NEOPLASIA SHEET

LECTURE 7

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❖ NEOPLASIA 7:

➢ Development of Sustained Angiogenesis:

- Tumors **cannot enlarge** beyond 1-2 mm in diameter **unless they are vascularized.**
- Cancer cells can stimulate neo-angiogenesis during which new vessels **sprout from previously existing capillaries** or by **vasculogenesis** in which endothelial cells are recruited from the bone marrow.
- Growing cancers stimulate neoangiogenesis during which vessels sprout from previously existing capillaries.
- Neovascularization has a **dual** effect on tumor growth:
  1. Perfusion supplies needed nutrients and oxygen
  2. Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, such as insulin-like growth factors (IGFs) and PDGF.
- Tumor vasculature is abnormal, leaky, dilated and has a haphazard pattern of connection.
- Angiogenesis is **required** not only for **continued tumor growth** but also for **access to the vasculature** and hence for metastasis.
- **Angiogenesis** *is thus a necessary* ***biologic correlate of malignancy***.
- Angiogenesis is controlled by a **balance** between angiogenesis promoters and inhibitors.
  - ✓ In angiogenic tumors this balance is in favor of **promoters**.
- The angiogenic **switch** involves **increased** production of **angiogenic factors** (PROMOTORS) and/or **loss** of angiogenesis **inhibitors**.
- Angiogenic factors (**promotors**) may be produced:
  1- Directly by the tumor cells themselves
  2- By inflammatory cells (e.g., macrophages)
  3- By stromal cells associated with the tumors
- The angiogenic inhibitors are **Proteases** that either **elaborated by the tumor cells** or by **stromal cells in response to the tumor angiogenic and anti-angiogenic factors.**

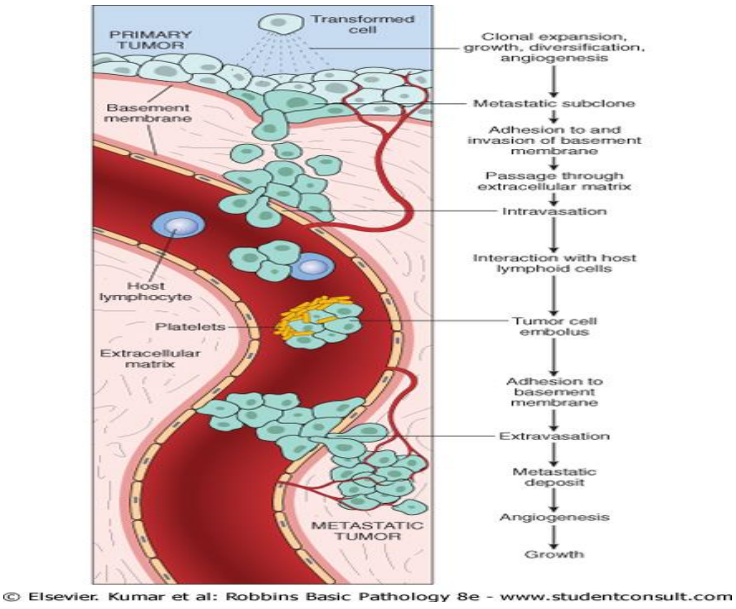
Angiogenic switch: a specific stage in tumor progression where the balance shifts, favoring factors that promote blood vessel growth.

- The angiogenesis inhibitors as [1]**angiostatin** and [2]**endostatin** are produced by **proteolytic cleavage** of [1]plasminogen and [2]collagen respectively.
- The angiogenic switch is controlled by several physiologic stimuli, such as **hypoxia**.
- Relative lack of oxygen → activation of hypoxia-induced factor-1α (**HIF1α**), an oxygen-sensitive transcription factor → stimulates production of **pro-angiogenic cytokines as VEGF.**
- HIF1α is **continuously produced** but in normal conditions the von Hippel-Lindau protein (**VHL**) **binds to HIF1α**, leading to **ubiquitination** and **destruction** of **HIF1α**.
- In **hypoxic** conditions, such as a tumor that has reached a critical size→ the lack of oxygen → **prevents HIF1α recognition by VHL protein → no destruction** of HIF1α → HIF1α **translocates** to the nucleus and **activates transcription** of its target genes such as **VEGF** (Vascular endothelial growth factor).
- VHL acts as a **tumor suppressor gene,** and germ-line **mutations** of the *VHL* gene are associated with **hereditary *VHL syndrome***:
    1- Renal cell cancers
    2- Pheochromocytomas
    3- Hemangiomas of the CNS
    4- Retinal angiomas
    5- Renal cysts
- **Mutations** involving tumor suppressors and oncogenes in cancers **also tilt the balance in favor of angiogenesis.**
- For example,
    - p53 **normally** stimulates expression of **antiangiogenic** molecules, such as **thrombospondin-1**, and **represses** expression of **proangiogenic** molecules such as **VEGF**.
    - Common **loss of p53** in tumor cells provides a **permissive environment for angiogenesis**.
    - The **transcription of VEGF** is also influenced by signals from the **RAS-MAP kinase pathway**, and mutations of *RAS* or *MYC* **up-regulate** the production of VEGF.

