexpression of a DNA repair component in one pathway compensates for a repair defect in another. Thus, circumventing cancer treatment and leading to therapeutic resistance.

Types of DNA damage repair

- Overlapping damage repair routes are initiated when DNA is damaged
- A dynamic & complex network of overlapping signals communicate to promote genome stability or trigger programmed cell death
- This network is coined: **DNA damage response**

Characterization of DDR-deficiency in tumors

- Deep durable response to platinum based treatments
- Familial syndromes are enriched with mutations in DDR pathway

Genomic phenotype:

- NGS - for example ATM
- Whole exome sequencing
- Whole genome sequencing - for example unstable genome
- Mutation signatures (DNA/RNA)

Clinical phenotype:

- Pre-Treatment (FOLFIRINOX) 3/12
- Post-Treatment (FOLFIRINOX) 9/12

Waddell et al. Nature. 2015
Genomic instability

- Cancers may have loss of genome integrity = genomic instability
- Cancers may have genome instability: chromosomal instability (CIN) or microsatellite instability (MSI)

**CIN**

- Genomic instability is characterized by major chromosomal structural rearrangements & mutations
- CIN phenotype linked to BRCAness subtype of GI cancers → DNA damaging agents

**MSI**

- MSI phenotype: Defects in MMR genes (*MLH1* and *MSH2*); Lynch syndrome
- Tumors with MSI are susceptible to small insertions and deletions
- MSI phenotype linked to immunotherapeutic strategies

Waddell et al., *Nature*. 2015;
Prevalence of DDR deficiency in GI cancer?
Prevalence of Mismatch repair across solid malignancies

Le et al Science; 2017;357:409-413.
Therapeutic approaches in DDR deficient GI tumors

MMR
- Checkpoint inhibition

Unstable genome / CIN
- Platinum based regiments
  - PARPi
A. TYPES OF DNA REPAIR

**TYPE OF DNA DAMAGE**
- Single-strand break
- Double-strand break

**DNA REPAIR MECHANISM**

<table>
<thead>
<tr>
<th>BER</th>
<th>DSB REPAIR</th>
<th>MISMATCH REPAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARP1</td>
<td>BRCA1</td>
<td>MSH2</td>
</tr>
<tr>
<td>XRCC1</td>
<td>BRCA2</td>
<td>ERCC4</td>
</tr>
<tr>
<td>LIGASE 3</td>
<td>PALB2</td>
<td>ERCC1</td>
</tr>
<tr>
<td>ATR</td>
<td>DNA-PK</td>
<td>MLH1</td>
</tr>
</tbody>
</table>

**PROTEINS INVOLVED IN REPAIR**

- BER
  - PARP1
  - XRCC1
  - LIGASE 3
  - ATR
- DSB REPAIR
  - BRCA1
  - BRCA2
  - PALB2
  - ATM
  - CHEK1
  - CHEK2
  - RAD51
- Mismatch repair
  - MSH2
  - MLH1
- NHEJ
- NER
Mismatch repair

MSI = Microsatellite instability

MMR = Mismatch repair

Detection:
PCR (microsatellite instability)
IHC (MMR protein)
Lynch syndrome

- Lynch syndrome, a hereditary non-polyposis colorectal cancer resulting from microsatellite instability, resulting from DNA mismatch repair impairment (MMR).

- Mismatch repair-deficiency: assessed by either PCR or IHC.

- For most cases, germline sequencing of MSH2, MSH6, PMS2 and MLH1 is performed to determine if the mismatch repair-deficiencies were associated with a germline change in one of these genes (whether the patients had Lynch Syndrome).

- Germline sequence changes diagnostic of Lynch syndrome: MSH2 being the most commonly mutated gene
Many cancer patients contain in their immune system the capacity to react selectively to their tumors through recognition of tumor-specific antigens.

When the interaction between the checkpoint ligands and their cognate receptors on the effector cells is blocked, a potent and durable anti-tumor response can be observed.

Mutation-associated neoantigens (MANAs) are encoded by cancers: mismatch-repair deficient cancers are predicted to have a very large number of MANAs that might be recognized by the immune system.
Programmed cell death protein 1 (PD1) receptor is an inhibitory receptor expressed by antigen-stimulated T cells. Interactions between PD1 and its ligand, PD-L1, expressed in many tumors activate signaling pathways that inhibit T-cell activity and thus block the antitumor immune response.

