The Nature of Cancer

The Biology of Cancer

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Introduction

• Thodor Boveri, pathologist (1902…. 1914) : Suggested that malignant tumors might be the result of a certain abnormal condition of the chromosomes, which may arise from multipolar mitosis.

• Tumors destroy man in a unique and appalling way, as flesh of is own flesh which has somehow been rendered proliferative, rampant, predatory and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study they remain the least understood.

(Francis Peyton Rous, tumor virologist, Nobel lecture, 1966)
introduction

• Most types of cells in the body carry a complete organismic genome far more information than any one of these cells will ever require.

• Many cells retain the ability to grow and divide long after organismic development has been completed for maintenance of adult tissues and repair of wounds.

• But this autonomy is a grave danger.

• Cells may gain access to information in their genomes that is normally denied to them which corrupts the genomic sequences and hence information content of the genome.
Tumors arise from normal tissues

- Histology showed that tumors, like normal tissues, were composed of masses of cells.

The ileum in the small intestine, viewed at low magnification, reveals the continuity between normal and cancerous tissue.

An invasive ductal breast carcinoma
• The new settlements, termed **metastases** traceable.

Two weeks after B16 mouse melanoma cells were injected into the tail veins of these mice

**Tumors are created by cells that have lost the ability to assemble and create tissues of normal form and function.**

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• However, cancer cells still have some **features of its origin** (normal cells).
• This suggested that all tumors should, in principle, be traceable back to the specific tissue or organ site in which they first arose, using the histopathological analyses of tumor sections to provide critical clues.
• So we may classify them according to their presumed tissues of origin.
• But functionally and histopathologically it was classified into:
  • **Benign**: Grew locally without invading adjacent tissues.
  • **Malignant**: that invaded nearby tissues and it cause more than 90% of deaths from cancer
• The great majority of primary tumors arising in humans are benign.

• Some benign tumors, however, may cause clinical problems because they release dangerously high levels of hormones.

• Thyroid **adenomas**

  Premalignant epithelial growths cause excessive release of thyroid hormone

• **pituitary adenomas**

  Acromegaly
  Cushing's Disease
  Prolactinomas
Tumors arise from many specialized cell types throughout the body

- The majority of human tumors arise from **epithelial tissues**.
- **Basement membrane** separates the epithelial cells from the underlying layer of supporting connective tissue cells, termed the stroma.

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• **In endothelial** cells basement membranes serve as a structural scaffolding of the tissues.

• But cells attach a variety of biologically active signaling molecules to basement membranes.

• **Carcinomas** responsible for more than 80% of the cancer related deaths in the Western world.

• **Examples:**

• Mouth, esophagus, stomach, small and large intestines, the skin, mammary gland, pancreas, lung, liver, ovary, uterus, prostate, gallbladder, and urinary bladder.
Normal epithelial tissues

A collecting tubule of the kidney

bronchiole of the lung

columnar epithelium of the gallbladder

endometrium of the uterus
• The epithelia of the lungs, liver, gallbladder, pancreas, esophagus, stomach, and intestines all derive from the inner cell layer, the **endoderm**.

• Skin arises from the outer embryonic cell layer (**ectoderm**)

• Ovaries originate embryologically from the middle layer, the **mesoderm**

• Therefore, in the case of carcinomas, histopathological classification is not informed by the developmental history of the tissue of origin.

• But most carcinomas fall into two major categories that reflect the two major biological functions associated with epithelia.
• **Squamous cell carcinomas;** The ones originate from supportive and protective cell layers, such as the epithelial cells lining the skin (keratinocytes) and the oral cavity.

• **Adenocarcinomas;** specialized secretory cells.

<table>
<thead>
<tr>
<th>Tissue sites of more common types of adenocarcinoma</th>
<th>Tissue sites of more common types of squamous cell carcinoma</th>
<th>Other types of carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>lung, colon, breast, pancreas, stomach, esophagus, prostate, endometrium, ovary</td>
<td>skin, nasal cavity, oropharynx, larynx, lung, esophagus, cervix</td>
<td>small-cell lung carcinoma, large-cell lung carcinoma, hepatocellular carcinoma, renal cell carcinoma, transitional-cell carcinoma (of urinary bladder)</td>
</tr>
</tbody>
</table>
Sarcomas; from mesenchymal cells such as (fibroblast, chondrocytes, adipocytes, myocytes and osteocytes)

Table 2.2 Various types of more common sarcomas

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Presumed cell lineage of founding cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma</td>
<td>osteoblast (bone-forming cell)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>adipocyte (fat cell)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>smooth muscle cell (e.g., in gut)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>striated/skeletal muscle cell</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>adipocyte/muscle cell</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>fibroblast (connective tissue cell)</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>endothelial cells (lining of blood vessels)</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>chondrocyte (cartilage-forming cell)</td>
</tr>
</tbody>
</table>

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Hematopoietic

- **Hematopoietic**: arise from the various cell types that constitute the blood-forming.

