Gastric Cancer: The Complexity of Stemness
Gastric Cancer: Global Impact

- 71% of stomach cancer cases occur in less developed countries
- 5th most common cancer in the world
- 1 million new cases are diagnosed globally each year
- 2 times as common in men than women
- 3rd leading cause of cancer deaths

Gastric Cancer: Facts and Trends in the US

30% 5-year survival\(^2\)

80,000 people living with stomach cancer\(^1\)

10,000 deaths per year\(^{1,2}\)

26,000 diagnosed annually\(^{1,2}\)

1.6% of all new cancer cases\(^1\)

While new cases and death rates have declined, proximal tumors are increasing by 1-3% per year\(^3\)

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Gastric Cancer: Treatment Algorithm and Progression

- **Surgery**

- **First Line**
  - Combination chemotherapy or chemoradiation and/or targeted therapy

- **Second Line**
  - Combination chemotherapy or chemoradiation and/or targeted therapy

- **Metastatic Disease**
  - Treatments remove or reduce bulk tumor cells

- **Palliative Care**

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Gastric Cancer: Prognosis

5-year Survival Based on Disease Stage at Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Localized</th>
<th>Regional</th>
<th>Metastatic</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage at Diagnosis</td>
<td>27%</td>
<td>28%</td>
<td>35%</td>
<td>—</td>
</tr>
<tr>
<td>Survival</td>
<td>66.9%</td>
<td>30.9%</td>
<td>5.0%</td>
<td>30.4%</td>
</tr>
</tbody>
</table>

The majority of patients in the US are diagnosed with late-stage disease

Gastroesophageal Junction Cancer: Similar to Gastric Cancer in Treatment and Prognosis

- The majority of GEJ cancers are diagnosed at the regional or distant stages\(^1\)
- Overall 5-year survival is low and linked to stage\(^1\)
  - Regional 12%
  - Distant 2%

GEJ, gastroesophageal junction.

Gastric Cancer: It’s Complicated

- Two major types: Intestinal and diffuse
- Cancers differ in anatomical region and layers of stomach wall affected
- Many different specialized cells exist within gastric units
- Microenvironment and *H. pylori* infection can influence the development of cancer
- Presence of **Cancer Stem Cells** may play a role in driving malignancy in gastric cancer
Cancer Stem Cells and Gastric Cancer: Key Discoveries

1997
CSCs first identified in lymphoma

2003
CSCs found in breast cancer

CSCs identified in multiple solid tumors

2009
Gastric CSCs discovered in humans

Multiple biomarkers for gastric CSCs identified

2007
Cell lines demonstrating stemness phenotypes found in human gastric biopsies

2011
G-CSCs predict poor overall survival

2012–present
Potential research targets in gastric cancer stemness pathways identified

CSCs, cancer stem cells; G-CSCs, gastric cancer stem cells.

Cancer Stem Cells: Characteristics

- Ability to self-renew and differentiate
- Convey tumorigenicity
- Show innate resistance to multiple conventional therapies
- Play a key role in metastasis
- Have dysregulated stemness signaling pathways

Cells with these properties have “**Stemness**” characteristics

*Bulk tumor cells

Cancer Stem Cells are Heterogeneous

**CSCs Display Heterogeneity**¹⁻³

- Different stemness characteristics may prevail at different times
- Many CSCs, but not all, can be identified by distinctive markers
- CSC marker profiles differ between tumors and can change over time

**Several biomarkers have been identified on gastric CSCs:** CD44⁺ and CD133⁺ are the most prevalent⁶

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**Cancer Stem Cell Markers**⁴⁻⁶

- ALDH⁺, ALDH₁⁵⁶
- a2b1⁺, A2B5⁺, ABCG2⁺
- BCRP1⁺, BMI1⁺
- CD24⁺, CD24⁻/low, CD34⁺, CD38⁻, CD44⁺, CD49f⁺, CD54⁺, CD71⁻, CD90⁺, CD90⁻, CD117⁻, CD123⁺, CD133⁺, CD138⁻, CD166⁺
- CXCR4⁺, CK20⁺, CEA⁺
- ESA⁺, EpCAM⁺
- Lineage⁻, LGR5⁺
- SSEA⁺, HLA-DR⁻, YAP1⁺

**Bold**=identified on gastric CSCs

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CSC, cancer stem cell.

Presence of Cancer Stem Cells Predict Poor Survival in Patients with Gastric Cancer

- G-CSCs are highly associated with the degree of malignancy, tumor grading and ranking and drug resistance\(^1\)

- High expression of G-CSC markers CD44+ and CD133+ were associated with worse overall survival, based on samples from surgically-resected gastric cancer patients between 2000-2004\(^2\)

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G-CSCs, gastric cancer stem cells.

Cancer Stem Cells are a subset of cells existing within a tumor with high tumor-initiating capabilities.

