PIP Digest

CCRA ACRC Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer

PIP PPP Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

UNDERSTANDING CANCER: Tumour Heterogeneity

The genetic diversity or 'heterogeneity' of cancer makes it a complex and challenging disease. This PIP Digest explains what the concept of tumour heterogeneity means for cancer treatment.

Key Concepts

- Intratumour heterogeneity
- Clonal evolution
- Cancer stem cells

Related PIP Digests

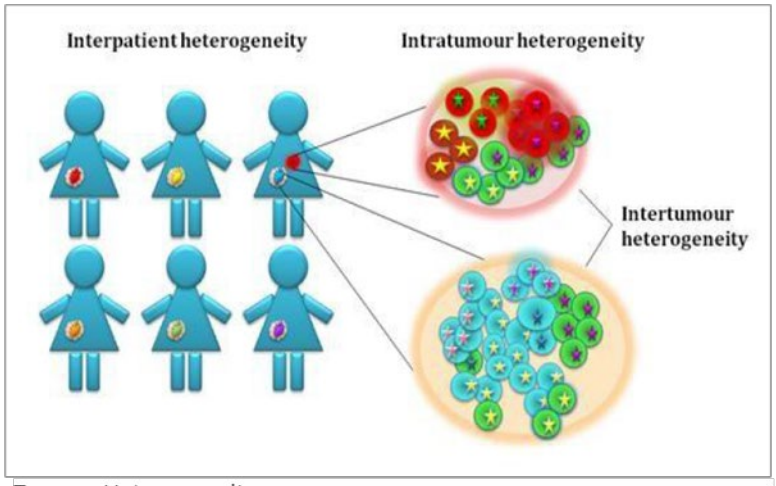
- Understanding Cancer: Epigenetics 101
- Understanding Cancer: Cancer Biomarker Basics
- Clinical Trials: Precision Medicine and Clinical Trials

"Every individual specimen of cancer is its own individual specimen of cancer. We have not encountered in our history a disease where every single instance of the disease is its own instance of the disease. That is a unique thing about cancer."

-- Siddhartha Mukherjee (2017)

For a very long time, cancer was considered a mass of fast-growing cells with similar mutations that could respond if only researchers could fine an effective treatment. Over time, though, researchers discovered that cancer not only varies between patients (**interpatient heterogeneity**), but that there is variation within one person's tumours (**intertumour heterogeneity**) and even within a single tumour (**intratumour heterogeneity**). Tumour heterogeneity describes differences in cancer cells' shape and structure (morphology), gene expression, metabolism, and capacity to move, proliferate, and metastasize.

For example, prostate cancer has been described as "multi-focal." This means that men with prostate cancer often have multiple tumours, each of which evolves independently and has different mutations. These variations greatly affect clinical care. A single biopsy or tissue sample cannot reveal the variability among and within tumours. A treatment plan made on partial information will likely fail to eradicate the cancer.



Tumour Heterogeneity
From: https://www.ous-research.no/lothe/?k=lothe%2Fcancer+type&aid=14844

The heterogeneity of tumours is the key reason why effective cancer treatment is so challenging. It is also the impetus behind a precision-medicine approach.

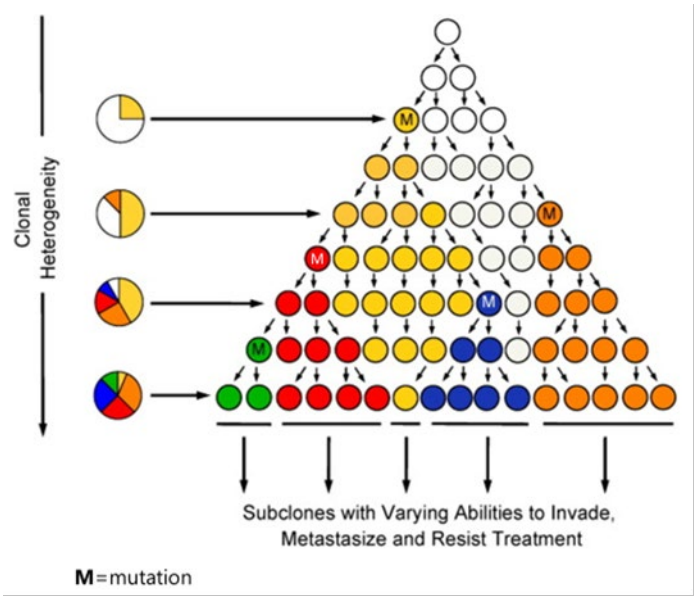
Models of Heterogeneity

Tumour cells are highly adaptive and undergo genetic, epigenetic, and phenotypic changes throughout tumorigenesis. Two models can help account for the heterogeneity of tumour cells: **clonal evolution** and the **cancer stem cell**.

