Lesson 2: Basic Tumor Biology – cell cycle, apoptosis, angiogenesis, metastasis

1. Why This Lesson Matters

In oncology, you are not only treating a lump or a report; you are dealing with **cells whose internal control systems have broken down**.
To design any rational integrative plan and to communicate intelligently with oncologists, you must understand:

- How normal cells control their growth
- What goes wrong in cancer cells
- Why cancers behave aggressively and come back

This lesson gives you that “inside view”.

2. The Cell Cycle – How Normal Cells Divide

Every cell in the body follows a structured sequence when it grows and divides. This is called the **cell cycle**.

Important phases:

- **G0 phase (Resting)**
  - Cell is alive and active but not dividing.
  - Many cells in the body stay in G0 for long periods.
- **G1 phase (Gap 1)**
  - Cell grows in size.
  - Makes proteins and prepares for DNA synthesis.
- **S phase (Synthesis)**
  - **DNA (DeoxyriboNucleic Acid)** is replicated.
  - Each chromosome duplicates so that when the cell divides, each daughter cell receives a complete set.
- **G2 phase (Gap 2)**
  - Cell checks the newly synthesized DNA for errors.
  - Prepares machinery for division.
- **M phase (Mitosis)**
  - Actual cell division.
  - One cell splits into two daughter cells.

Between these phases, there are **checkpoints**:

- **G1/S checkpoint** – checks if cell is ready to copy DNA; if DNA is damaged, repair is attempted.
- **G2/M checkpoint** – checks if DNA replication is complete and accurate before mitosis.
- Other internal controls also exist to detect serious damage.

In normal tissues, if the damage is too severe, the cell undergoes **apoptosis**:

- **Apoptosis** = programmed cell death, a controlled process where the cell “commits suicide” for the greater good of the body.

In cancer, many of these checks and apoptosis signals are defective, so abnormal cells keep surviving and multiplying.

3. DNA, Genes and Mutations – The Core Problem

3.1 DNA and Genes

- **DNA (DeoxyriboNucleic Acid)** is the chemical that carries genetic information in almost all living organisms.
- A small segment of DNA that carries the instructions to make a specific protein is called a **gene**.
- Genes are like “software codes” for proteins that control:

- Growth
- Division
- Repair
- Death
- Communication between cells

Any lasting change in the DNA sequence is called a **mutation**.

3.2 What is a Mutation?

A **mutation** is a permanent alteration in the DNA sequence of a gene.

- Sometimes harmless or “silent”
- Sometimes beneficial (rare)
- Many times, harmful or disruptive

If mutations occur in genes that control cell growth, repair or death, they can be the starting point of cancer.

3.3 Causes of DNA Damage and Mutation

DNA damage can be caused by:

- **Chemical carcinogens**
  - Tobacco smoke (polycyclic hydrocarbons)
  - Industrial chemicals (benzene, asbestos-associated compounds)
  - Aflatoxins from fungal contamination of food
- **Physical agents**
  - Ionizing radiation (X-rays, gamma rays)
  - Ultraviolet (UV) radiation from sunlight
- **Biological agents**
  - Oncogenic viruses (e.g. HPV – Human Papilloma Virus; HBV – Hepatitis B Virus; HCV – Hepatitis C Virus; EBV – Epstein–Barr Virus)
  - Certain bacteria and parasites via chronic inflammation
- **Lifestyle factors**
  - Poor diet, obesity, alcohol, chronic stress, sleep deprivation
  - These often act by promoting chronic low-grade inflammation and metabolic disturbance.
- **Spontaneous errors**
  - Errors during DNA replication that are not perfectly corrected.

The body has **DNA repair systems**, but if the damage is frequent and intense, or repair genes themselves are mutated, errors accumulate. Over years, this can lead to cancer.

From an Ayurvedic viewpoint, long-term exposure to such factors is similar to **chronic nidāna-sevana** leading to sustained **doṣa-prakopa**, **agni-mandya** and **dhātu-dushti**.

4. Oncogenes and Tumor Suppressor Genes

Not all genes are equally important in cancer. Two major categories are central:

4.1 Proto-Oncogenes and Oncogenes

- **Proto-oncogenes** are normal genes which help cells grow and divide in a regulated way.
- When these proto-oncogenes are mutated or abnormally activated, they become **oncogenes**.

Oncogenes act like a **jammed accelerator pedal** in a car:

- They send continuous “grow and divide” signals, even when the cell should stop.
- Examples (just for awareness): growth factor genes, growth factor receptor genes, certain signaling proteins.

