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Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

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“Founding the Centre of Transgenic Technologies”

BIOCEV

Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

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Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

Talk focus

1. Canonical branch of the Wnt signaling pathway
2. Principles underlying intestinal homeostasis and malignant transformation thereof
3. Inherited colorectal cancer syndromes and murine experimental models
4. Sporadic cololectal cancerogenesis and ditto
5. Molecular stratification of colorectal disease

The canonical branch of the Wnt signaling pathway

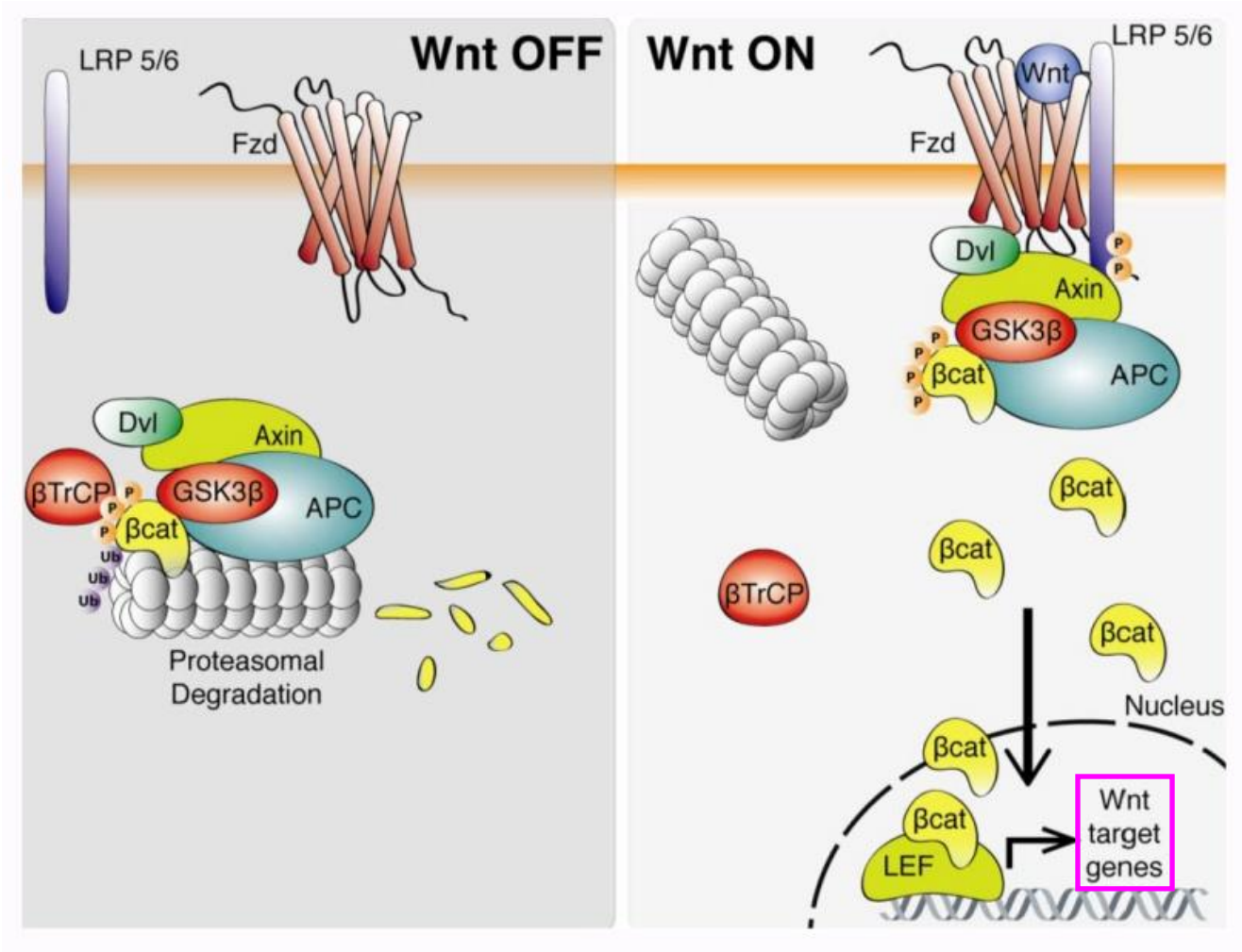
Mammals: 19 independent *WNT* genes

Role: involved in embryogenesis and self-renewal of adult tissues

Cellular processes governed by Wnt signaling: determination of cell fate, proliferation, stem cell self-renewal

