Neoplasia lec4

Intro

• Cancer occurs due to successful breach of anticancer mechanisms, i:e of regulatory mechanisms in our cells and tissues that prevent uncontrolled proliferation.

• Each cancer cell needs to acquire certain phenotypic characteristics to become malignant.

• Of course, these phenotypic characteristics reflect genetic mutations (or alterations)

• The phenotypic characteristics needed for cancer cells to survive are called: the hallmarks of cancer.

Hallmarks of Cancer

• Hallmarks of cancer: changes in cell physiology resulting from genetic changes that result in cancer.

the original scientific work:

• Douglas Hanahan and Robert A. Weinberg published in 2000 a review article about the expanding knowledge of tumorigenesis. They suggested that ALL tumor cells need to acquire SIX traits in order for the cells to be transformed to malignant cells.

• These six traits were called: hallmarks of cancer

• The 2013 article described the 6 characteristics (hallmarks) and emphasized the importance of genomic instability and tumor promoting inflammation as two enablers of malignancy (they enable and help the development of the 6 hallmarks.

• Also two new, emerging hallmarks were discussed: evasion of the immune system and reprogramming of metabolism

• Moreover, the stromal, host derived cells are thought to play a major role in carcinogenesis as they provide a suitable microenvironment of the tumor to evolve.

• FOR CANCER TO DEVELOP: we need the 8 characteristics (hallmarks) plus the 2 enabling characteristics and the correct microenvironment.

• All the above are acquired as mutations or epigenetic alterations accumulating over time so no single mutation is enough to cause cancer.

• Carcinogenesis is a multistep process.

• Each step results from a genetic change

• Each genetic change results in acquiring a certain phenotype (one of the hallmarks)

• There is no specific sequence of acquiring these phenotypes, the main issue is to acquire them all.

Hallmarks of cancer

• 1. Self-sufficiency in growth signals • 2. Insensitivity to growth inhibitory signals

• 3. Evasion of cell death • 4. Limitless replicative potential

• 5. Sustained angiogenesis • 6. Ability to invade and metastasize

• 7. Reprogramming of metabolism • 8. Evasion of the immune system

Two enablers

• Enablers (help in the tumorigenesis process and set the right conditions for genetic changes to develop)

• 1. genomic instability • 2. Inflammation

Tumor microenvironment

• Tumors need a suitable environment to flourish.

• This is obtained from the host cells: Stromal cells, mainly fibroblasts and pericytes.

1. Self-sufficiency in growth signals

• Tumors proliferate regardless of the normal regulatory mechanisms.

• This is achieved by mutations in proto-oncogenes

• Oncogenes cause increased growth by increasing oncoproteins which act as growth factors, growth factor receptors, transcription factors etc.

Physiologic cell proliferation

• 1. Growth factor binds to its receptor

• 2. This causes transient limited activation of the receptor

• 3. The activated receptor activates signal transducing proteins on the inner leaflet of the plasma membrane and the transduced signal is transmitted through the cytosol to the nucleus

• 4. Activation of nuclear regulatory factors that regulate DNA transcription

• 5. Entry into cell cycle

*Increased growth can happen if there is interference with any of the 5 steps:

Increased GF, increased receptor number or activation, increased signal transduction, increased transcription factors, entry to cell cycle etc.

Growth factors

• Some tumors produce their own growth factors, ie factors they respond to.

• This creates an autocrine loop

• Eg glioblastomas produce PDGF and express its receptor

• Tumor cells can interact with their stroma to produce growth factors.

• This is an example of how microenvironment (interaction with host cells including stromal cells) can help tumors to grow.

GF receptors

• GF receptors can increase cell proliferation in two situations:

• 1. Overexpression of the receptor. So, Receptor is hyper responsive to GF even in levels that don't normally trigger proliferation.

• 2. Mutant receptor proteins. So the receptor itself is mutated and acquires a configuration that is always stimulated. This causes continuous mitogenic signal even in the absence of GF.

** Remember that when a GF (or indeed any ligand) binds to its receptor, this causes conformational changes in the receptor proteins, so its shape changes and this change is what activates the receptor.

If there is a mutation that causes conformational change resulting in the receptor's shape being in the active state, then we don't need any stimulator for the receptor to function! It's in the alert, functioning state continuously.

Signal transducing proteins

• Main signal transducing proteins involved: RAS and ABL

RAS

• RAS is the most commonly mutated oncogene in humans

• 30% of human cancers contain RAS mutation

• Even higher incidence in colon and pancreatic carcinomas

<u>How does RAS function normally?</u>

• RAS is a small protein that binds GDP and GTP (it's a G protein)

• It is inactive with GDP binding. If a growth factor binds to a receptor, GDP is switched to GTP. This Actives RAS. Activation is short lived as GTPase hydrolyses GTP to GDP. GTPase activating proteins (GAPs) prevent over activation of RAS, so they act as brakes of RAS activation.