- 7% of cancer-associated mortality in the United States are **Lymphomas** which include tumors of the **lymphoid** lineages (B and T lymphocytes).

- **Leukemia**: white blood cells tumors.

- **Myeloma**: is a cancer of the plasma cells.

- **Myelodysplastic syndromes**
Neuroectodermal Tumors

- **Neuroectodermal Tumors** arises from cells that form the central and peripheral nervous systems.
- **Gliomas** from Glial cells. **Glioblastomas** arise from astrocytes.
- **Neuroblastomas** in embryo nerve cells **Schwannomas** and medulloblastomas.

### Table 2.4 Various types of neuroectodermal malignancies

<table>
<thead>
<tr>
<th>Name of tumor</th>
<th>Lineage of founding cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>highly progressed astrocytoma</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>astrocyte (type of glial cell)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>arachnoidal cells of meninges</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Schwann cell around axons</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>cone cell in retina</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>cells of peripheral nervous system</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>cells lining ventricles of brain</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>oligodendrocyte covering axons</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>granular cells of cerebellum</td>
</tr>
</tbody>
</table>
Some types of tumors do not fit into the major classifications

- **Transdifferentiation**, Such a change in phenotype may affect both normal and cancer cells. E.g, *epithelial–mesenchymal transition* (EMT) in cancer borders.
- **Melanomas** are derived from melanocytes, the pigmented cells of the skin and the retina.
- But melanocytes arise from the embryonic neural crest.
Dedifferentiated equals anaplastic, in that it is no longer possible to use histopathological criteria to identify the tissues from which they have arisen.

- Well-differentiated tumors resemble their tissue of origin, whereas poorly-differentiated or undifferentiated (anaplastic) tumor cells appear primitive and lack specialization along any particular cell line. In general, benign tumors tend to be well-differentiated. Malignant tumors run the gamut from well-differentiated to undifferentiated.
Cancers seem to develop progressively

- Between the normal and highly malignant tissue architectures lies many intermediate appearance which may represent a distinct steps.
- **Hyperplastic** still normal with small modifications. (cell division)

However, they have not penetrated the basement membrane
• **Metaplasia**, a type of normal cell layer is displaced by cells of another type that are not normally encountered in this site within a tissue.

- **Barrett’s esophagus** is Premalignant condition characterized by the replacement of the normal stratified squamous epithelium lining of the esophagus by simple columnar epithelium with goblet cells.

Ulcerated adenocarcinoma developed here from cells of gastric origin
• **Dysplastic**, this is more abnormal (cytologically).

• **Nuclear size and shape:**
  - increased nuclear staining by dyes, increased ratio of nuclear versus cytoplasmic size.
  - Increased mitotic activity, and lack of the cytoplasmic features associated with the normal differentiated cells of the tissue.

Dysplasia is considered to be a transitional state between completely benign growths and those that are premalignant.
• **Adenomas**, polyps, papillomas, skin warts: Substantial expansion, creating a macroscopic mass. (dysplastic)
• They respect the basement membrane, which continues to separate them from the underlying stroma.
• If they do, they are considered to be benign
Invasive carcinomas

• A further degree of abnormality is represented by growths that do invade underlying tissues.
• Carcinoma cells break through a basement membrane and invade into the adjacent stroma
• In the case of epithelial tissues, the term “carcinoma” is usually applied to growths that have acquired this degree of invasiveness.

• **Neoplasms** benign and malignant.

• normal → hyperplastic → dysplastic → neoplastic → metastatic (by no means proven)
Tumors are monoclonal growths

- Lets accept that tumors arise through the progressive alteration of normal cells.
- Does it arise from one cell or many cells each give a subpopulation of cancer cells.
- Monoclonal or polyclonal

Epigenetic Changes are natural events and will be maintained in the new generations, exactly as X chromosome inactivation.

**lineage tracing:** The lineage of a cell can be followed *in vivo* from its embryonic ancestor.
lineage tracing

- **Epigenetics** naturally occurring and its nongenetic.
- X chromosome inactivation and lineage tracing.
- Glucose-6-phosphate dehydrogenase (G6PD) is located on the X chromosome.
- 30% of African American women are heterozygous at this locus.
- This is an indication for monoclonal origin of cancer cells.

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Other confirmations

- **Myelomas**, which derive from the B-cell precursors of antibody-producing plasma cell.
- Normally they are millions of distinct subpopulations. According to *(immunoglobulins)*.

All the myeloma cells in a patient produce the identical antibody molecule.
Chromosomal aberrations

• Often, a very peculiar chromosomal abnormality—the clear result of a rare genetic accident—is seen in all the cancer cells within a tumor mass.

Which confirms that all the malignant cells within this tumor descend from the single ancestral cell.
Is it polyclonal?

• Say 10 cells turned to be cancer cells each of which will develop its own clone and one of them will be dominant after some time.

• Also instability of tumor cell populations (genetic instability).

• So its almost monoclonal but, The resulting genetic heterogeneity may mask the true monoclonal origin of this cell population.