Neoplasia 18 lecture 6

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ILOS

- 1. understand the role of TGF beta, contact inhibition and APC in tumorigenesis.
- 2. implement the above knowledge in understanding histopathology reports.
- 3. understand the basic concepts of cell aging.
- 4. realize the importance of avoiding senescence as a hallmark of cancer.

Subjects discussed in this lecture:

- 1. continuation of second hallmark: insensitivity to growth inhibition.
- A. TGF beta pathway
- B. Contact inhibition
- C. APC gene

- 2. third hallmark: limitless replicative potential.

Continuation of insensitivity to growth inhibitors

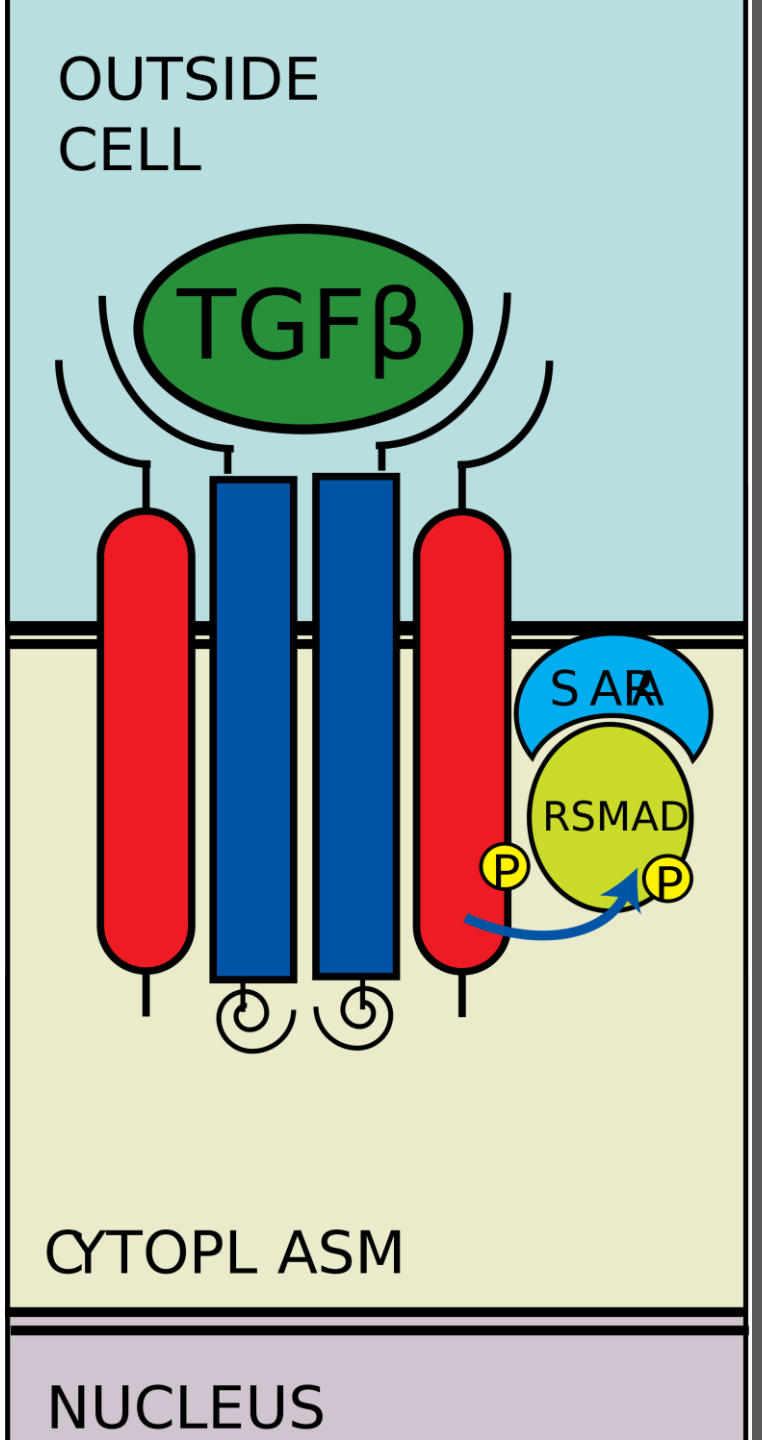
- RB and TP53 genes which we discussed previously cause growth inhibition by controlling the cell cycle.
- There are other genes that are involved in inhibiting proliferation.
- Inhibitory signals are similar to stimulatory ones regarding their mode of action.
- This means there is an inhibitory factor that binds to a receptor which causes transmission of the signal through cytosolic proteins to the nucleus to inhibit transcription factors.
- The steps above are well understood in growth factors pathways (which we already discussed) but for growth inhibition the specific molecules involved are not exactly known.
- The best known pathway of growth inhibition is the TGF beta pathway which we will discuss next..

