

APC (adenomatous polyposis coli – tumor suppressor gene) → long arm Cr 5
gatekeeper gene

- cloned in 1991 through
 - identification of interstitial deletion on Cr5q in FAP pts (loss of heterozygosity – LOH)
 - linkage analysis
- later studies demonstrated that APC plays a pivotal role also in sporadic CRC (>70% – peculiar feature of CRC)
- > 90% APC gene mutation → premature STOP signal → truncated protein
this abnormal protein typical of APC mutations can be used for genetic screening

why is the role of the “non-mutated” APC gene product (i.e. APC protein) in physiological conditions?
what has β -catenin to do with?

- β -catenin: protein necessary to keep a monolayer cylindric type of epithelium together
- it belongs to a protein complex that contains GSK, axin, APC (destruction complex)

APC is the transporter protein, the other components are “skeleton” components, necessary for cell survival → because it is the transporter, it does NOT directly causes cancer

APC is responsible for β -catenin proteolysis

by 2 hit mutation or deletion, APC is downregulated

if β -catenin in the cytoplasm goes over the threshold level, it translocate into the nucleus going over the nuclear membrane (protein overflow)

gut (main) role: absorption

two types of absorption

1. transcellular
2. intracellular (sort of phagocytosis)

cells next to each other open and close → necessity to have “muscles”

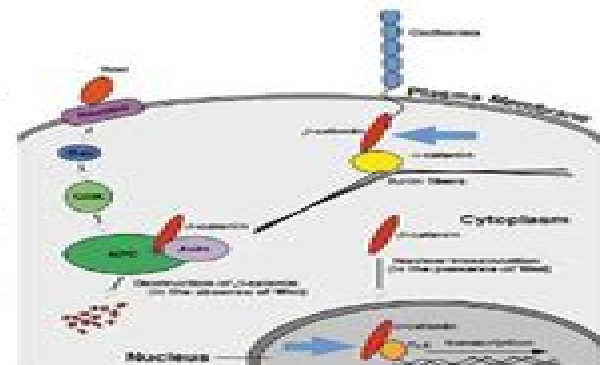
in physiological condition, APC is linked to GSK/axin/ β -catenin leading them to destruction

mutated APC → β -catenin accumulation with consequent translocation into the nucleus, linked to the TCF (= tumor cell factor) → this complex leads to oncogenes activation (transcription) in the nucleus

are APC mutation the only cause of β -catenin accumulation? what happens in patients with normal APC and high levels of β -catenin?

Wnt = wingless/intern gene whose recessive mutation is characterized by wingless *Drosophila Melanogaster*

- ➔ human genes coding for Wnt proteins: in the absence of Wnt ligands, β -catenin is destroyed
- ➔ Wnt → frizzled → dishevelled (Dsh) activation → high affinity to the destruction complex
Wnt is the ligand for frizzled receptors: when activated, this receptor activates an internal cytoplasmatic protein called dishevelled that, once activated, gets to the destruction complex (high affinity)
 - Wnt overexpressed leads to tumor onset due to β -catenin accumulation
 - absence of Wnt ligands, β -catenin is destroyed



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