Antibodies targeting PD1 or PD-L1 block the PD1 pathway and reactivate T cell activity.
Immune checkpoint inhibitors in MSI tumors

NOT ALL MMR PATIENTS ARE EQUAL

Le et al Science; 2017;357:409-413.
A. TYPES OF DNA REPAIR

TYPE OF DNA DAMAGE
- Single-strand break
- Double-strand break
- Mismatch repair
- Bulky adducts

DNA REPAIR MECHANISM
- BER
- DSB REPAIR
- HR
- NHEJ
- NER
- MMR

PROTEINS INVOLVED IN REPAIR
- PARP1
- XRCC1
- LIGASE 3
- ATR
- BRCA1
- BRCA2
- PALB2
- ATM
- CHEK1
- CHEK2
- RAD51
- ATR
- KU70/80
- DNA-PK
- XRCC4
- ERCC4
- ERCC1
- MSH2
- MLH1

Golan T, Javle M. JNCCN; 2017
BRCA1/2 and hereditary malignancies

The *BRCA1* and *BRCA2* tumor suppressor genes repair DNA damage to prevent tumor development

Mutations in these genes predispose an individual to malignancy

The cancers associated with mutations in *BRCA1* and *BRCA2* have been studied since their discovery in 1994 & 1995
Subtypes of pancreatic cancer

PDCA are classified into four molecular subgroups based on structural variations

BRCA PDAC usually demonstrate DSBR/unstable genome hallmarks

Case report: Positive outlier

Global Prevalence of gBRCA mutation  
~7%

Familial PC: 3%–17.2%
Overall survival and clinical characteristics of PDAC in BRCA mutation carriers

Probability of OS by platinum treatment at stage III and IV

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of pts</th>
<th>Treatment</th>
<th>mOS (months)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>III &amp; IV</td>
<td>43</td>
<td>Platinum - 22</td>
<td>22 [6-27]</td>
<td>0.0389</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non Platinum - 21</td>
<td>9 [4-12]</td>
<td></td>
</tr>
</tbody>
</table>

DNA repair is more error-prone when BRCA 1/2 proteins are deficient.

Two Major Mechanisms for the Repair of DNA Double-Stranded Breaks

- **Homologous Recombination Repair (HRR)**
  - Non-functioning HRR may be due to BRCA 1 or BRCA 2 deficiency

- **Non-Homologous End-Joining (NHEJ)**
  - Less precise, more error-prone

Non-functioning HRR results in:
- Accumulation of additional mutations
- Chromosomal instability
- Increased risk for malignant transformation

Proteins involved:
- PARP1
- XRCC1
- LIGASE 3
- BRCA1
- BRCA2
- PALB2
- ATM
- CHEK1
- CHEK2
- RAD51
- KU70/80
- CAN-PK

**BER** = base excision repair; **HRR** = homologous recombination repair; **NHEJ** = non-homologous end-joining.
Poly (ADP-ribose) polymerase (PARP)

PARP1 and 2 involved in cellular response to single-strand DNA breaks (SSB) •
Inhibition of PARP results in: •
catalytic enzyme effect -
“trapping” of protein on DNA -
inhibition of replication fork progression -
increased dsDNA breaks $\rightarrow$ dependent on functioning homologous recombination for repair

PARP inhibition $\rightarrow$ therapeutic implications for tumors with defects in DNA repair • pathways (tumors with germline mutations in \textit{BRCA1/2}, \textit{CHEK2}, \textit{PALB2 ATM}, tumors with high Homologous Recombination Defect (HRD) scores)

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

A Progression-free Survival

<table>
<thead>
<tr>
<th>Progression-free Survival</th>
<th>Olaparib Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>53.0%</td>
<td>23.0%</td>
</tr>
<tr>
<td>12 months</td>
<td>33.7%</td>
<td>14.3%</td>
</tr>
<tr>
<td>18 months</td>
<td>27.6%</td>
<td>9.6%</td>
</tr>
<tr>
<td>24 months</td>
<td>22.1%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>

Median, 7.4 months vs. 3.8 months
Hazard ratio, 0.53 (95% CI, 0.35–0.82)
P=0.004

Olaparib (N=92; 60 events)
Placebo (N=62; 44 events)

No. at Risk

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>92</th>
<th>69</th>
<th>50</th>
<th>41</th>
<th>34</th>
<th>24</th>
<th>18</th>
<th>14</th>
<th>10</th>
<th>8</th>
<th>7</th>
<th>5</th>
<th>3</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>62</td>
<td>39</td>
<td>23</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
NOT ALL GERMLINE BRCA PATIENTS ARE EQUAL

Responder

Non-Responder

Apr 2014

Feb 2015

Sep 2014

Jan 2015
WGS and transcriptome analysis identified 12% DDR deficiency and associated with anti-tumor immune activation.