TGF beta pathway

- TGF beta (transforming growth factor beta) is a potent inhibitor of cell proliferation.
- TGF beta binds to receptors.
- Receptors activated .. Transmit signal through SMAD proteins to the nucleus
- Transmitted signals to the nucleus result in transcriptional activation of CDKIs and repression of MYC and CDK4.
- The result is growth inhibition.

TGF Beta

- TGF beta is a negative growth regulator.
- It binds to transmembrane receptors
- This binding stimulated second messengers in the cytosol.. Of the SMAD family
- The message reaches the nucleus: to inhibit growth through upregulation of CDKI and down regulation of CDK4 and MYC.



- Mutations affecting TGF beta signaling causes cancer
- These mutations involve TGF beta receptor or SMAD molecules that transduce anti-proliferative signals from the receptor to the nucleus
- Mutations affecting type 2 receptor seen in colon, stomach and endometrial cancer
- SMAD4 is mutated in pancreatic cancer.

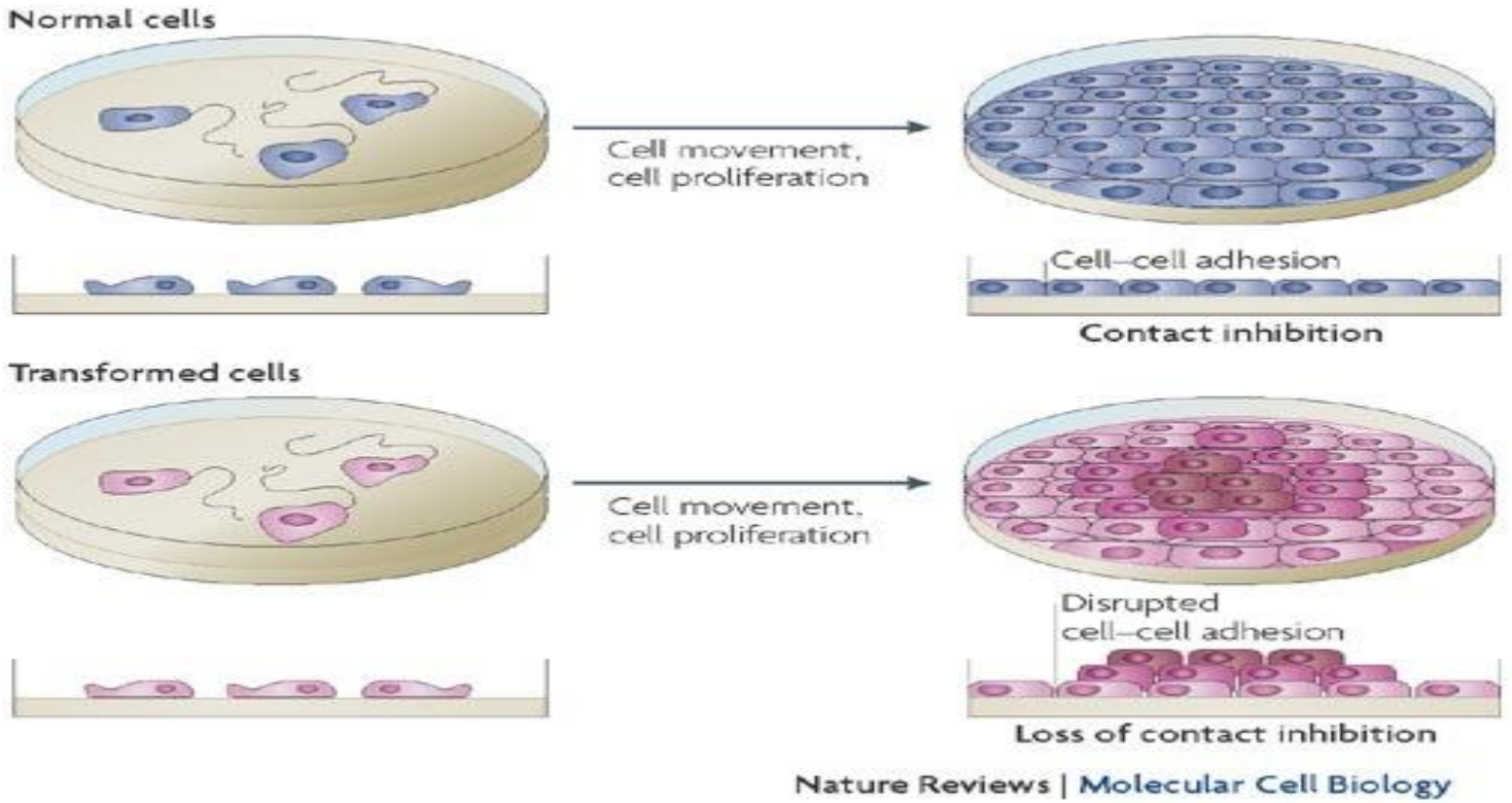
note

- 100% of pancreatic 83% of colon at least one component of is TGF b pathway is mutated

Contact inhibition