4.2 Tumor Suppressor Genes

- **Tumor suppressor genes** normally act as **brakes**:
  - They slow down or stop cell division.
  - They repair DNA damage.
  - They can trigger apoptosis when damage is severe.

When tumor suppressor genes are **mutated, deleted or inactivated**, the brakes fail.

So cancer often arises when:

- Growth **accelerators (oncogenes)** are stuck “on”
  AND
- Growth **brakes (tumor suppressor genes)** are not working

This double effect leads to uncontrolled, unregulated cell proliferation.

Ayurvedic reflection: a similar conceptual idea is when **pravritti** of doṣa is excessively stimulated (akin to accelerator) and **niyama** and **nirodha** mechanisms (body’s homeostatic controls, akin to brakes or ojas-mediated protection) fail.

5. Apoptosis and Immortality of Cancer Cells

5.1 Apoptosis – Physiological Cell Death

Apoptosis is normal, orderly cell death:

- Cells shrink, DNA is cut into small, regular fragments.
- Cell contents are neatly packaged and removed by immune cells.
- There is **no inflammation** or damage to neighboring cells.

It is essential for:

- Removing damaged or old cells
- Shaping tissues during development
- Maintaining tissue balance

5.2 Resisting Apoptosis – Cancer’s Trick

Cancer cells develop ways to:

- Ignore signals that tell them to die
- Overexpress proteins that prevent apoptosis
- Downregulate proteins that promote apoptosis

Result:

- Damaged cells that should have died continue to live, divide, and accumulate further mutations.

5.3 Replicative Immortality

Normal cells can only divide a limited number of times. This limit is controlled partly by:

- **Telomeres** – protective caps at the ends of chromosomes that shorten with each cell division.
- When telomeres become too short, the cell stops dividing or undergoes apoptosis.

Cancer cells often:

- Activate **telomerase**, an enzyme that maintains telomere length.
- This allows them to divide many more times than normal – they gain **replicative immortality**.

In Ayurvedic conceptual language, these processes reflect a loss of **maryādā (boundaries) of dhātu-vṛddhi** and failure of natural **kṣaya / samyak-kshaya** processes. Instead of balanced turnover, there is one-sided, unregulated proliferation.

6. Hallmarks of Cancer – The Essential Behaviour Pattern

Researchers have described a set of recurring features present in most cancers. These are called the **"hallmarks of cancer."** You don't need to remember complex molecular pathways yet; focus on the behaviors.

Key hallmarks:

1. **Sustained proliferative signaling**
   - Cancer cells send or receive constant signals to grow and divide.
   - They act as if growth factors are always present.
2. **Evading growth suppressors**
   - They ignore signals that normally tell cells to stop growing.
   - They bypass the instructions of tumor suppressor genes.
3. **Resisting cell death (apoptosis)**
   - Abnormal cells that should have died remain alive.
   - They block death pathways and enhance survival pathways.
4. **Enabling replicative immortality**
   - They maintain telomere length and keep dividing beyond normal limits.
5. **Inducing angiogenesis**
   - **Angiogenesis** = formation of new blood vessels.
   - Tumor cells release substances that stimulate nearby blood vessels to grow towards them.
   - This supplies them with oxygen and nutrients.
6. **Activating invasion and metastasis**
   - They lose respect for tissue boundaries.
   - They produce enzymes that break down surrounding tissue.
   - They change their adhesion properties, allowing them to move and invade other sites.

Additional enabling features often discussed:

- **Deregulating cellular metabolism** – shifting to abnormal ways of using glucose and energy.
- **Avoiding immune destruction** – hiding from or suppressing the immune system.
- **Promoting inflammation** – using chronic inflammation as a growth support.

Ayurvedic parallels can be thought of as:

- Persistent **doṣa prakopa** (uncontrolled movement/activity)
- Breakdown of **dhātu-sāmya** and **srotas-saumya** (normal tissue and channel harmony)
- **Ojokṣaya** and deranged **vyādhi-kṣamatva** (disease resistance), allowing abnormal cells to survive and expand
- Chronic **śotha** (inflammation) becoming a nidus for further damage

Remember: these are conceptual bridges for understanding, not direct one-to-one translations.

7. Tumor Microenvironment – The "Neighborhood" of Cancer Cells

Cancer cells do not grow in isolation. They modify and exploit their surrounding environment, known as the **tumor microenvironment**.

Key components:

- **Stromal cells** – fibroblasts, immune cells, endothelial cells (forming blood vessels), supporting cells.
- **Extracellular matrix (ECM)** – structural proteins and ground substance around cells.
- **Signaling molecules** – cytokines, chemokines, growth factors, enzymes.