Connor AA et al Jama Oncology 2016
WGS and transcriptome analysis identified 12% DDR deficiency and associated with anti-tumor immune activation.
DNA Damage Response (DDR) Mutations in Pancreatic Cancer

- 17 – 25% of pancreatic adenocarcinomas harbor mutations in the DDR genes
  - Homologous recombination DNA damage response (HR-DDR) mutations
  - BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51, and others

- Know Your Tumor® (KYT) Dataset
  - 16.5% HR-DDR

- Caris Database Review
  - 16.9% HR-DDR

HR-DDR Deficiencies Predict OS Improvement in Platinum-Treated Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>N (G16 Total)</th>
</tr>
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<tbody>
<tr>
<td>ATM</td>
<td>28 (4.5%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>18 (2.9%)</td>
</tr>
<tr>
<td>SMARC4</td>
<td>10 (1.6%)</td>
</tr>
<tr>
<td>BAP1</td>
<td>8 (1.3%)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>8 (1.3%)</td>
</tr>
<tr>
<td>BRR1</td>
<td>6 (1.0%)</td>
</tr>
<tr>
<td>PALB2</td>
<td>5 (0.8%)</td>
</tr>
<tr>
<td>CHEK2</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>FANCA</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>FANCC</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>RAD50</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>STAG2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>BARD1</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>CHEK1</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>FANC6</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Pishvaian and Brody, Oncology Hematology
Pishvaian, et al. Clinical Cancer Research
Hewlett, et al. JCO Precisional Medicine
Aguirre, et al. Cancer Research
Willkens, et al. JCO
Lowery, et al. Clinical Cancer Research
Waddell, et al. JAAPA
Bailey, et al. JAAPA
Blankin, et al. JAAPA
Collison, et al. JAAPA

Critical insight

DDR deficient tumors that are responding to platinum might not necessarily respond to a PARPi strategy.

Not all DDR mutations are created equal!
BRCA1/2 in cholangiocarcinoma

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>BRCA2 mutation</th>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>First-line: Gemcitabine + Capcitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Second-line: PARPi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Third-line: PARPi</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SHB-3</th>
<th>BRCA2 GL_6174deIT</th>
<th>IV</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First-line: Gemcitabine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second-line: Gemcitabine + SFU</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Third-line: PARPi</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UCF-3</th>
<th>BRCA1 SM_W1718</th>
<th>I</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First-line: Gemcitabine + Cisplatin</td>
<td>28.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second-line: Cisplatin + SFU</td>
<td>53.08</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>BRCA1/2 in cholangiocarcinoma</th>
<th>The Oncologist</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Golan T et al</td>
<td></td>
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</tbody>
</table>
Prolonged overall survival of metastatic gastric cancer patients with BRCA germline mutations treated with DDR therapeutics

Halpern N. et al. Annals of Oncology, Volume 29, Issue suppl_5, June 2018
Prevalence of HR-DDR mutated genes

HR-DDR genes as defined:

ATM, ATRX, BARD1, BLM, BRCA1/2, BRIP1, FANCA/C/D2/E/F/G/L, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, or WRN

Biliary tract - 11.1%, N= 343
Pancreatic - 10.4%, N= 833
Colorectal cancers - 10.0%, N= 2,454
Gastroesophageal cancers - 20%

Heeke AL, et al. JCO Precis Oncol, 2018
DDR drugs in development

Golan et al. JNCCN; 2017
Defining DDR subtype in GI malignancies is evolving.

The clinical implementation of these all subsets is still limited. However, the DDR subtype has promising clinical value.

BRCA subtype & MSI are each unique predictive biomarkers.

MSI tumors demonstrate efficacy to checkpoint inhibitors. Novel combinatorial IO strategies are currently being evaluated.

DDR deficient tumors that are responding to platinum might not necessarily respond to a PARPi strategy.

DDR subtype: novel drugs in development.