- Normally cells proliferate in organized fashion. Monolayers are formed and contact between adjacent cells inhibits further growth.
- This process is called contact inhibition.
- In cancer cells: contact inhibition is lost so cells pile upon each other.

Contact inhibition



- Contact inhibition is mediated by cadherin molecules.
- If E cadherin (= epithelial cadherin) is lost: no contact inhibition….. Cells proliferate in an uncontrolled fashion.

- E cadherin’s function is facilitated by NF2 (neurofibromatosis 2) protein

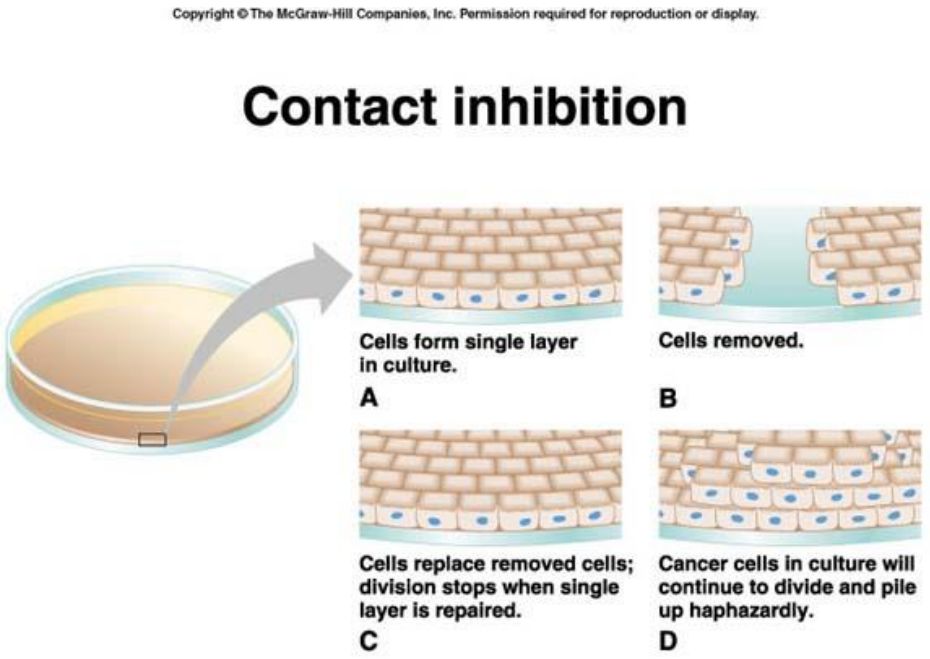
- NF2 gene’s protein product is neurofibromin 2=merlin which facilitates contact inhibition
- Homozygotic loss of NF2 causes neural tumors (neurofibromatosis syndrome)

E cadherin

- E cadherin is important to “keep cells together”
- Tumors with loss of E cadherin tend to grow in an individual cell fashion : they don’t form glandular or other cohesive structures.
- Example: there are two types of breast carcinoma, invasive ductal and invasive lobular.. The tumor cells in the ductal type form glandular structures, whereas in the lobular type, they grow in individual cell pattern.