Wnt target genes:
c-Myc, *Cyclin D1*, *Axin2*

Inappropriate activation leads to onset of cancer

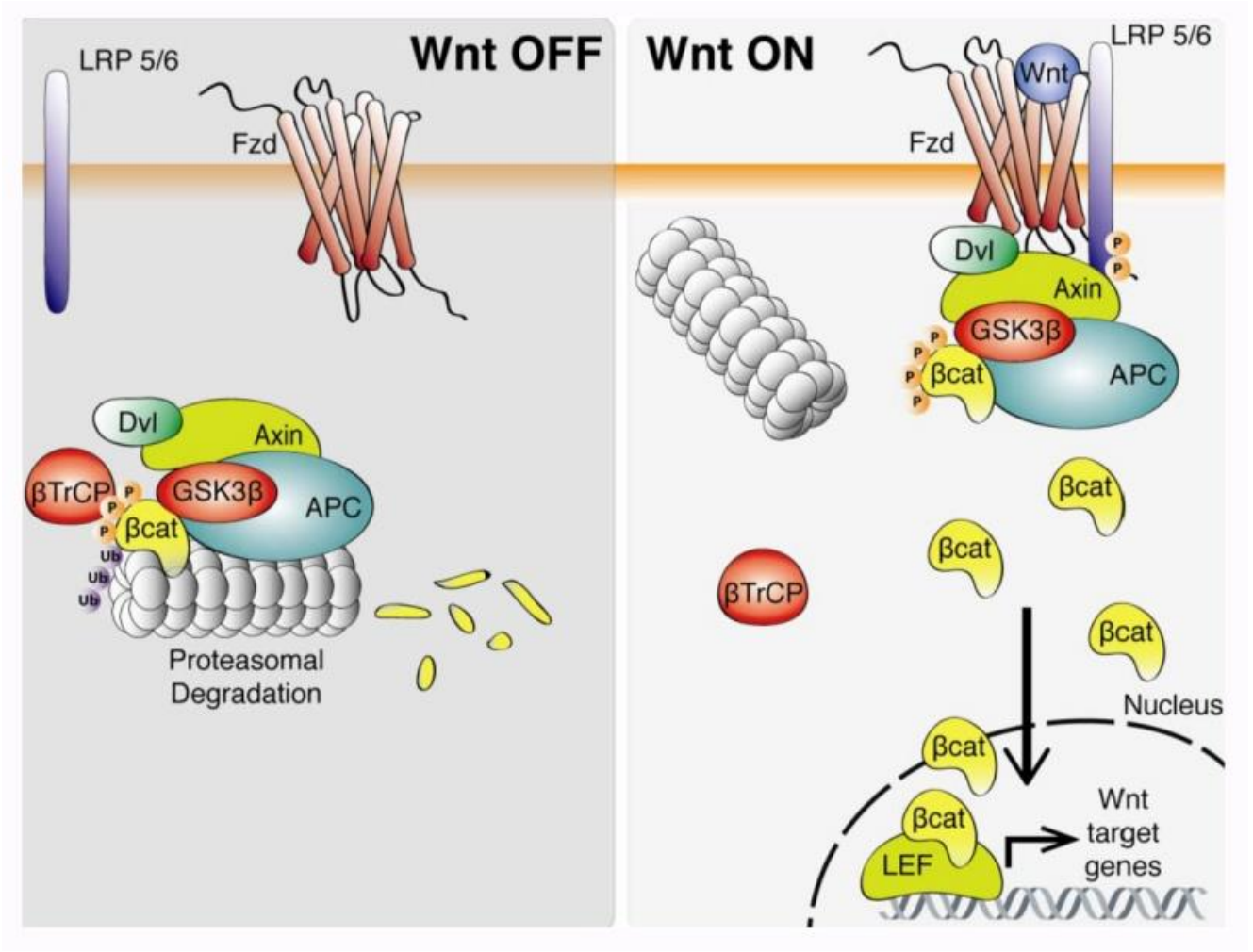


adopted from Inestroza, N. & Varela-Nallar, L.; Trends in Cell Signaling Pathways

The canonical branch of the Wnt signaling pathway

Question No.1

What is the central essence of beta-catenin signaling?