Clonal Evolution Model

Also called the stochastic model, clonal evolution proposes that cancer cells go through genetic and epigenetic changes over time. In this model, most cancer cells possess the mutations that give them their malignant properties. Each mutation increases the probability of the next. (See diagram, moving from top to bottom, in which each mutation is symbolized with a new colour and the letter "M".)

Just as animals evolve through natural selection, tumours also progress, via survival of the fittest. Cells containing malignant mutations gain a selective advantage over other cells, dominating and outliving them.



Clonal Evolution Model
From: http://www.cubocube.com/dashboard.php?a=254&b=257&c=1

Cancer Stem Cell Model

According to the cancer stem cell model, only a small subset of cells possess the unique biological properties necessary for tumor initiation, maintenance, growth, and spreading. These "cancer stem cells" are analogous to normal stem cells in that they can make copies of themselves and also differentiate into other types of cells.

Cancer stem cells represent a very small portion of tumour cells. They maintain their own numbers through self-renewal. They give rise to the bulk of the tumour by producing fast-dividing cells that differentiate into a variety of cancer cell types. Cancer stem cells have the powerful ability to spread cancers to other parts of the body by breaking away from the bulk of the tumour, entering the bloodstream, and invading other tissues.

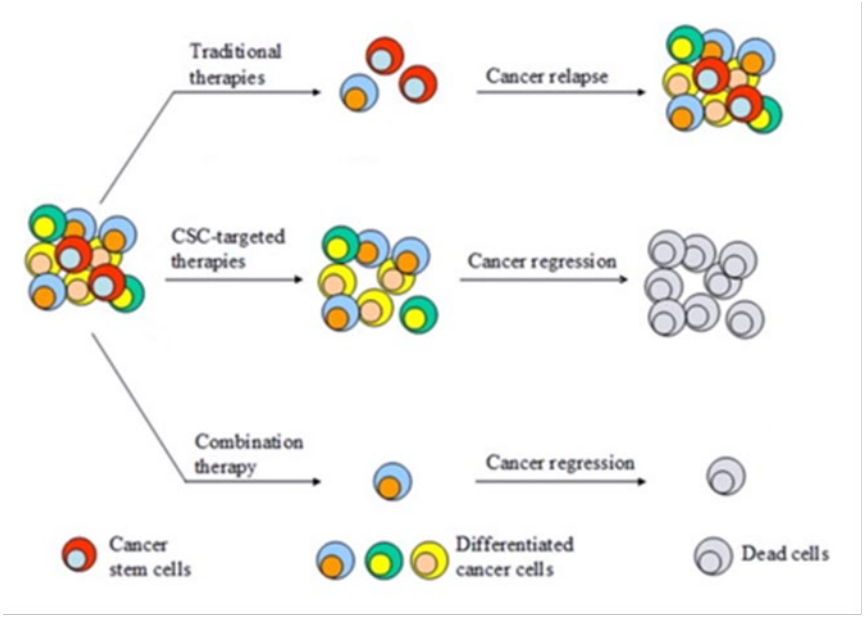
Clonal evolution and stem cell models are not mutually exclusive. They can both play a role in tumour development and may act in a synergistic manner. The concept of "cell plasticity" (the ability of cells to take on characteristics of other cells) has partly reconciled both the clonal evolution and cancer stem cell models. Plasticity suggests that clonal evolution can give rise to stem-like cancer cells. For this reason, research on treatments and interventions typically take both models into account.

Clinical Implications of Tumour Heterogeneity

Effective treatments require researchers to unravel the complexity of tumours. Clonal evolution suggests that more heterogeneous tumours are more challenging to treat. Treatments that target certain mutations and not others may make cancers more resistant to future treatments. Detecting cancer at the earliest clinical stages, before clonal evolution increases heterogeneity too much can make a major difference to the success of a treatment.

Measuring tumour heterogeneity requires biopsies and gene sequencing of tumour tissue from multiple sites. It can be onerous for patients and clinicians. Researchers are exploring ways to quantify tumour heterogeneity by analyzing cancer cells shed in the blood with less invasive liquid biopsies.

