Boston BioMedical MEDSTORY®
Targeting Cancer Stem Cells
STORY FLOW MAP

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Version 3

STORY TENSION

Today I'm going to talk to you about the treatment of cancer, where's it's been and where it may be going. Let me start by sharing with you a very interesting experiment...

Take a human tumor and pulverize it. Then use specialized technology to extract 100 cells with specific characteristics and implant those cells into a mouse. Wait 1 month. What you observe is that the mouse develops a tumor identical to the human tumor from which it came. Now repeat the process using 20,000 cells FROM THE SAME HUMAN tumor that did NOT have those specific characteristics and implant them into a mouse. This time, to your surprise, no tumor forms. **Why?**

This experiment has been replicated many times with different human tumors. And these results CONTRADICT the current therapeutic approach about human cancers, namely, that ALL the cells within a single tumor at a given point in time are essentially all the SAME, i.e., that they are equally malignant, and all equally worthy of being targeted for destruction in order to achieve therapeutic success.

The 100 cells were **Cancer Stem Cells** isolated from the human tumor which had **tumor-initiating ability,** unlike the 20,000 cells that were non-CSCs and did not have this ability

ATTACK POINT

1

The concept that Cancer Stem Cells are the primary drivers of tumor growth and metastasis is known as the **Cancer Stem Cell Hypothesis.**

Is there strong evidence for this concept?

Yes

The Cancer Stem Cell Hypothesis is a radical departure from the current model of cancer (known as Clonal Evolution) in which ALL cells within a tumor are considered equally malignant and therefore ALL cells are targeted with the SAME conventional chemo, radiation, or other therapies

"The notion that all cells within a tumor are equal is an illusion."—Robert Weinberg

The CSC Hypothesis explains an important observation in cancer medicine: that tumor shrinkage is poorly predictive of overall survival

Tumors shrink because the non-CSCs making up the bulk of the tumor were sensitive to chemo/radiation but the tumor recurred and led to death because the CSCs regrew the tumor and metastasized

CSCs were first discovered in hematopoetic cancers but have now been documented in many solid tumors, including breast, lung, pancreas, colon, and brain

CSCs comprise the most malignant fraction of the total number of cancer cells within a tumor, varying from <1% up to 30%, depending on the tumor type

TENSION & RESOLUTION 1

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What do we mean when we say that CSCs are **"more malignant"** than non-CSCs within the same tumor?

In fact, there is evidence that chemotherapy and radiation can actually INCREASE the proportion of highly malignant CSCs within a tumor, making them even more difficult to treat. If confirmed, this would suggest that a major shift in the approach to cancer therapy might result in improved outcomes for patients

If the CSC Hypothesis is correct, then approving therapies based on their ability to shrink tumors is likely to lead to more failures because such therapies are not killing the most malignant cells in the tumor—CSCs!

The CSC Hypothesis posits that although CSCs within a single tumor are **genetically** identical to non-CSCs in the tumor, their **epigenetic** expression patterns gives them a distinctive **highly malignant phenotype**

We mean that CSCs have 2 characteristics of highly malignant cells:

1. High tumor-initiating ability (also known as "tumorigenicity")

2. High metastatic potential

TENSION & RESOLUTION 2

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WHY do CSCs have **high tumor-initiating ability**?

In the same way that a single normal stem cell can give rise to an entire normal organ, a cancer stem cell can give rise to an entire tumor. In normal stem cells, this is called "organ-forming ability". In CSCs, this is called "tumor-initiating ability".

Both normal stem cells and Cancer Stem Cells have TWO abilities that **define** them as stem cells:

(1) The ability to self-renew indefinitely, to make exact copies of themselves, making them essentially "immortal"

— AND —

(2) The ability to differentiate into various non-CSCs which can proliferate for a limited number of generations and eventually die off

The ability of Cancer Stem Cells to regrow an entire tumor has been demonstrated in both hematopoietic and multiple solid tumors

EXAMPLES

TENSION & RESOLUTION 3

But CSCs not only can regrow tumors from a single cell, they are also highly metastatic.

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WHY do CSCs have **high metastastic potential**?

CSCs that have undergone Epithelial-Mesenchymal Transition (EMT) take on the features of migration, invasiveness, and survival that greatly increase the ability of these cells to metastasize to distant sites

Non-CSCs are:

Less likely to enter the circulation and seed distant sites

Unable to start new tumor growth at distant sites because they have low tumor-initiating ability

TENSION & RESOLUTION 4

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But there's a problem:

Conventional chemotherapy and radiation preferentially kill non-CSCs, i.e., CSCs are much more resistant to these therapies

Why are CSCs so hard to kill?

A key factor is that CSCs have **low proliferation rates** or are not proliferating at all for long periods of time (quiescence or dormancy)

IN ADDITION, there are several **other factors** that contribute to the resistance of CSCs to conventional therapy:

drug efflux proteins
DNA repair activation
low reactive oxygen species (ROS)
anti-apoptosis protein overexpression
aberrant developmental signaling
microenvironmental stimuli

TENSION & RESOLUTION 5

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Can CSCs be specifically identified within tumors?

Yes

Molecular and phenotypic markers are present in CSCs from various tumor types.

EXAMPLES of CSC Markers
Breast: ESA+, CD44+, CD24-low, ALDH1
Brain: CD133+, BCRP1+, A2B5+
Colon: CD133+, CD44+, ALDH1high
Lung: CD133+, CD49f+, CD90+

Similarly in head and neck, leukemia, liver, multiple myeloma, pancreatic, & prostate

CSCs can also be identified and targeted because they overexpress specific "stemness pathways" that characterize the CSC phenotype

EXAMPLES of CSC Signaling Pathways (also known as "stemness pathways")
STAT3
Wnt/ß-catenin
Hedgehog
Notch
NANOG

TENSION & RESOLUTION 6

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The Good News Is:

It **IS** possible to selectively target and kill CSCs!

Several approaches have been taken:

(1) Target signaling pathways associated with "high stemness" in CSCs

(2) Test thousands of compounds (high-throughput screening) against CSCs

(3) Target CSCs using immune-based therapies

EXAMPLE
BBI608, which targets the Stat3 stemness pathway, blocked tumor recurrence **AND** metastasis of human xenografts implanted in mice

EXAMPLE
High-throughput screening of 16,000 compounds revealed 20 compounds that selectively kill CSCs

EXAMPLE
Natural killer cells directed at specific CSC surface antigens have been developed that selectively target and kill CSCs

TENSION & RESOLUTION 7

CORE STORY CONCEPT

There is a wealth of evidence supporting the Cancer Stem Cell Hypothesis—that cancers contain Cancer Stem Cells which are highly malignant, i.e., possess high tumor-initiating and metastatic potential which non-CSCs do not.

This is a radical departure from the current therapeutic approach which assumes that all cells within a tumor are equally malignant. CSCs can be specifically identified using molecular markers and can be specifically targeted therapeutically.

CSCs are also highly resistant to conventional chemotherapy and radiation which probably underlies tumor relapse and metastasis in many patients with a variety of tumor types.

Boston BioMedical is at the forefront of developing CSC-targeted therapies that are currently being evaluated in preclinical and clinical studies.
This new approach to cancer therapy is highly promising.

STORY PROGRESS