merlin protein and contact inhibition

- Please remember that contact inhibition is an important process to limit and regulate cell growth
- If contact inhibition is lost growth can go unchecked
- E cadherin is the most important factor causing contact inhibition
- Merlin protein facilitated contact inhibition
- if merlin is lost then contact inhibition is lost and tumors occur
- Loss of function mutation in merlin protein is the underlying genetic defect in NF2(neurofibromatosis type 2)



APC (adenomatous polyposis coli) gene

- APC gene is a tumor suppressor gene
- Suppresses growth by regulating intracellular **beta catenin** level.

- Beta catenin is a protein that stimulates growth… APC protein acts as a tumor suppressor through inhibiting beta catenin function.

Functions of beta catenin

Beta catenin stimulates growth by two ways:

1. Inhibits contact inhibition by binding to E cadherin and stimulating TWIST and SLUG transcription regulators that decrease cadherin expression
2. Stimulates growth by increasing transcription of growth promoting genes like cyclin D1 and MYC .

- APC suppresses growth by being part of a complex that destructs the beta catenin.

- Beta catenin is an important component of WNT signaling
- WNT is a soluble factor that induces cell proliferation by binding to a receptor and transmit signals that prevent degradation of beta catenin
- Now beta catenin to nucleus .. Transcription activator in conjunction with another molecule TcF

recap

- In quiescent cells not exposed to WNT, cytoplasmic beta catenin is degraded by destruction complex (of which APC is a main component)
- Loss of APC means that B catenin is not degraded and WNT pathway activated without the WNT
- This leads to transcription of growth promoting genes cyclin D1 ,MYC and transcription regulators: TWIST AND SLUG that repress E cadherin and thus reduce contact inhibition

