Neoplasia lec7

Hallmarks of cancer, a reminder:

- 1. self sufficiency in growth signals
- 2. insensitivity to growth inhibitory signals
- 3. evasion of cell death
- 4. limitless replicative potential
- 5. reprogramming of metabolism
- 6. sustained angiogenesis
- 7. ability to invade and metastasize
- 8. evasion of the immune system
- Till now we covered the first five hallmarks.
- In this lectures we will cover hallmarks 6 and 7.

Sixth hallmark: sustained angiogenesis

- Tumors cannot grow for more than 1-2mm without blood supply
- This 1-2 mm zone is the maximum direct diffusion distance.
- Angiogenesis important for tumors to:

1. Supply oxygen and nutrients.

2. Get rid of waste products.

3. Gain access to host blood vessels which is important for invasion and metastasis.

4. The endothelial cells in these vessels secrete growth factors that can help tumor growth.

- Tumor blood vessels are abnormal: they are leaky, dilated and have haphazard pattern of connections.

Angiogenesis

• Angiogenesis is accomplished by factors secreted from the parenchymal tumor cells as well as the stroma. Also inflammatory cells surrounding the tumor can produce angiogenic factors.

• The balance between pro-angiogenic and anti-angiogenic factors controls formation of new blood vessels

• Main pro-angiogenic: VEGF= vascular endothelial growth factor

• Main anti-angiogenic: TSP1= thrombospondin 1

Angiogenic switch

• Tumors usually stay in situ or small for several years, at this stage there is no angiogenesis

• Angiogenesis switch happens when VEGF (and other proangiogenic factors) increases and TSP 1 (or other antiangiogenic factors) decreases.

How we increase proangiogenic factors?

• VEGF produced from tumor cells or macrophages

• Protease (secreted from tumor cells or stromal cells) can release FGF (an angiogenic agent) from ECM.

How we decrease anti-angiogenic factors?

• TSP1 is produced from fibroblasts in response to tumor cells, TSP is anti angiogenic factor.

• Normal P53 induces synthesis of TSP1. So if p53 is deleted, decreased TSP1.

What causes the angiogenic switch?

• Hypoxia is an important factor that favors angiogenesis

• Hypoxia stimulates production of hypoxia –inducible factor 1alpha (HIF 1 alpha)

• HIF is a transcription factor which will stimulate production of VEGF

• HIF is destructed by VHL (von Hipple- Lindau) protein

• Hypoxia prevents VHL from recognizing HIF, no destruction and more angiogenesis.

Von Hippel- Lindau syndrome

• VHL gene is a tumor suppressor gene (because it decreases angiogenesis)

• Rarely some people inherit defective VHL gene, they develop tumors like renal cell carcinoma, pheochromocytoma.

7th hallmark: ability to invade and metastasize

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

Invasion-metastatic cascade

•Steps needed for metastatic spread are called: invasion -metastatic cascade

•The steps include:

Clonal expansion, growth, diversification, angiogenesis – metastatic subclone

Adhesion to and invasion of basement membrane – passage through the ECM

Intravasation – interaction with host lymphoid cells – tumor cell embolus

Adhesion to basement membrane – extravasation – metastatic deposit

Angiogenesis – growth.

(Go back to the picture for better visualization)

• The two main steps are: invasion of ECM and vascular dissemination and homing

ECM invasion

•In order to metastasize, cells need to enter the blood vessels.

•First tumor cells need to invade the underlying basement membrane then through interstitial connective tissue and then penetrate vascular basement membrane.

•This process is repeated when tumor cells exit the blood vessel to the metastatic site.

• Invasion of ECM (both basement membrane and interstitial matrix) is a dynamic process that needs several steps.

• 1.loosening of tumor cells

• E cadherin works as a glue that keeps cells together

• For cells to become loose, they need to decrease E cadherin.

• 2. Degradation of ECM

• Proteases degrade ECM components.

• These proteases are produced from tumor cells, OR the tumor cells send signals to stromal cells or inflammatory cells to secrete them.

• 3.Changes in attachment of tumor cells to ECM proteins

• Normal epithelial cells have integrin receptors that attach to collagen and laminin in ECM

• These receptors help maintain cells in the resting differentiated state

• If this normal adhesion is lost cells die by apoptosis

• Cancer cells lose this adhesion, but they evade apoptosis.

• Also, the ECM is modified by collagenase and other proteases actions that create new adhesion sites.

• 4.locomotion

• = migration of the tumor cells through the ECM.

• Complex process that uses receptors and signaling proteins that affect actin cytoskeleton

Factors used for locomotion include:

• Tumor derived cytokines (autocrine motility factor)

• Cleavage products of matrix components have chemotactic activity

• Some growth factors (insulin like growth factor) have chemotactic activity that facilitates locomotion.