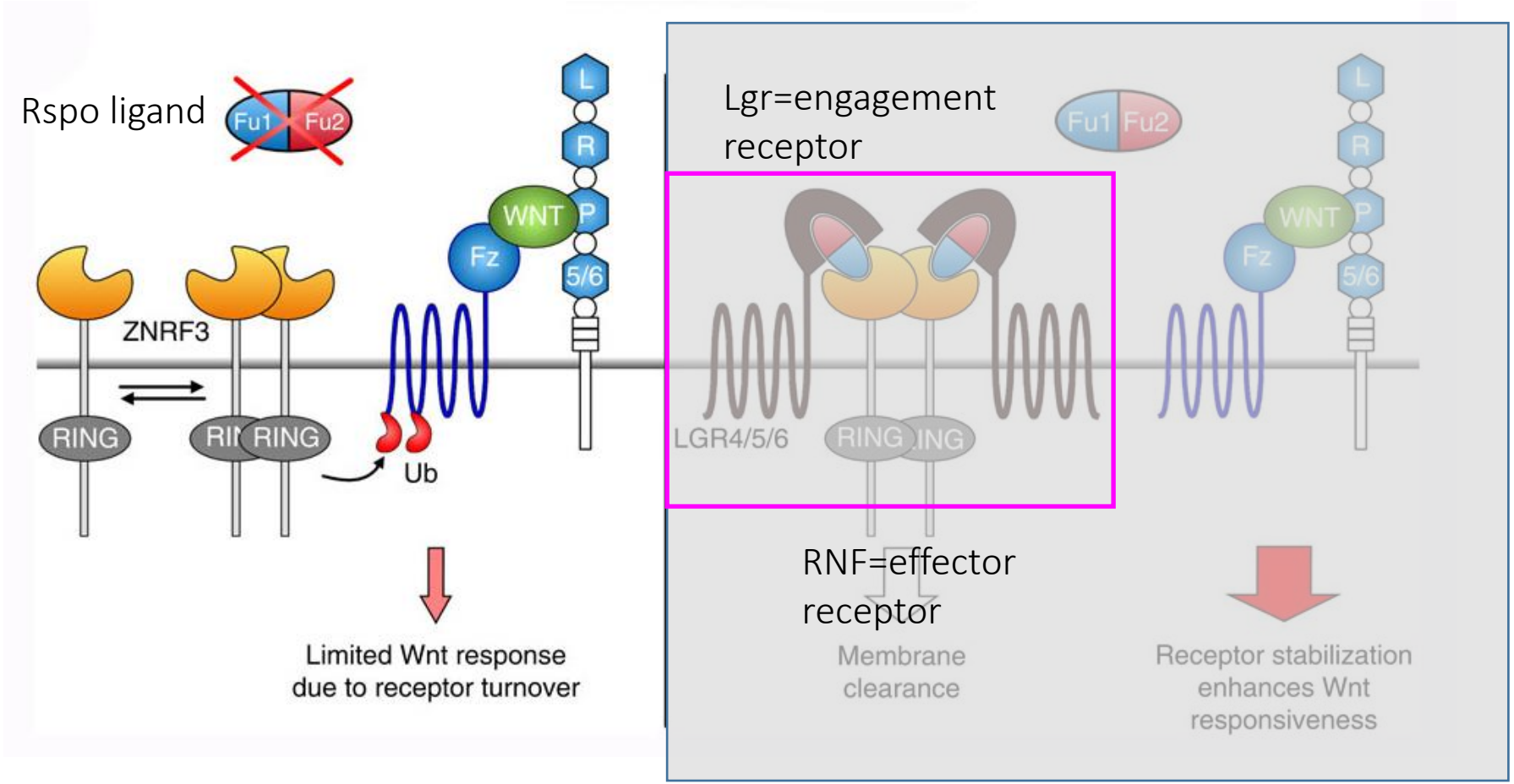


adopted from Inestroza, N. & Varela-Nallar, L.; Trends in Cell Signaling Pathways