The diagram below shows how the cancer stem cell model suggests that treatments designed to kill differentiated cells but not stem cells will not stop tumour growth and metastasis. Specifically targeting cancer stem cells can halt these things, and eventually lead to differentiated cancer cells dying off.

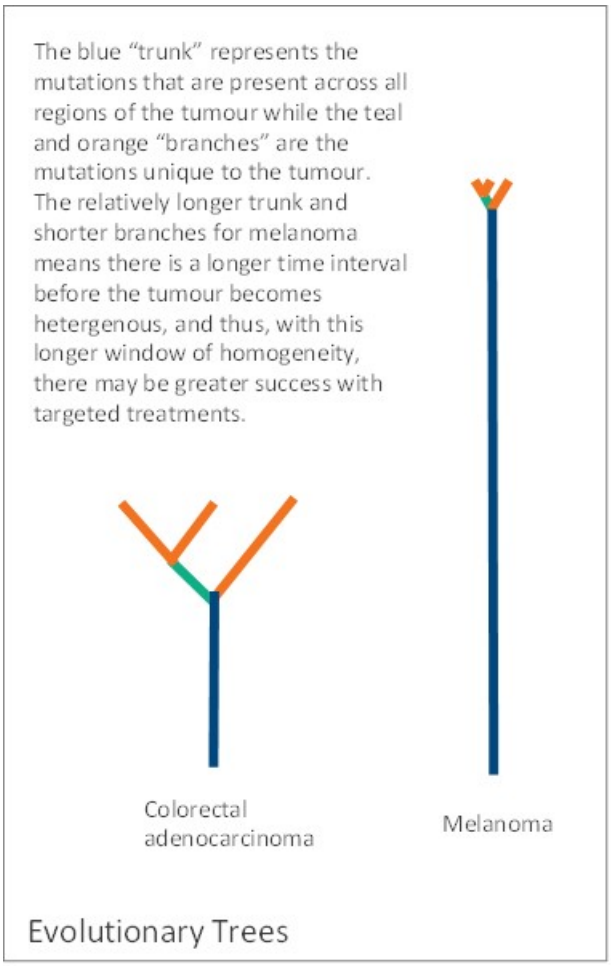


Cancer Stem Cells and Therapeutic Implications
Adapted from: Han L et al. (2013). Cancer stem cells: therapeutic implications and perspectives in cancer therapy. *Acta Pharmaceutica Sinica B*, 3(2):65-75.

Combination therapies that target both stem cells and differentiated cancer cells may be even faster and more effective. Cancer stem cells are, however, very hard to kill, which presents challenges for researchers seeking such combination therapies.

Tumour Phylogenetics

"Tumour phylogenetics" is an area of cancer research, where the progression of a patient's tumour (its mutational history) is analyzed and compared with large data sets of tumours from other patients and depicted in terms of an "evolutionary tree." Research advances in this area have already provided key insights about different tumour types (see diagram below). On the horizon…scientists continue to work towards identifying the key drivers of heterogeneity so that they can ultimately discover ways to turn "back the clock" and restore tumours to an earlier and less heterogenous state, where presumably they would be more sensitive to treatment.



Adapted from: McGranahan N, Swanton C. (2017). Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. *Cell*, 68(4):613-28.

View these videos to expand your understanding of tumour heterogeneity:

- Roche Tissue with Dr. Eric Walk. *Tissue Heterogeneity*. (YouTube) March 18, 2014 [10:01 minutes] https://www.youtube.com/watch?v=Wv4fbx1tnVc
- University of Glasgow. *The Cancer Stem Cell Hypothesis and The Clonal Evolution Model.* (YouTube) May 26, 2014 [4 :15 minutes] https://www.youtube.com/watch?v=50wt39Cpklk
- CIC bioGUNE with María dM Vivanco. Breast Cancer heterogeneity. (YouTube) Dec 16, 2019 [2:34 minutes] https://www.youtube.com/watch?v=8UBm9bdhUzs
- Phospho Biomedical Animation. *How does cancer cope with genetic chaos?* (YouTube) January 10, 2017 [3:45 minutes] https://www.youtube.com/watch?v=qWDXuDqmMEo
- IFOM - Istituto FIRC di Oncologia Molecolare. *Cancer stem cells.* (YouTube) December 19, 2017 [2:13 minutes] https://www.youtube.com/watch?v=hPtagJa0myI

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