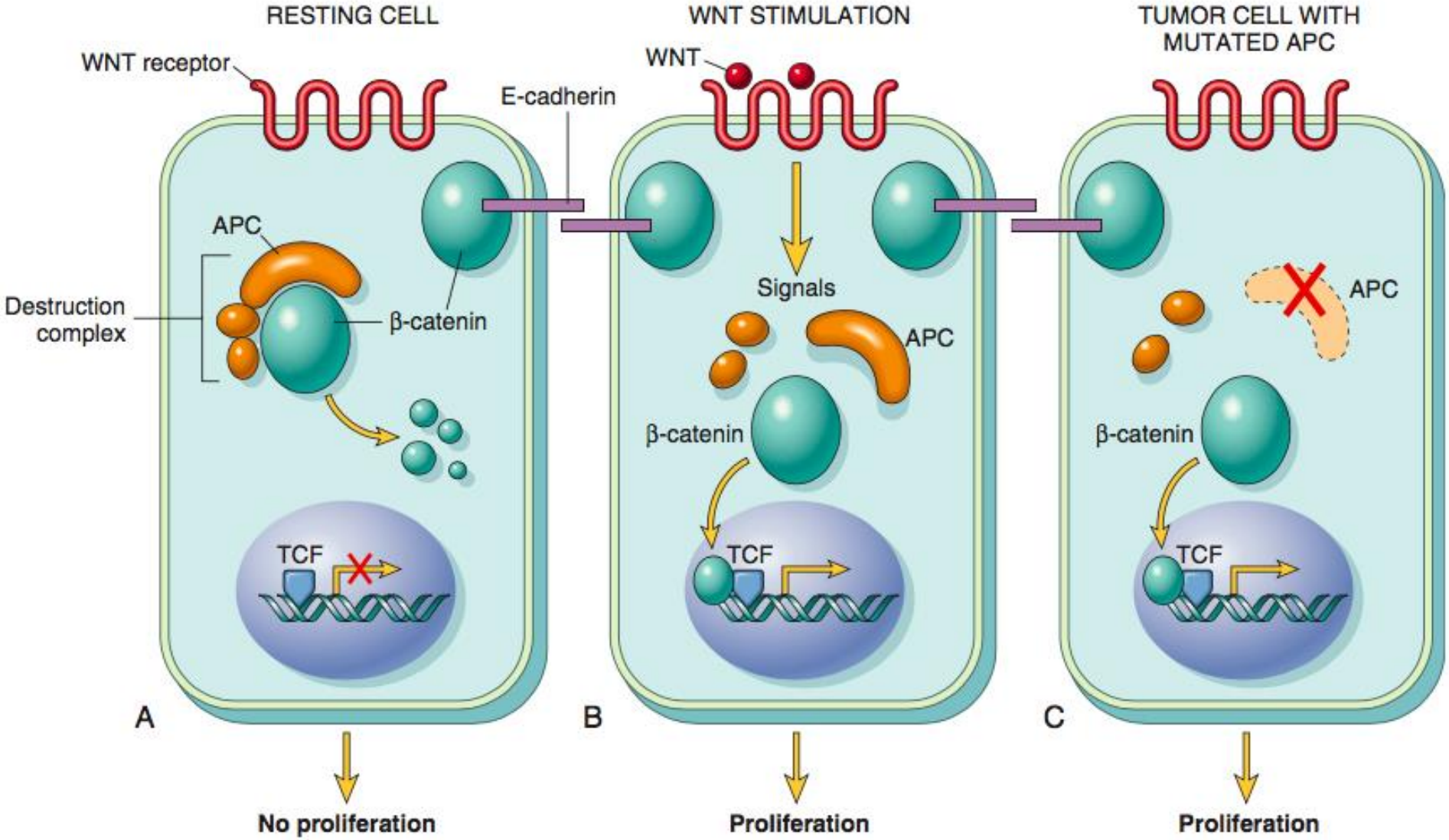
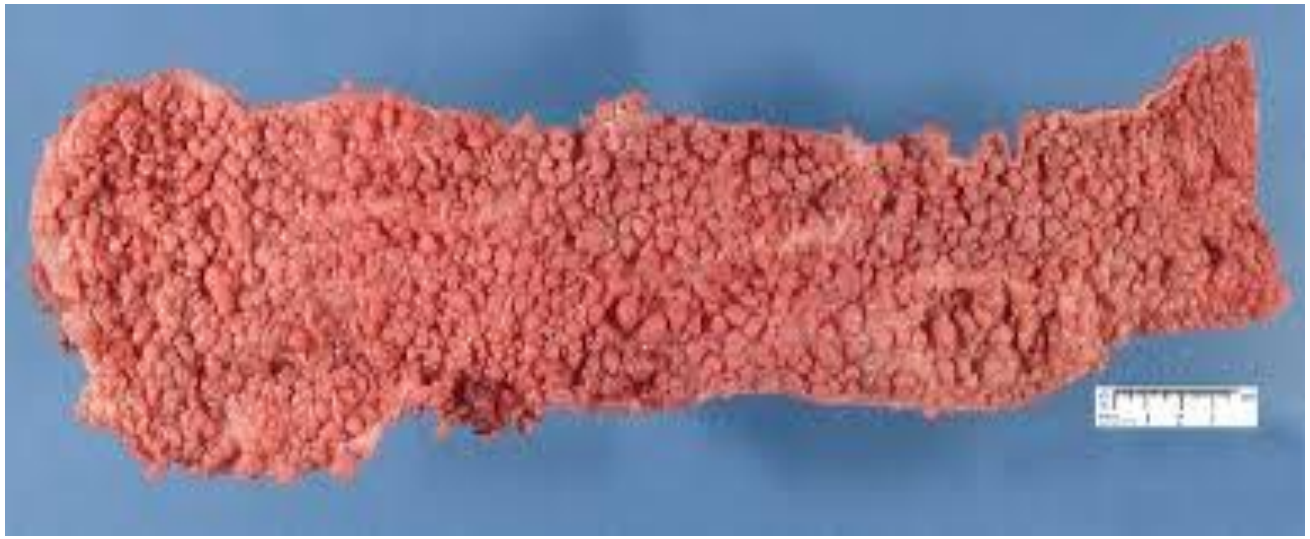


Fig. 6.22 The role of APC in regulating the stability and function of β-catenin. APC and β-catenin are components of the WNT signaling pathway. (A) In resting cells (not exposed to WNT), β-catenin forms a macromolecular complex containing the APC protein. This complex leads to the destruction of β-catenin, and intracellular levels of β-catenin are low. (B) When cells are stimulated by secreted WNT molecules, the destruction complex is deactivated, β-catenin degradation does not occur, and cytoplasmic levels increase. β-Catenin translocates to the nucleus, where it binds to TCF, a transcription factor that activates several genes involved in the cell cycle. (C) When APC is mutated or absent, the destruction of β-catenin cannot occur. β-Catenin translocates to the nucleus and coactivates genes that promote the cell cycle, and cells behave as if they are under constant stimulation by the WNT pathway.

