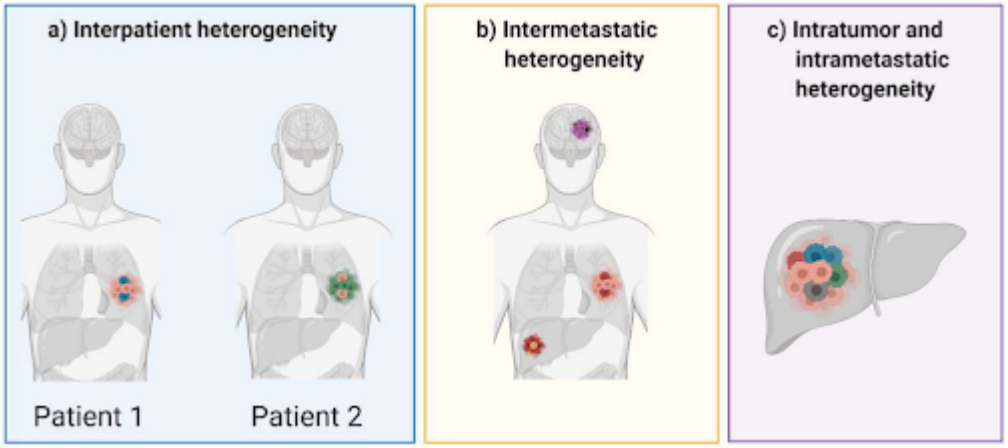
Module 5.1: Learn - Biology

5.1 Biology/Stats

Heterogeneity in cancer

Each cell line in the CCLE is clonal (divisions of a specific cell in the tumor so all the cells are very alike), but in actuality there are a lot of differences or heterogeneity involved in cancer. This is important to keep in mind when thinking about the implications of our studies in the cell lines and how they might translate to actual tumors in the patients (which is the ultimate reason we study cancer in the lab, to help treat cancer patients). Each cell line in the CCLE is a single piece in the massive puzzle of cancer.

1. Interpatient heterogeneity: differences between tumors in different patients
    - Tumors the same type in a similar location in the body be genetically quite different as different sets of mutations can drive the progression of a tumor
    - This is the focus of many cancer studies, contributes to differential patient responses to therapy and is the basis for precision medicine approaches.
2. Intersite/intermetastatic heterogeneity: differences between distinct tumors within an individual patient
    - Tumors can show many genetic changes when they are found in their primary location where they formed and when they have traveled through the body forming metastatic tumors
    - Different metastatic tumors in separate parts of the body can have genetic differences that allow the tumors to grow in a different organ
3. Intratumor/intrametastatic heterogeneity: differences between cellular populations in a distinct tumor
    - a. Within a tumor, there is a mix of cell types
    - b. You can have a clonal mutation, mutations that are in every cell in the tumor and may include the mutation that kicked off tumor formation in the first place
    - c. After the tumor grows, you can have subclonal mutations that are only found in a specific subset of the tumor cells, which might be secondary mutations that lead to different rates of cancerous processes in different parts of the tumor



In the annotation information for the CCLE you have seen information about whether the tumor the cell line was c a primary tumor (in the original location) or a metastatic tumor (where cells have traveled the primary location to a body). The multiple levels of heterogeneity in tumors makes it especially important to know that CCLE cell lines a that could recapitulate specific features of tumor cells in the body and findings need to be verified before they car gene expression results from cell line studies are validated by staining for the translated protein product in pathol and other methods of assessing gene expression in tumors inside the body.

Cancer cell types

The CCLE contains cell types from tumors that formed in many different parts of the body. These comprise the n cells:

1. Carcinomas
    a. Arise in epithelial cells that line the body cavities
    b. Most common
    c. Named after the type of epithelial cells that are mutated
        - Adenocarcinoma: glandular tissue, such as the breast, colon, and prostate
        - Basal cell carcinoma: basal (lower) layer of the epidermis (skin)
        - Squamous cell carcinoma: squamous epithelial cells, which are found just beneath the outer surface o stomach, intestines, lungs, bladder, and kidneys

- Transitional cell carcinoma: transitional epithelium (urothelium), which are various-sized, multi-layered bladder, ureters, and kidney

2. Sarcomas
    a. Arise in bone, muscle, blood, fat, and other soft tissue cells known as mesenchymal cells
    b. Bone and soft tissue sarcomas include:
        - Dermatofibrosarcoma protuberans: type of skin cancer
        - Kaposi sarcoma: skin, lymph nodes, internal organs, and mucous membranes
        - Leiomyosarcoma: smooth muscle tissue
        - Liposarcoma: fatty tissues
        - Malignant fibrous histiocytoma: bone or soft tissue
        - Osteosarcoma: type of bone cancer

3. Leukemia
    a. Leukemia cells and leukemic blast cells are abnormal white blood cells that form in bone marrow stem cel are made
    b. Unlike some other cancers, leukemia cells do not bind together to form a tumor
    c. Instead, these abnormal white blood cells build up in the blood and bone marrow, crowding out healthy blo
    d. Four types of leukemia:
        - Acute lymphoblastic leukemia (ALL)
        - Acute myelogenous leukemia (AML)
        - Chronic lymphocytic leukemia (CLL)
        - Chronic myelogenous leukemia (CML)

4. Lymphomas
    a. Blood-related cancers that arise from lymphoid tissues in the lymphatic system, a part of the immune syst throughout the body
    b. Can develop in different types of white blood cells (B-cells, T-cells, and NK cells)
    c. Can begin anywhere in the body and feed on nutrients in the lymph fluid
    d. Two main forms:
        - Hodgkin lymphoma

- Non-Hodgkin lymphoma (NHL)

5. Myelomas

   a. Type of cancer cells that develop in plasma—white blood cells that produce antibodies
   b. Occur when a plasma cell becomes abnormal, then divides to replicate, forming myeloma cells
   c. Collect in the bone marrow and soft tissue to form a tumor
   d. When it affects several bones, it is known as multiple myeloma
   e. Can also affect other tissues and organs, such as the kidneys

In the CCLE annotation, you have seen information about the tissue or organ in the body the tumor was found in. tissue in which the tumor was formed, as well as physical characteristics and genetic features of the individual, w expression of genes in the tumor cells and thus also in cell lines like the ones in the CCLE.