• Stromal cells secrete hepatocyte GF / scatter factor (HGF/SCF)

Vascular dissemination and homing of tumor cells

• After the steps mentioned previously the tumor cells can enter the blood vessel

• Once in the blood vessels, they can be destroyed by the immune cells, so they need to evade this (next lecture)

• Some tumor cells circulate in the blood individually, others form emboli (small aggregates) that bind leukocytes and platelets to protect themselves from being recognized by the immune system.

• These tumor cells circulate in the blood, but at a certain point they must exit the vessel to tissues

• The site of extravasation (site of metastatic deposit) generally can be predicted by the location of the primary tumor and its vascular and lymphatic drainage

• Many tumors metastasize to the organ that presents the first capillary bed they encounter.

• However, in many cases the natural pathway of drainage doesn't explain the distribution of metastasis.

• Why tumors choose certain sites for their metastatic spread and not others?

• This is related to:

• A. expression of adhesion molecules in the tumor cells, whose ligands are present in the endothelium of target organs

• B. expression of chemokines and their receptors

• C. once they reach the target site, tumor cells must colonize the site. Their growth in the metastatic site depends on the host stroma. If the host stroma at a specific site doesn't allow the tumor cells to live there, they cannot survive.

• Although tumor cells can escape their site of origin it is more difficult for them to colonize new sites.

• Tumor cells are continually shed from tumors, some of which can be detected in the blood even in people who will never have metastases. Because these cells fail to live in the new environment.

• Some though might live for long periods and be dormant and form metastases later when there are suitable conditions.

• Tumor dormancy is described mainly in melanoma, breast and prostate cancer. This means these tumors can recur a long time after initial treatment.

**Tumor dormancy: Prolonged survival of micro-metastases without progression.

Molecular genetics of metastases

• Are there any genes that control the metastatic phenotype?

• Possibly TWIST and SNAIL/ SLUG. They promote epithelial to mesenchymal transition (EMT).

EMT

• = tumor cells downregulate some epithelial markers like E cadherin and upregulate some mesenchymal markers like vimentin and sma (smooth muscle actin)

• These molecular changes are associated with phenotypic changes, so the cells become spindly, and functional change (they are more capable to invade and metastasize).

Clinical aspects related to metastasis

• Metastasis is the single most important factor dictating outcome of cancer.

• Localized cancer that is confined to the organ it originated from has the best prognosis.

• We measure prognosis by the five year survival rate.

• 5 year survival means the percentage of people who live at least 5 years after being diagnosed with cancer.

• For example, 5-year survival rate of 65% means that 65 out of 100 people who are diagnosed with cancer will be still alive 5 years after the initial diagnosis.

• 5 year survival of Localized colorectal cancer is around 95% whereas it is 6% for metastatic colorectal cancer, so metastasis dramatically affects survival.

Tumor stage

• Tumor stage measures the extent of tumor spread in the body.

• For each tumor, there is stage called TNM stage.

• T measures the tumor size/ or extent of local invasion (depending on the tumor type)

• N measures lymph node involvement.

• M measures the presence of metastasis.

• The higher T, N or M, the higher the stage, which means the worse the prognosis.

Grading and staging of cancer

• Grading is determined by cytologic and histologic appearance of the tumor

• In general well differentiated tumors are less aggressive than poorly differentiated ones

• However, staging is more important than grading in determining outcome and prognosis.

Example of staging: colon cancer

• T: describes the extent of involvement of the wall.

• T1: tumor invades the mucosa and submucosa

• T2: tumor invades muscularis propria (muscularis externa)

• T3: subserosa (serosal fat) involved

• T4: direct invasion to adjacent structures.

• N: describes the number of LN involved

• M: describes if there is metastasis or not.

TNM Staging of cancer colon

Tis	Carcinoma in situ
T1	Tumor invades submucosa
T2	Extending into the muscularis propria
T3	Penetrating through the muscularis propria into subserosa
T4	Tumor directly invades other organs or structures
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 lymph nodes
N2	Metastasis in 4 or more lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Summary

• Angiogenesis provides tumors with blood, oxygen, nutrients and growth factors.
• The balance between pro-angiogenic (VEGF) and anti-angiogenic factors (TSP1) controls formation of new blood vessels. The balance is tipped towards more neoangiogenesis under the influence of HIF.

• Metastatic spread of cancer occurs via the invasion-metastatic cascade, the most important steps of which include degradation of ECM, vascular dissemination and homing.

• Tumor metastasis is controlled by genes including TWIST and SNAIL/ SLUG which promote epithelial to mesenchymal transition (EMT)

• Metastasis is the most important factor that determines the outcome which is measured by the 5 year survival.

• TNM stage describes the extent of tumor spread. Each tumor has a specific and different TNM stage.

• T refers to the size in some tumors or to extent of local invasion in others. N refers to lymph node involvement. M to distant metastasis.