

Neoplasia 2023/24

lecture 7

Dr Heym Awad

MD, FRCPath

Second hallmark of cancer: insensitivity to growth inhibitors, continuation

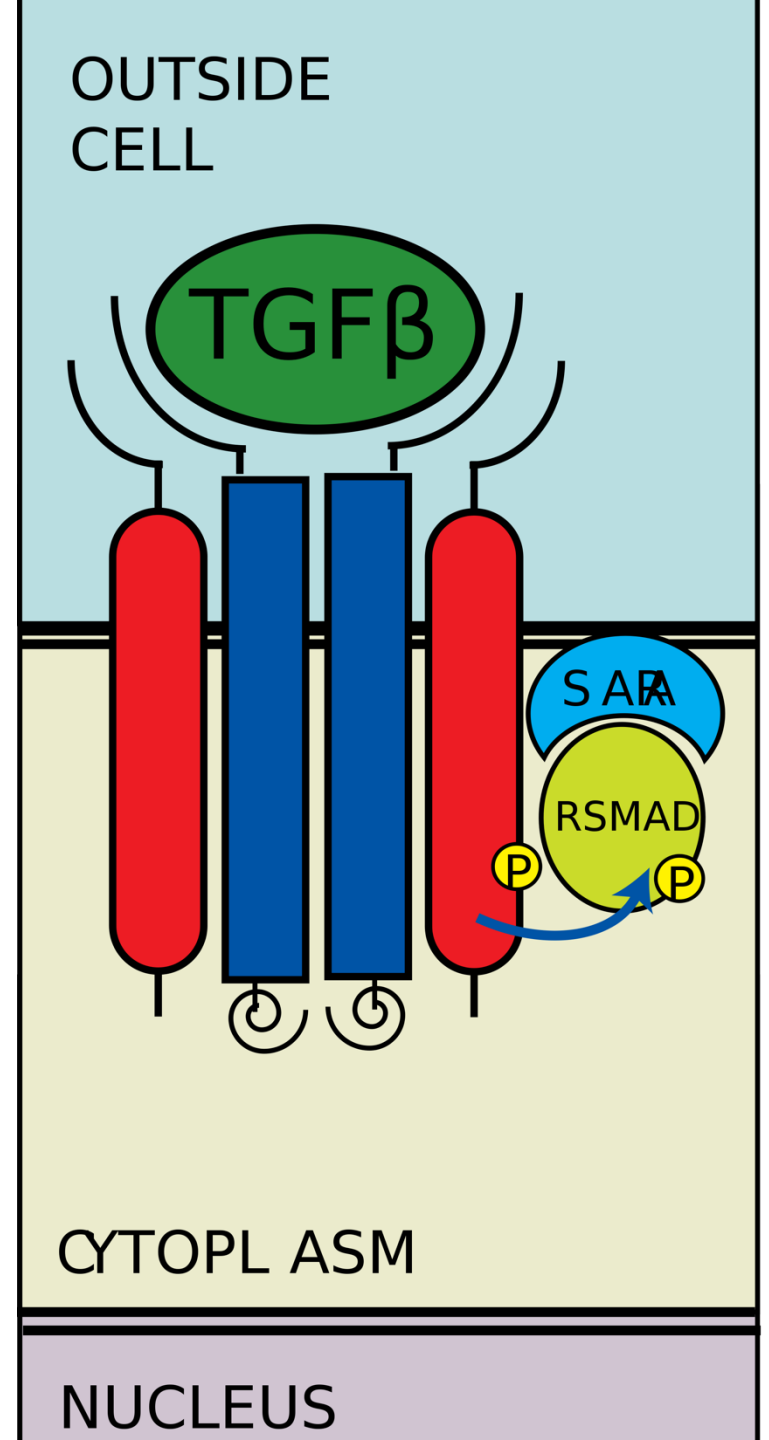
- Normally growth inhibition is achieved by tumor suppressor genes. Loss or decreased function of tumor suppressor genes allows cancer cells to proliferate without being affected by inhibitory growth signals.
- Main genes/ pathways mutated to cause insensitivity to growth inhibition:
 1. RB gene
 2. TP53 gene
 3. TGF beta pathway
 4. Contact inhibition
 5. APC gene

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 suppression 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 stimulates 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 TGF beta receptor seen in colon, stomach and endometrial cancer
- SMAD4 is mutated in pancreatic cancer.