✓ Anti-VEGF antibody is now approved for the treatment of several types of cancers.

➢ Invasion and Metastasis:

- **Invasion and metastasis** are the major causes of cancer related **morbidity** and **mortality** that result from complex interactions involving **cancer cells, stromal cells, and the extracellular matrix (ECM).**



- Steps of metastasis:

1-Local **invasion**.

2-**Intravasation** into blood and lymph vessels.

3-**Transit** through the vasculature.

4-**Extravasation** from the vessels.

5-Formation of **micrometastases**.

6-Growth of micrometastases into **macroscopic tumors.**

(refer to video 2 last page)

- The metastatic cascade can be subdivided into two phases:
    1- Invasion of ECM.
    2- Vascular dissemination and homing of tumor cells

1. *Invasion of Extracellular Matrix (ECM)*

- Human tissues are organized into a series of **compartments separated** from each other **by two types of ECM**:
    1. Basement membranes.
    2. Interstitial connective tissue.
- ECM is composed of:
    1- Collagens
    2- Glycoproteins
    3- Proteoglycans

✦ Invasion of the ECM is an active process that requires four steps:

1- **Detachment** of tumor cells from each other.
2- **Degradation** of ECM.
3- **Attachment** to novel ECM components.
4- **Migration** of tumor cells. (locomotion)

- ***loosening* of tumor cells** needs **to loss of E-cadherins** that act as intercellular glues that keep the cells together. (first step of invasion)
- Their (Cadherins) **cytoplasmic** portions bind to β-catenin.
- **E-cadherin can transmit antigrowth signals by sequestering β-catenin**.
- *E-cadherin function is lost in almost all epithelial cancers by:*
    *1- **mutational** inactivation of E-cadherin genes.*
    *2- by **activation of β-catenin** genes.*

3- *by **inappropriate** expression of the **SNAIL** and **TWIST transcription factors**, which **suppress E-cadherin expression**.*

- **Oncogenes** are **SNAIL** and **TWIST**, which encode transcription factors whose primary function is to **promote** a process called **epithelial-to-mesenchymal transition (EMT).**
- **In EMT**, carcinoma cells **down-regulate** certain **epithelial markers** (e.g., **E-cadherin**) and **up-regulate** certain **mesenchymal markers** (e.g., **vimentin** and **smooth muscle actin**).
- These changes are believed to **favor the development of a promigratory phenotype that is essential for metastasis.**
- **Loss of E-cadherin** expression seems to be a **key event in EMT**, and SNAIL and TWIST are transcriptional repressors that promote EMT by **down-regulating E-cadherin expression.**
- EMT has been documented mainly in breast cancer.
- The second step in invasion is local *degradation of the basement membrane and interstitial connective tissue*.
- Tumor cells may **either** **secrete proteolytic enzymes** themselves or **induce** stromal cells (e.g., fibroblasts and inflammatory cells) **to elaborate proteases.**

✓ Multiple different families of **proteases** are present:

1- Matrix metalloproteinases (**MMPs**).
2- **Cathepsin D.**
3- **Urokinase plasminogen activator**.

- **MMPs** regulate tumor invasion not only by **remodeling insoluble components** of the basement membrane and interstitial matrix but also by **releasing ECM-sequestered growth factors**.

➢ **Cleavage products** of collagen and proteoglycans also have **chemotactic**, **angiogenic**, and **growth-promoting effects.**

- **MMP-9** is a gelatinase that **cleaves type IV collagen** of the epithelial and vascular basement membrane and **stimulates release of VEGF** from ECM-sequestered pools.
- **Benign** tumors of the breast, colon, and stomach show **little type IV collagenase activity**, whereas their **malignant** counterparts **overexpress** this enzyme.