Tumor microenvironment

CCLE cell lines have been derived from tumor cells but it's important to know that they are growing in a complete environment than what these cells were seeing inside the body. In the body, tumor cells would be interacting witl types including immune cells, vascular endothelial cells from neighboring blood vessels, and many others.

This video illustrates how different cells interact within and on the surface of a tumor in the body: **The Tumor Mic (https://www.youtube.com/watch?v=85qfMcj9m9g)** (**Tumor Microenvironment Video Transcript (https://docs.google.com/document/d/1BzFaCeyTN_tqNdLUccu7lYXL-qeZ-bQV4xplpPXDGS0/edit?usp=sharing)**).

Over time, cancer progression happens when tumors find ways to fight the body's ability to get rid of damaged ce environment there is likely no reason for cells to adapt in that way. Studies that use cell lines try to account for th growth factors and stimuli in the growth medium that tries to mimic the tumor microenvironment as much as poss even allowing cells to grow in three dimensions to produce something that looks more like the original tumor. Ce include growing multiple cell lines together (called "co-culture" studies) to try to mimic the diversity of cell types th in the body.

In the CCLE annotation, you can find information about the liquid growth medium in which the cell lines were mai (such as DMEM and RPMI) as well as growth factors and stimuli that are added to the medium to help the cells g mimic factors the cells saw when they were tumor cells growing in the body.

Tumor immune cells

One major component of cells that can be found in the tumor microenvironment is immune cells.

This video shows how different types of immune cells can affect the tumor (they use melanoma as an example, b tumors in many organs of the body): **Tumour Immunology and Immunotherapy (https://youtu.be/K09xzIQ8zs Immunology and Immunotherapy Video Transcript (https://docs.google.com/document/d/1jH3PWyy1DPB5W c5B410l5tNZZM8Qn1IrfWd4c/edit?usp=sharing)**)

In summary, we have:

1. NK cells: sense stress molecules on the surface of cells
2. Dendritic cells: activate cytotoxic T cells
3. Cytotoxic T cells: sense tumor-associated antigens (surface markers) and destroy the cell
4. Helper T cells: help activate and recruit more cytotoxic cells

Effect of genetic sex on tumor immune cells and tumor microenvironment

As it turns out, sex chromosomes can have an effect on the immune system and this can lead to sex differences section, we will be reading a paper that describes how the loss of the Y chromosome in bladder cancer drives ca off the adaptive immune response normally meant to detect and eliminate cells that are stressed or damaged.

Journal Club: Y chromosome loss in cancer drives growth by evasion of adaptive immunity

https://www.nature.com/articles/s41586-023-06234-x (https://www.nature.com/articles/s41586-023-06234-x)

As you read this paper, think about the following questions:

1. What kinds of health problems have been observed in males that have lost their Y chromosomes in specif
2. What kinds of model systems did they develop for use in this study?
3. What Y chromosome genes did they study to assess loss of chrY?
4. Was loss of chrY associated with better or worse prognosis for cancer patients?
5. What did they measure to determine the behavior of cells with and without chrY?
6. What is CRISPR-Cas9 and what was this technique used for in this study? (Google stuff if you don't know
7. What changes to the immune cells in the tumors were observed with loss of chrY?

8. What were the key findings in this study?
9. How did they test the importance of these findings for treating patients?

Please go to the Journal Club assignment for this module to participate in the discussion. Here are those Perusa
if you need them:

- **Accessing Perusall through Canvas (https://www.youtube.com/watch?v=bs_Z_3wqib4)** (**Accessing Peru
  **Canvas Video Transcript (https://docs.google.com/document/d/1ql6li6Au6ccO-xoTpQRM_ilF5Z6FMeGtbRG
  usp=sharing))
- **Intro to Perusall (https://www.youtube.com/watch?v=M8bOP7yF_6I)** (**Perusall Introduction Video Transc
  (https://docs.google.com/document/d/1OPT_i7YrembK3518QiKaYcgClgsM-BRbuCCc7Y-BQXU/edit?usp=sharing

Additional Resources

- Tumor Heterogeneity
  - **Tumor Heterogeneity: A Great Barrier in the Age of Cancer Immunotherapy (https://doi.org/10.339**
  - **Chapter 4 - Tumor Heterogeneity (https://doi.org/10.1016/B978-0-12-804010-2.00004-7)**
  - **Tumour heterogeneity and resistance to cancer therapies (https://doi.org/10.1038/nrclinonc.2017.16**
- Cancer cell types
  - **What are cancer cells? (https://www.verywellhealth.com/what-are-cancer-cells-2248795)**
- Tumor Microenvironment
  - **Tumor Functional Heterogeneity Unraveled by scRNA-seq Technologies (https://doi.org/10.1016/j.t**