The LGR-R-spondin interaction augments Wnt signaling

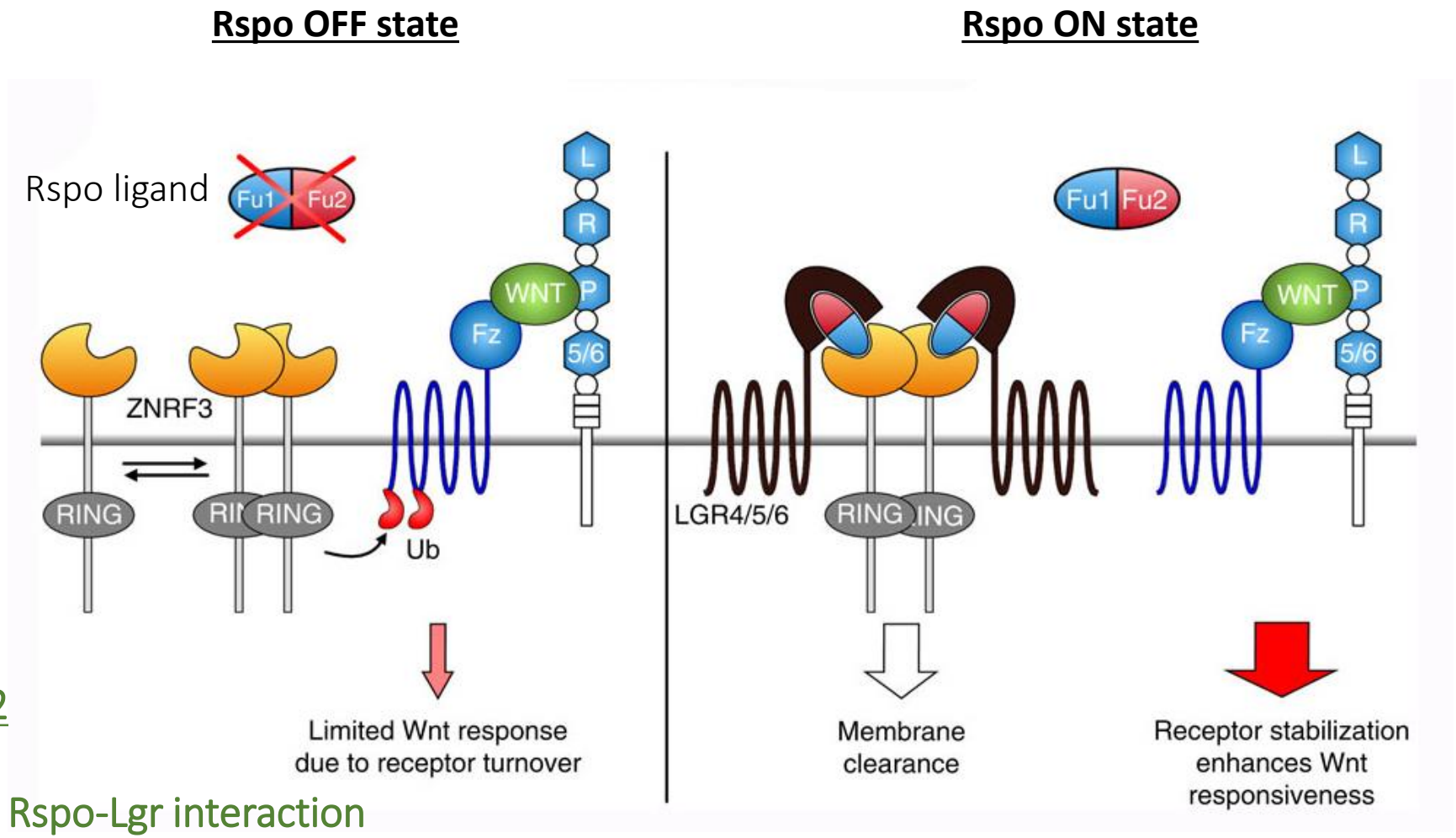
Rspo OFF state

Rspo ON state



adopted from Zebisch, M. *et al*.; Nature communications 2013