APC adenomatous polyposis coli

- APC syndrome is similar to inherited retinoblastoma, both are inherited in an autosomal dominant fashion, but in both the gene responsible for the syndrome is a recessive, tumor suppressor gene.
- In APC syndrome :one APC allele lost in germ line. Patients with this single loss develop intestinal polyps (adenomatous polyps= adenoma).. Hundreds of adenomas.
- These patients acquire a second mutation in the other APC gene, and this homozygous loss results in colonic adenocarcinoma.
- Patients have 100% risk of malignancy, so prophylactic total colectomy is performed
- 70-80% of sporadic colon cancers have APC mutation
- Colonic cancers with normal APC have mutated beta catenin making them undegradable by APC

FAP syndrome: colon full of adenomas!



Third hallmark: limitless replicative potential

- Normal cells: limited capacity to duplicate (usually 60 -70 doublings)
- After these doublings cells lose capacity to replicate and become senescent
- This is because of progressive shortening of telomeres

CELLULAR AGING

- Age is one of the strongest independent risk factors for many chronic diseases, such as cancer, Alzheimer disease, and ischemic heart disease

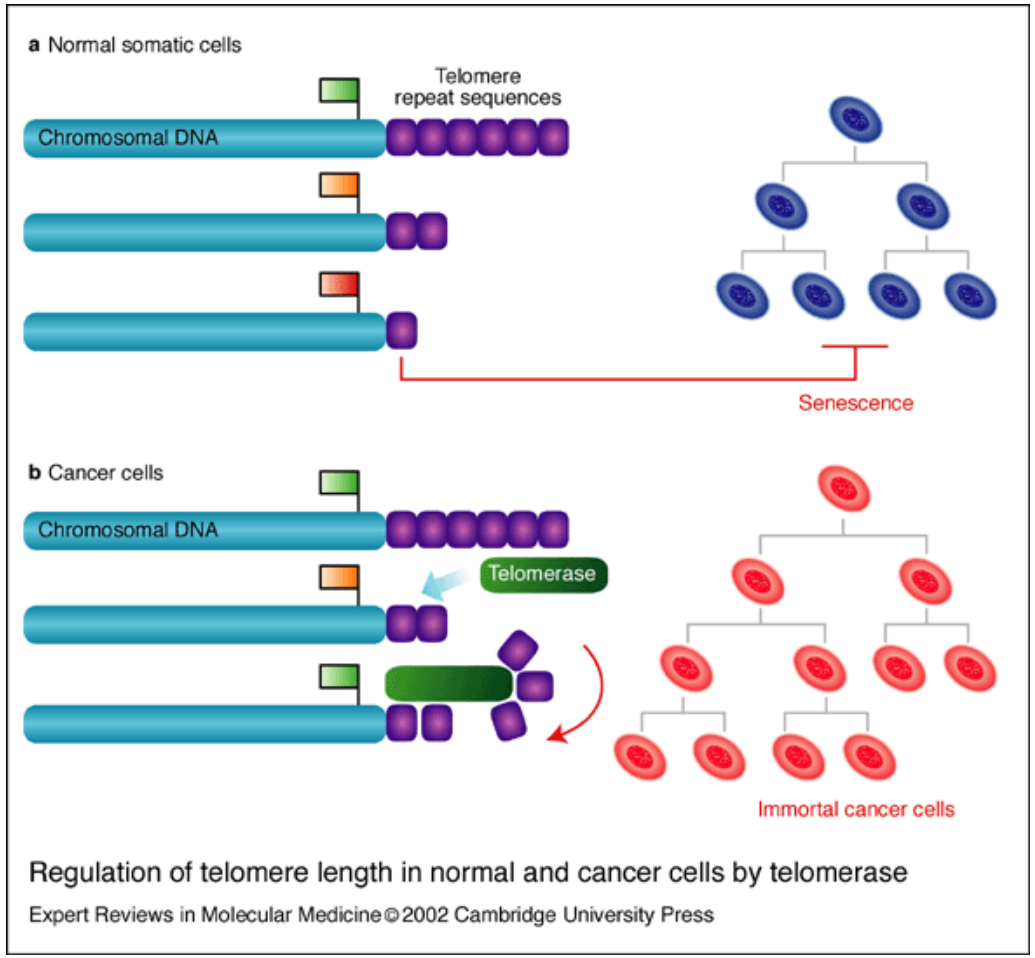
- *Cellular aging is the result of a* ***progressive decline in the life span and functional capacity of cells****.*