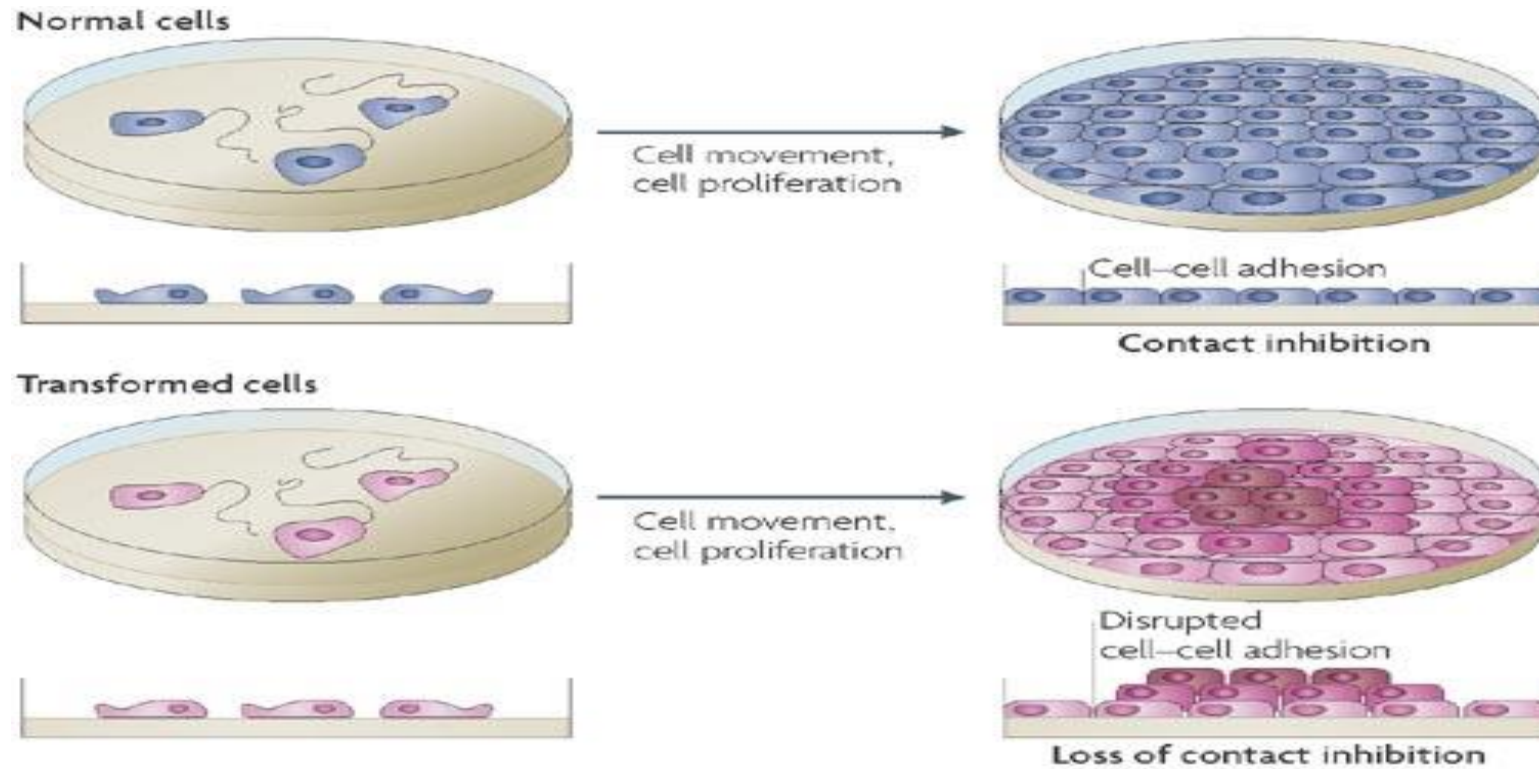
note

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

Contact inhibition

- Normally cells proliferate in an 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