The LGR-R-spondin interaction augments Wnt signaling



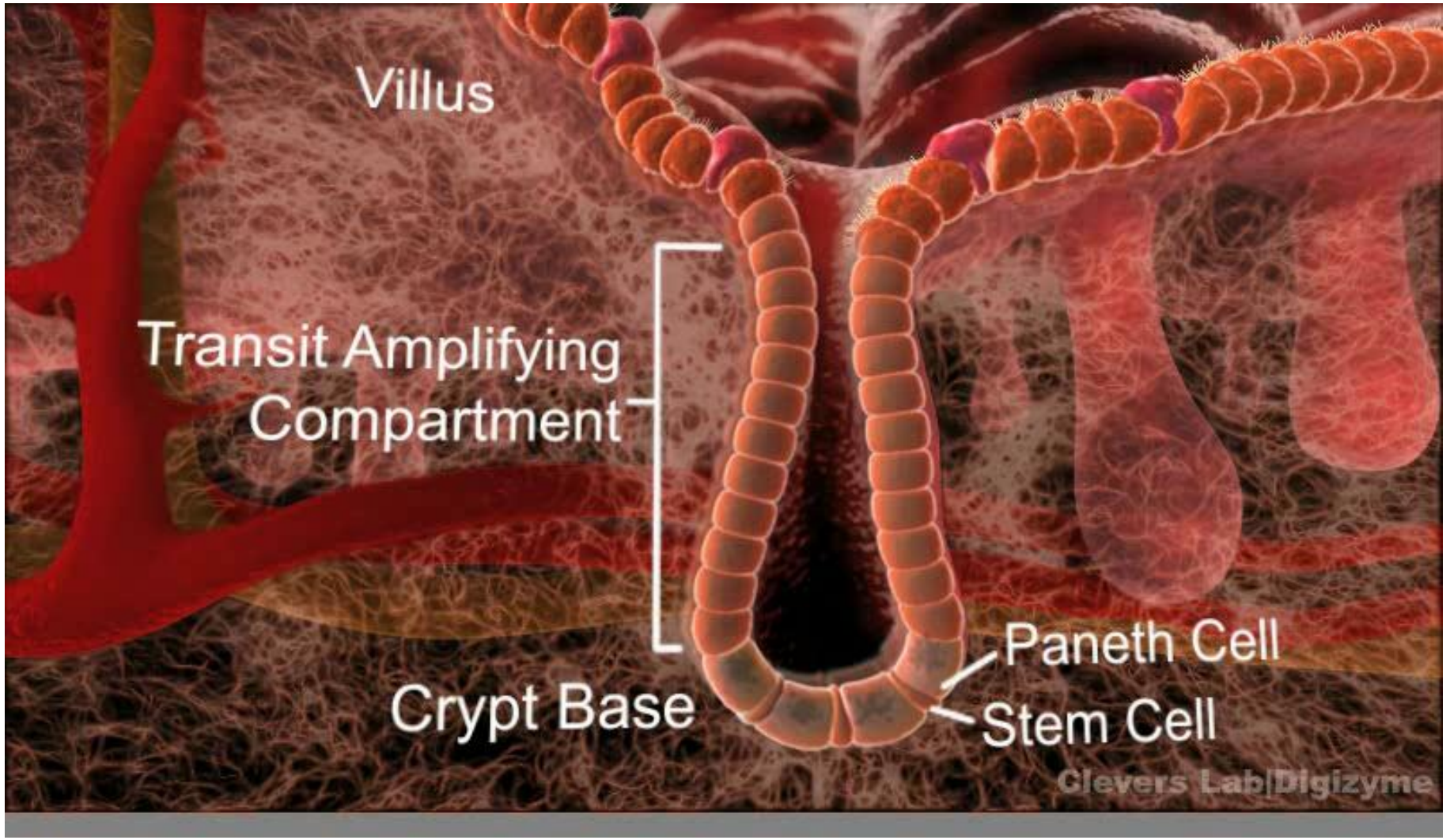
Question No.2

How does the Rspo-Lgr interaction augment Wnt signaling?