**if the activation is larger than the regulation it will lead to uncontrolled growth then eventually cancer

• Activated RAS acts via two pathways to send signals to the nucleus

1. mTOR pathway.

2. RAF- MAPK pathway

These two pathways send messages to the nucleus to express transcription factors that allow cells to enter cell cycle and proliferate.

• If 1 or 2 are mutated it can mimic RAS effect. Eg RAF mutated in 60% of melanomas

<u>How RAS is activated (mutated)</u>

• Point mutation in an amino acid residues within the GTP binding pocket or in the enzymatic region of GTP hydrolysis

• Both result in defective hydrolysis. Leading to trapped RAS in active phosphorylated GTP bound RAS.

ABL

• Proto-oncogene with tyrosine kinase activity regulated by internal negative regulatory domain

• ABL-BCR translocation. Results in a hybrid gene

• The hybrid gene produces novel tyrosine kinase which is always active and stimulating proliferation. This is the Philadelphia chromosome we talked about previously.

• ABL-BCR pathway activates all the downstream signals of RAS.

• CML =chronic myelogenous leukemia : t(9;22)= Philadelphia chromosome. ABL-BCR fusion gene, tyrosine kinase which is always turned on.

• Kinase inhibitors can be used to treat CML

• Imatinab/gleevec Inhibits the kinase and treats the leukemia

• = targeted therapy

Nuclear transcription factors

• Most commonly involved in human cancers: MYC

myc

• Can activate or repress expression of other genes

• Myc activates cyclins and cyclin dependent kinases CDK (so cells enter cell cycle and divide)

• Myc also inhibits cyclin dependent kinase inhibitors (CDKI)

Entry into cell cycle

• All the stimuli mentioned till now aim for quiescent cells to enter the cell cycle.

• Each phase in the cell cycle depends on successful completion of the previous one

• Cycle stops when essential gene function is lost

<u>cyclins</u>

• Progression through cell cycle, is regulated by proteins called cyclins

• Cyclins activate CDK (cyclin dependent kinases)

• Cyclin and CDK form complexes that phosphorylate target proteins that drive the cell through the cell cycle.

• Cyclins : D, E, A , B (they appear in this sequence) check sequence from slides

• SO: cyclin/CDK complexes cause proliferation.

• Theses are inhibited by cyclin dependent kinase inhibitors (CDKI)

• CDKI important for enforcing the checkpoints and delaying cell cycle.

• Mutations causing increased cyclins or CDK cause self sufficiency in growth signals.

• Mutations inhibiting CDKI will cause increased growth.

• Examples: cyclin D is activated in several tumors mainly lymphomas.

summary

• Transformed cells acquire several mutations resulting in several phenotypes.

• There are 8 phenotypes needed in each transformed cell and these are called the hallmarks of cancer.
• All these hallmarks must be gained through mutations, but there is no specific sequence for acquiring them.

• We don't need 8 mutations for the 8 phenotypes as one mutation might cause more than one phenotype.

• these 8 are: self sufficiency of growth factors, insensitivity to growth inhibitory signals, evasion of cell death and the immune system, changes in metabolism, immortality , sustained angiogenesis and ability to invade and metastasize.

• Genomic instability and inflammation act as enablers of malignancy; they set the proper environment for mutations to occur.

• Tumors also need a proper microenvironment provided by host stromal cells.

• Self sufficiency in growth signals can occur through increased growth factors, growth factor receptors, signal transduction proteins, transcription factors or cell cycle stimulators.

• GF can be synthesized by tumor cells or host stromal cells.

• GF receptors can be activated via overexpression or changes in their architecture that makes them active even without binding to GF.

• Signal transduction can increase via increase in any protein involved in second messengers that convey growth signals to the nucleus. These include RAS and ABL plus their downstream protein pathways (BRAF- MAP kinase and MTOR pathways)

• RAS is the most commonly mutated oncogene in humans.

• RAS is a G protein that is stimulated upon phosphorylation of GDP to GTP.

• Point mutations that cause entrapment of RAS in the activated state cause cell transformation.

• ABL is a protooncogene that can be stimulated via translocation (9;22) with formation of ABL-BCR fusion gene that encodes a kinase which is active and causes cell proliferation. This causes a leukemia that can be treated by blocking the kinase.

• Cell cycle is stimulated by cyclins/ Cyclin dependent kinase(CDK) complexes. Increase in Cyclins or CDK can transform cells.

• Cyclin/CDK complexes are normally regulated by CDK inhibitors.. A decrease in the inhibitors can also transform cells.