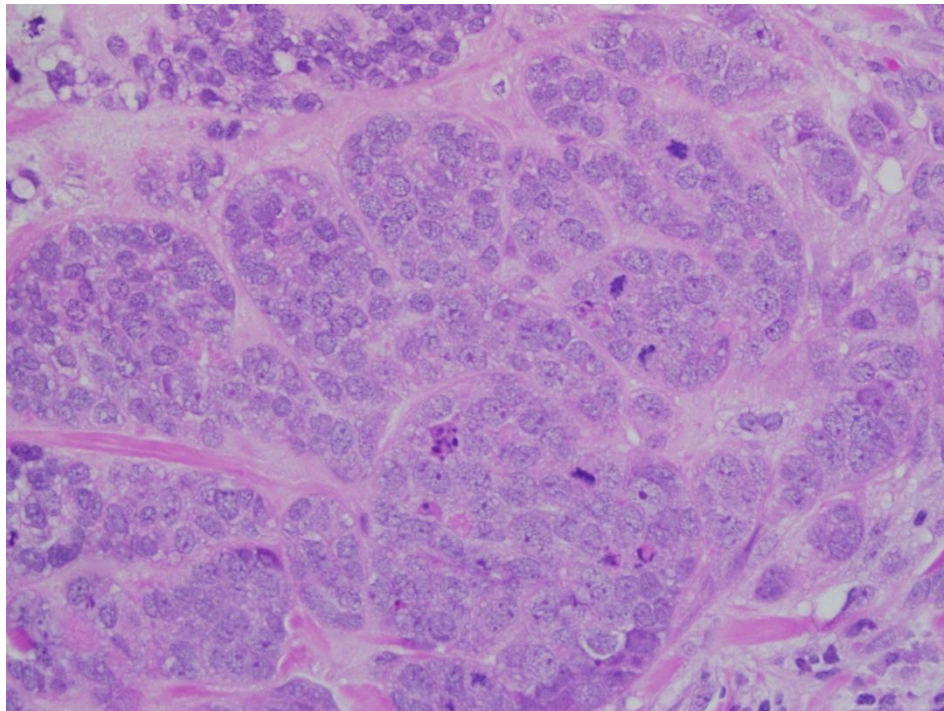


- Contact inhibition is mediated by cadherin molecules.
- If E cadherin (= epithelial cadherin) is lost: no contact inhibition.....
Cells proliferate in an uncontrolled fashion.

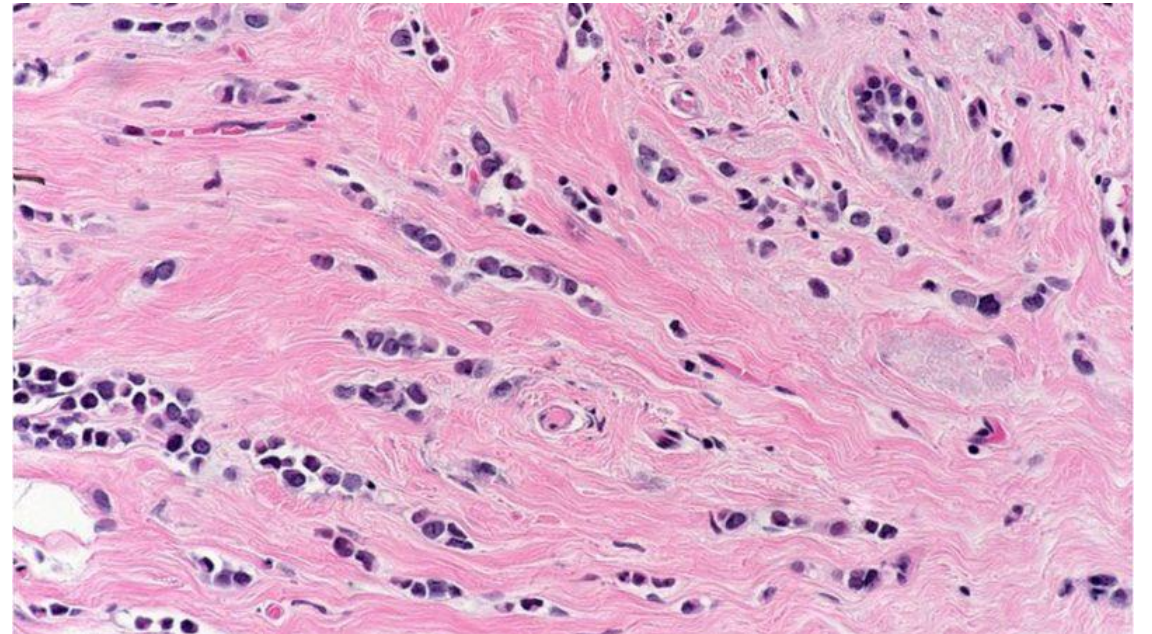
E cadherin

- 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. In this lobular pattern E cadherin is lost.. See next slide

Invasive ductal carcinoma, there is cohesion between cancer cells caused by E cadherin.



Invasive lobular carcinoma, E cadherin is lost so there is no cohesion. Tumor cells grow as individual cells.