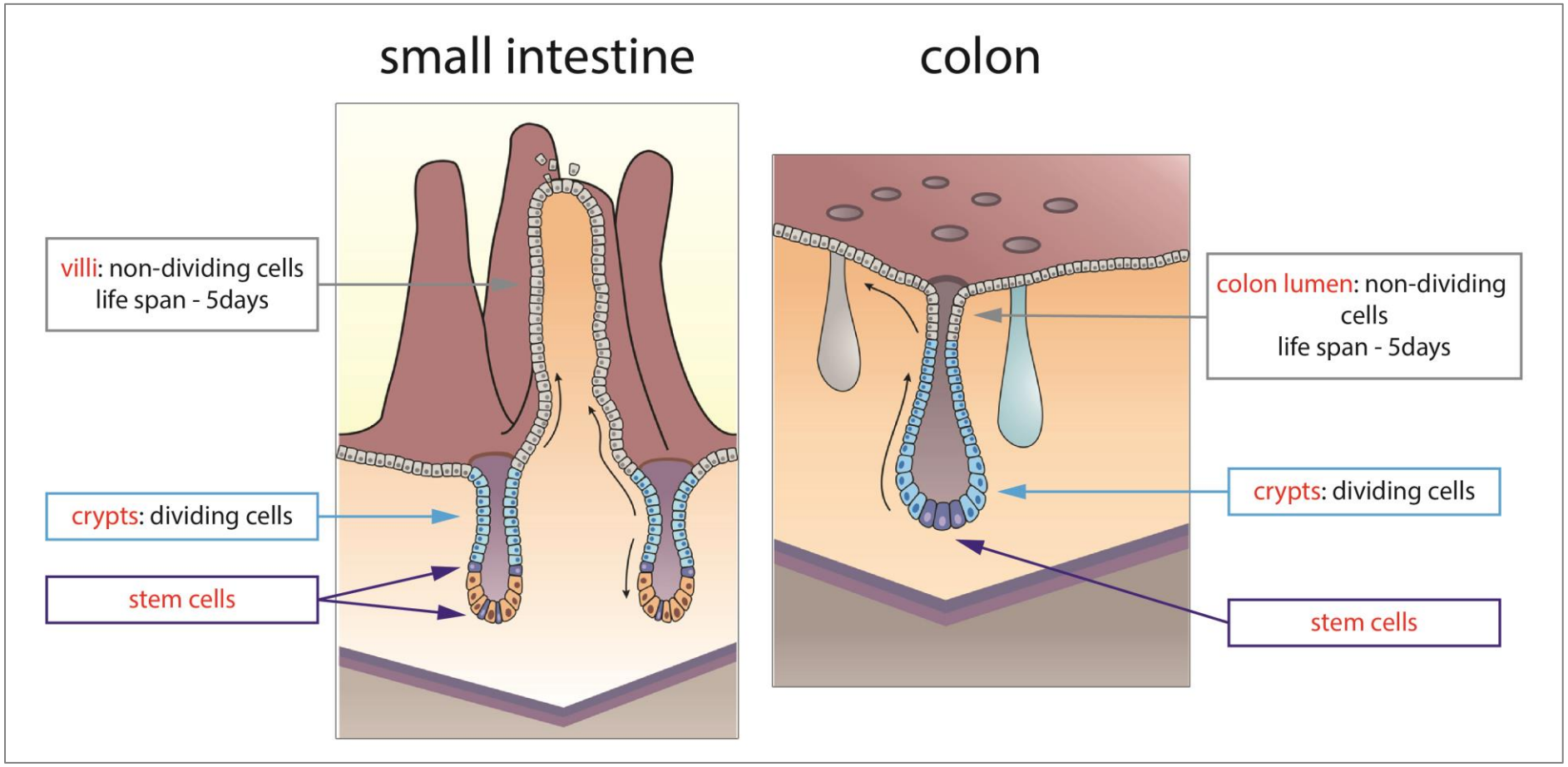
adopted from Zebisch, M. *et al.*; Nature communications 2013