Cancer cells:

- Secrete substances that recruit new blood vessels (angiogenesis).
- Attract immune cells but then subvert them to support tumor growth.
- Change the structure of ECM to facilitate invasion and metastasis.
- Create regions of low oxygen (hypoxia) and acidity that select for more aggressive cell clones.

Clinical importance:

- Many newer cancer treatments (targeted drugs and some immunotherapies) work by disrupting these interactions, not just by directly killing tumor cells.
- The “soil” (terrain) matters as much as the “seed” (tumor cell).

Ayurvedic reflection:

- The concept of **deśa** (terrain), **srotas** health, and the quality of **dhātu** around the lesion is crucial.
- When **srotas** are blocked, vitiated, or weakened, and **agni** is disturbed, the environment becomes favorable for abnormal growths to flourish.

8. From Biology to Clinical Behavior

Understanding these molecular and cellular events explains many clinical observations:

- Why some tumors grow very fast, while others are slow.
- Why cancers can recur after apparently successful surgery or chemo.
- Why they can become resistant to drugs:
  - Surviving cells adapt, develop new mutations, or change their microenvironment.
- Why multi-modal therapy (surgery + chemo + RT + targeted) is often needed:
  - Each modality attacks different aspects of tumor biology.

For an integrative Ayurvedic clinician, this understanding should lead to:

- Respect for the complexity and adaptability of cancer
- Avoidance of simplistic language like “this single herb melts all tumors”
- A **multi-pronged supportive approach**:
  - Correct **agni** and reduce **ama**
  - Support **ojas** and immunity
  - Manage inflammation and oxidative stress
  - Support organ function and tissue repair
  - Enhance mental and emotional resilience

9. Conceptual Mapping with Ayurveda

Let us very briefly map the key ideas:

- **Uncontrolled proliferation, immortality**
  → In Ayurveda, excessive **kapha and meda vṛddhi** initially, with progressive **mamsa and other dhātu vikṛti** and loss of regulatory control.
- **Genetic mutations and DNA damage**
  → Long-term **nidāna-sevana**, **agni-mandya**, **ama**, **raktadushti**, and **śotha** create an internal milieu favorable for cellular distortions.
- **Evasion of apoptosis, immune escape**
  → Progressive **ojokṣaya** and **vyādhi-kṣamatva hāni**, failure of **rakta and rasa dhātu** to maintain purity and surveillance.
- **Angiogenesis and invasion**
  → Deranged **rakta and mamsa** with damaged **srotas**, loss of normal **maryādā** (boundaries) of tissues.

The aim in later lessons and modules will be to see how our available tools (your specific formulations, Panchakarma support where appropriate, diet, yoga, counseling) can positively influence some of these processes, particularly at the

level of **agni**, **ama**, **ojas**, **śotha**, and organ function, within safe limits and in synchrony with modern treatments.

10. Key Take-Home Messages

1. Normal cells follow a **regulated cell cycle** with checkpoints and apoptosis; cancer cells bypass these control systems.
2. **DNA mutations** in critical genes (oncogenes and tumor suppressor genes) are central events in cancer development.
3. Oncogenes act like an **overactive accelerator**; tumor suppressor genes are **brakes** that, when lost, allow uncontrolled growth.
4. Cancer cells resist apoptosis and may become **immortal**, partly via telomerase activation.
5. The **hallmarks of cancer** describe a characteristic behavior pattern: sustained growth signaling, evasion of suppressors, resistance to death, immortality, angiogenesis, invasion, and metastasis.
6. The **tumor microenvironment** (terrain) is as important as the tumor cells themselves.
7. Ayurvedic concepts of **doṣa–dūṣya–srotas**, **agni**, **ama**, **ojas** and **śotha** provide a rich conceptual framework to understand this complexity and to plan rational integrative care.
8. This biological understanding keeps us humble, realistic, and precise while designing Ayurvedic oncology protocols.

11. Review Questions

1. Describe the main phases of the cell cycle and the purpose of cell cycle checkpoints.
2. What is a gene mutation? List at least four causes of DNA damage.
3. Explain the difference between a proto-oncogene and an oncogene.
4. What are tumor suppressor genes and what happens if they are lost or mutated?
5. Define apoptosis. Why is resistance to apoptosis important for cancer cells?
6. List at least five hallmarks of cancer and explain any two in simple language.
7. What is the tumor microenvironment and why is it important in cancer behavior?
8. How would you conceptually relate chronic **śotha** and **ama** to the process of carcinogenesis?
9. How can this understanding of tumor biology influence your approach to Ayurvedic supportive treatment?

End of Lesson 2