APC (adenomatous polyposis coli) gene

- APC gene is a tumor suppressor gene
 - Suppresses growth by regulating intracellular **beta catenin** level.
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- 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 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 protein that induces cell proliferation by binding to a receptor and transmit signals that prevent degradation of beta catenin
- Undegraded beta catenin moves to the nucleus where it acts as a transcription activator

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 even 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

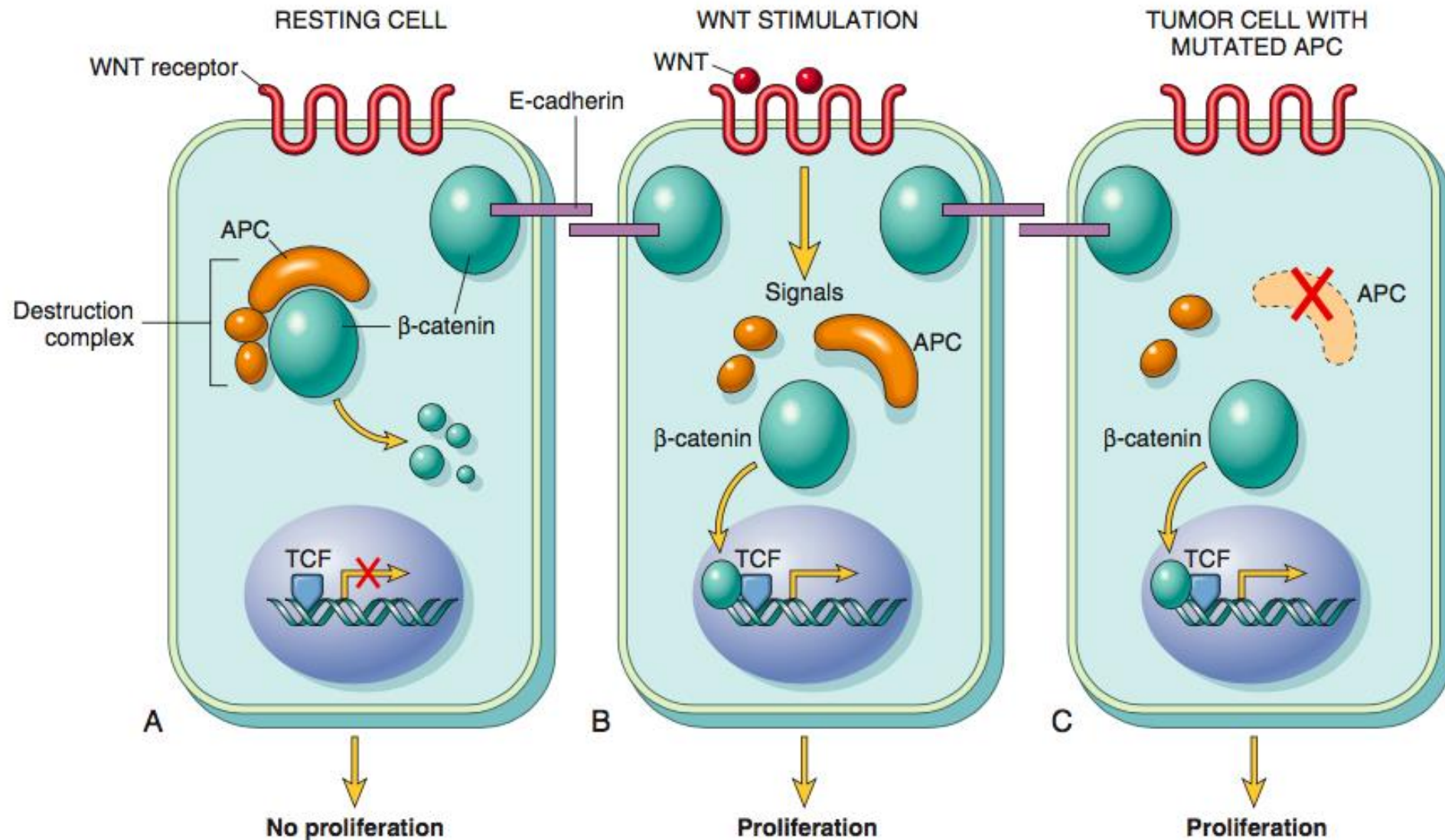


Fig. 6.22 The role of APC in regulating the stability and function of β -catenin. APC and β -catenin are components of the WNT signaling pathway. (A) In resting cells (not exposed to WNT), β -catenin forms a macromolecular complex containing the APC protein. This complex leads to the destruction of β -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.

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.

*Thank
you*