- *Several mechanisms (cumulative DNA damage, decreased cellular replication capacity, Defective protein homeostasis*

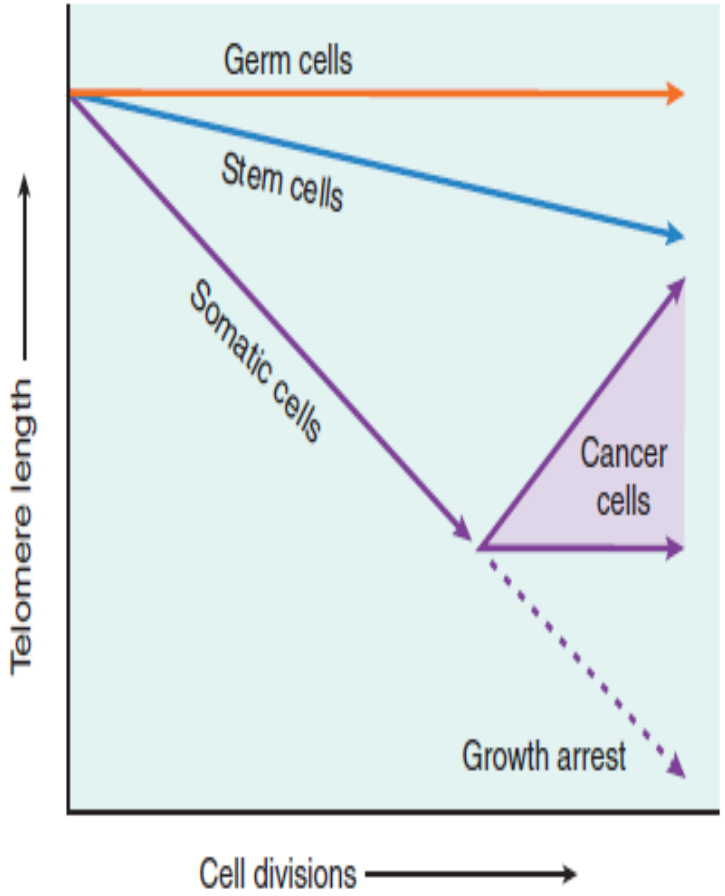
telomeres

- Each cell has a limited replicative potential.
- This is because chromosomes have repeated nucleotide sequences at the ends of each chromosome.
- With each cell replication, telomeres shorten.. Till they become too short and the chromosomal ends fuse together which causes cell death by apoptosis.
- Stem cells have limitless replicative potential because they have telomerase enzyme which uses its RNA nucleotide sequence to replace the lost telomeres.
- Cancer cells upregulate telomerase transcription and become immortal.