- The **levels** of metalloproteinase **inhibitors are reduced** so that **the balance is tilted greatly toward tissue degradation.**
- **Overexpression** of MMPs and other **proteases** have been reported for many tumors. Because of these observations, attempts are being made to use protease inhibitors as therapeutic agents.
- The third step in invasion involves *changes in attachment of tumor cells to ECM proteins*.
- **Normal epithelial cells have receptors**, such as integrins, for basement membrane laminin and collagens that are polarized at their basal surface.
- These receptors help to maintain the cells in a resting, differentiated state.
- **Loss of adhesion** in normal cells leads to **induction of apoptosis**.
- **Cleavage of the basement membrane proteins** collagen IV and laminin by MMP-2 or MMP-9 **generates novel sites that bind to receptors on tumor cells and stimulate migration**.
- ***Locomotion*** is the final step of invasion.
- Migration is a complex, **multistep** process that involves many families of receptors and signaling proteins that eventually **impinge on the actin cytoskeleton.**
- Such movement seems to be **potentiated** and **directed** by **tumor cell-derived cytokines**, such as **autocrine motility factors**.
- Cleavage products of matrix components (e.g., collagen, laminin) and some growth factors (e.g., insulin-like growth factors I and II) have chemotactic activity for tumor cells.
- **Stromal cells also produce paracrine effectors of cell motility**, such as hepatocyte growth factor/scatter factor (**HGF/SCF**), which bind to receptors on tumor cells.
- **Concentrations of HGF/SCF are elevated** at the advancing edges of the highly invasive brain tumor glioblastoma multiforme, supporting their role in motility.

2. ***Vascular Dissemination and Homing of Tumor Cells:***

- In the **bloodstream**, some tumor cells **form emboli** by **aggregating and adhering to circulating leukocytes**, particularly **platelets**.
- Aggregated tumor cells are thus **afforded some protection from the antitumor host effector cells.**

- **Most** tumor cells, however, **circulate as single cells**.
- **Extravasation** of free tumor cells or tumor emboli **involves adhesion** to the vascular endothelium, **followed by egress** through the basement membrane into the organ parenchyma by mechanisms similar to those involved in invasion.

✦ The site at which metastases occur is related to two factors:

1. The anatomic location and vascular drainage of the primary tumor.
2. The tropism of particular tumors for specific tissues.

- The site of extravasation and the organ distribution of metastases generally can be **predicted by the location of the primary tumor and its vascular or lymphatic drainage.**
- Many tumors **metastasize** to the organ that represents **the first capillary bed they encounter after entering the circulation.**
- In many cases the natural pathways of drainage do not readily **explain** the distribution of metastases, for example,
  - lung cancers tend to involve the adrenals with some regularity but almost never spread to skeletal muscle.
- The mechanisms of site-specific homing involves:
  1. The expression of adhesion molecules by tumor cells whose ligands are expressed preferentially on the endothelium of target organs.
  2. chemokines and their receptors.
     - chemokines participate in directed movement (chemotaxis) of leukocytes.
- Human breast cancer **cells express high levels of the chemokine receptors *CXCR4*** and ***CCR7***.
- The **ligands** for these receptors (i.e., **chemokines CXCL12** and **CCL21**) are **highly expressed only in those organs where breast cancer cells metastasize**.
- It is speculated that **blockades** of chemokine receptors **may limit metastases.**
- **After extravasation tumor cells are dependent on a receptive stroma for growth.**
- Tumors may **fail** to metastasize to certain target tissues **because they present a nonpermissive growth environment.**
- The precise localization of metastases cannot be predicted with any form of cancer.

It means that while general patterns of metastasis are observed for certain cancers (e.g., lung cancer often spreads to adrenal glands), the exact location of metastasis for an individual case cannot be precisely predicted. It highlights the variability and complexity of metastasis in cancer.

Here's a quiz on this lecture.

FEEDBACK.

* Videos and lectures:

1- Lecture 7 (DR. Maha Shomaf)
2- Metastasis.
3- Lecture 7 pt.1 (2022- skip start)
4- Lecture 7 pt.2 (2022)