**Tumorigenesis**
Due to unregulated self-renewal and differentiation.

**Metastasis**
Due to EMT-mediated increase in migration and invasiveness.

**Resistance**
Due to activation of multiple resistance-mediating genes.

**Innate resistance** to conventional chemo- and radiotherapies may underlie tumor recurrence.

**Acquisition of transient stemness** increases ability to metastasize.

EMT, epithelial-mesenchymal transition.
Cancer Stem Cells Differ from Gastric Stromal Stem Cells in Their Lack of Regulation

Gastric Stromal Stem Cells¹⁻³

Regulated Cell Division

Unregulated Cell Division

Self-Renew

Differentiate

Mutation and epigenetic changes

Gastric Cancer Stem Cells can be Derived from Several Sources via Stemness Pathways

1. Gastric Stromal Stem Cells\textsuperscript{1,2}

2. Bone Marrow Stem Cells\textsuperscript{1,2}

Mutations and epigenetic changes promote loss of regulation and **activate stemness pathways**

Migrate to stomach in response to injury

3. Differentiated Cells\textsuperscript{3}

4. non-Stem Cancer Cells\textsuperscript{3}

De-differentiation through **activation of stemness pathways** acquires stem-like properties

G-CSCs, gastric cancer stem cells.

Key Stemness Signaling Pathways Drive Malignancy in Gastric CSCs

- Dysregulation or activation of these pathways can result in stemness characteristics
  - Self-renewal
  - Differentiation
  - Migration
  - Tumorigenicity
  - Innate resistance

JAK, Janus kinase; STAT, signal transducer and activator of transcription.

Gastric Cancer Stem Cells are Regulated and Maintained by the Microenvironment

- The tumor microenvironment, or stem cell niche, surrounding G-CSCs helps maintain stemness capabilities.

- Soluble factors secreted by stromal cells signal pathways for:
  - Proliferation
  - Invasion
  - Tumor immunity
  - Angiogenesis

CSCs, cancer stem cells; G-CSCs, gastric cancer stem cells; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; ROS, reactive oxygen species; SDF-1α, stromal-derived factor-1α; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGFA, vascular endothelial growth factor A.

**H. Pylori: Inflammation and Influence on Stemness Pathways**

- **H. pylori**
  - Dysregulates stemness pathways, ie, Wnt, notch, hedgehog, FGF/BMP

- Chronic inflammation
  - Influences transition of G-SC to G-CSC
  - G-CSCs
    - Self-renewal
    - Differentiation
    - Migration
    - Tumor initiation
    - Resistance

- Immune response recruits BMD-MSC for tissue repair
  - Accumulated mutations result in G-CSCs

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BMD-MSC, bone marrow-derived mesenchymal stem cell; G-CSC, gastric cancer stem cell; G-SC, gastric stem cell.

Clinical Evidence of Stemness in Gastric Cancer

G-CSC marker expression in human gastric tumors has been correlated with...

- Lymph Node Metastasis\(^1,2\)
- Staging\(^1,2\)
- Overall Survival\(^1-3\)
- Vessel Invasion\(^1,3\)
- Recurrence\(^3,4\)
- Resistance to Traditional Therapies\(^3\)

G-CSCs, gastric cancer stem cells.

Targeting Cancer Stemness: Goals

Conventional therapies kill non-Stem Cancer Cells, resulting in tumor shrinkage.

But CSCs show innate resistance to therapy and remain viable.

Therapies targeting CSCs.

CSCs re-establish the tumor due to their ability to self-renew and differentiate.

Tumor may lose ability to proliferate and then degenerates.

Research aimed at developing inhibitors that target CSCs may lead to more durable responses and tumor degeneration compared to the effects of chemotherapy.

CSC, cancer stem cell.

Potential Targets in Cancer Stem Cells: Biomarkers of Gastric Cancer

- Cell surface biomarkers can be used to identify and target G-CSCs
- Biomarkers are integral to stemness pathways
  - CD133 (prominin-1) has a role in Wnt pathway activation
  - CD44 is involved in adhesion to extracellular matrix and enhancement of efflux pumps
- Multiple potential biomarker targets exist in gastric cancer
  - CD44, CD24, CD133, ALDH1, LGR5

G-CSCs, gastric cancer stem cells.
Zhao Y. World J Gastroenterol. 2015;21:112-123.
Potential Targets of Cancer Stemness: Pathways in Gastric Cancer

- Several key components of stemness pathways have been identified as potential targets for inhibiting G-CSCs.
- Normally, these factors are only expressed during early development.
- Therefore, their inhibition would not be expected to adversely affect normal cells.

G-CSCs, gastric cancer stem cells.

Summary: Gastric Cancer is Complicated

- Patients with Gastric Cancer Stem Cells have poor clinical outcomes
- Gastric Cancer Stem Cells and activation of stemness pathways in gastric cells drive malignancy
- Gastric Cancer Stem Cells appear to be derived from endogenous sources
  - Gastric stromal stem cells and bone marrow-derived mesenchymal stem cells
  - Differentiated cells can also acquire stemness properties
- The microenvironment and H. pylori infection can regulate and influence various stemness pathways that drive gastric cancer progression
- Current research goals are to target stemness pathways via Gastric Cancer Stem Cells biomarkers or key factors in these pathways, which may produce more durable treatment responses
References

Zhao Y. World J Gastroenterol. 2015;21:112-123.
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