Cell Senescence & Telomeres



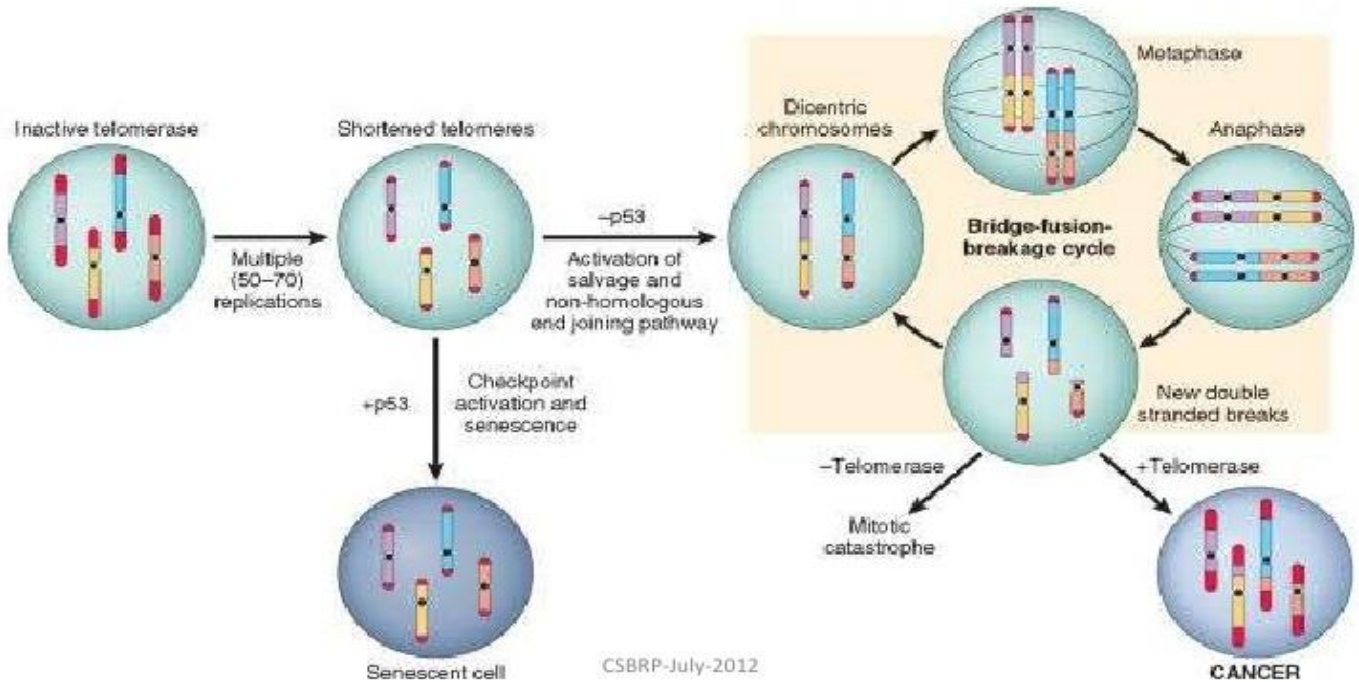
Regulation of telomere length in normal and cancer cells by telomerase



- Cells avoid senescence by activating telomerase.
- Telomere length is maintained in all cancer cells.. Mainly by upregulation of telomerase but also by other mechanisms like DNA recombinations

- If cells have short telomere and no telomerase… then shortened telomeres fuse and cells divide causing more DNA breaks (this happens of course if the cell cycle checkpoints are disabled)
- This bridging, fusion, breakage cycle continues and ends in mitotic catastrophe unless the cell acquires telomerase activation

Sequence of events in the development of limitless replicative potential



summary

- TGF beta- SMAD pathway is mutated in several cancers, mainly pancreatic and colorectal. The pathway is the most well understood growth inhibition one and if mutated, loss of growth inhibition occurs.
- Contact inhibition regulates cell growth. It is mainly mediated by E cadherin and merlin.
- Tumors with lost E cadherin result in non-cohesive, usually single cell growth.
- APC gene is a tumor suppressor gene mutated in familial and sporadic colorectal carcinoma.
- APC acts by being part of a destruction complex that destructs a growth stimulator (beta catenin).
- If the destruction complex is lost via deletions or deactivation mutations.. Beta catenin will be activated and translocated to the nucleus to stimulate other transcription factors.
- The third hallmark of cancer is ability to have limitless replications. This is acquired via upregulating telomerase enzyme.

Test your understanding: read this pathology report and spot the mistake there

- Sections taken from the breast mass show a tumor forming glandular structures lined by atypical cells with a high mitotic rate. The tumor cells are are negative for E cadherin stain. The features are those of an invasive lobular carcinoma.

answer

- This is a strange report that doesn’t make sense!
- If the cells form glands then this is a ductal not lobular carcinoma.
- Negative E cadherin means that the cells lost the protein that glues them together, so they should grow in an individual cell pattern rather than in glandular structures.
- Note: if the E cadherin is really negative then the tumor is a lobular carcinoma.. But in this case it will not form glands.

- TAKE HME MESSAG: always read histopathology reports carefully. Phone your pathologist if you need an explanation of any point or to question any findings or results… being able to correctly interpret these reports and to keep good communication with the pathologist is important to give your patients the correct management.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