The epithelial lining: architecture and principles underlying it´s self-renewal

Crypt base columnar (CBC) cells: non-quiescent stem cells from the crypt bottom



The crypt is the ”niche” for intestinal stem cells



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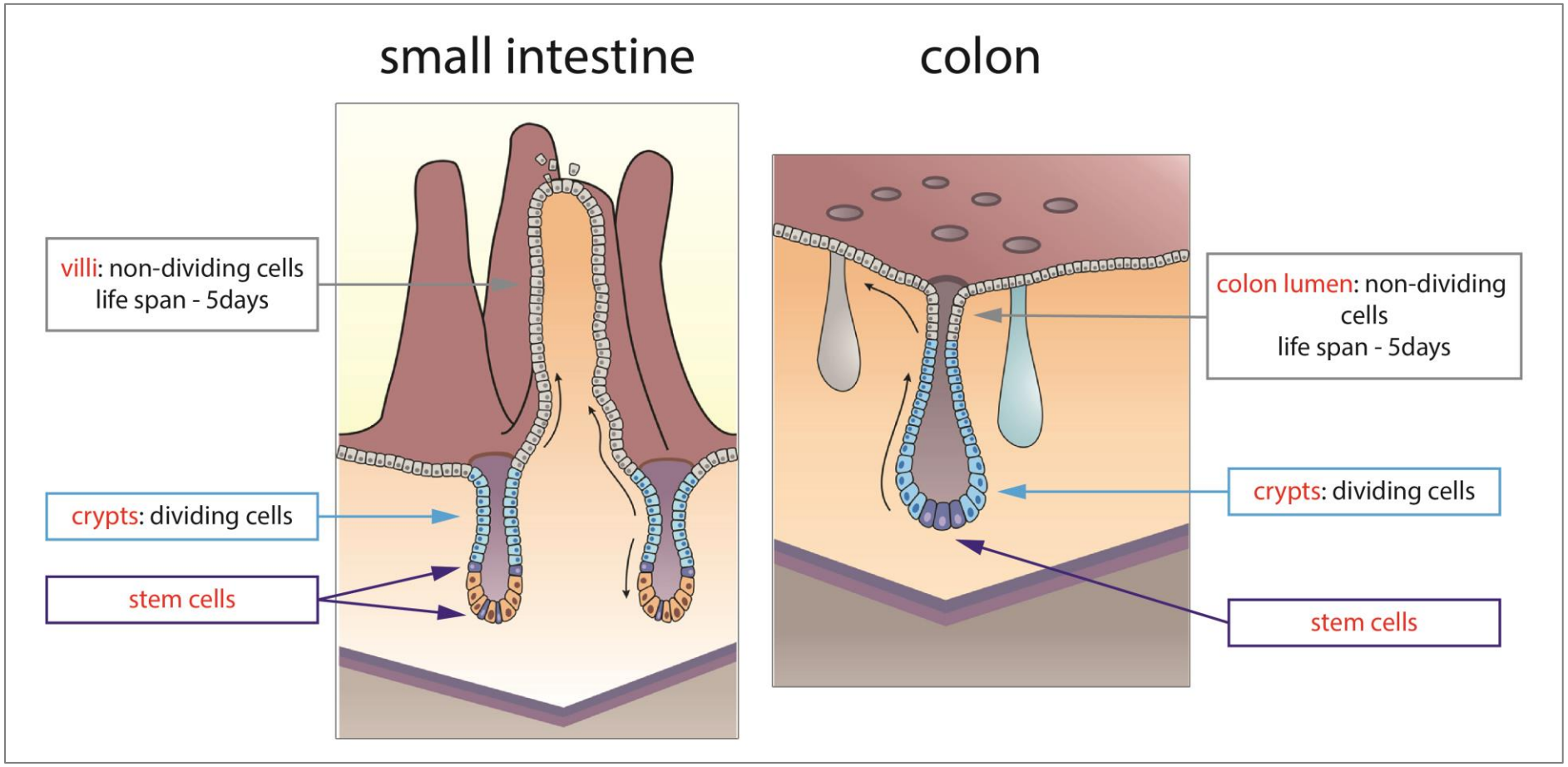
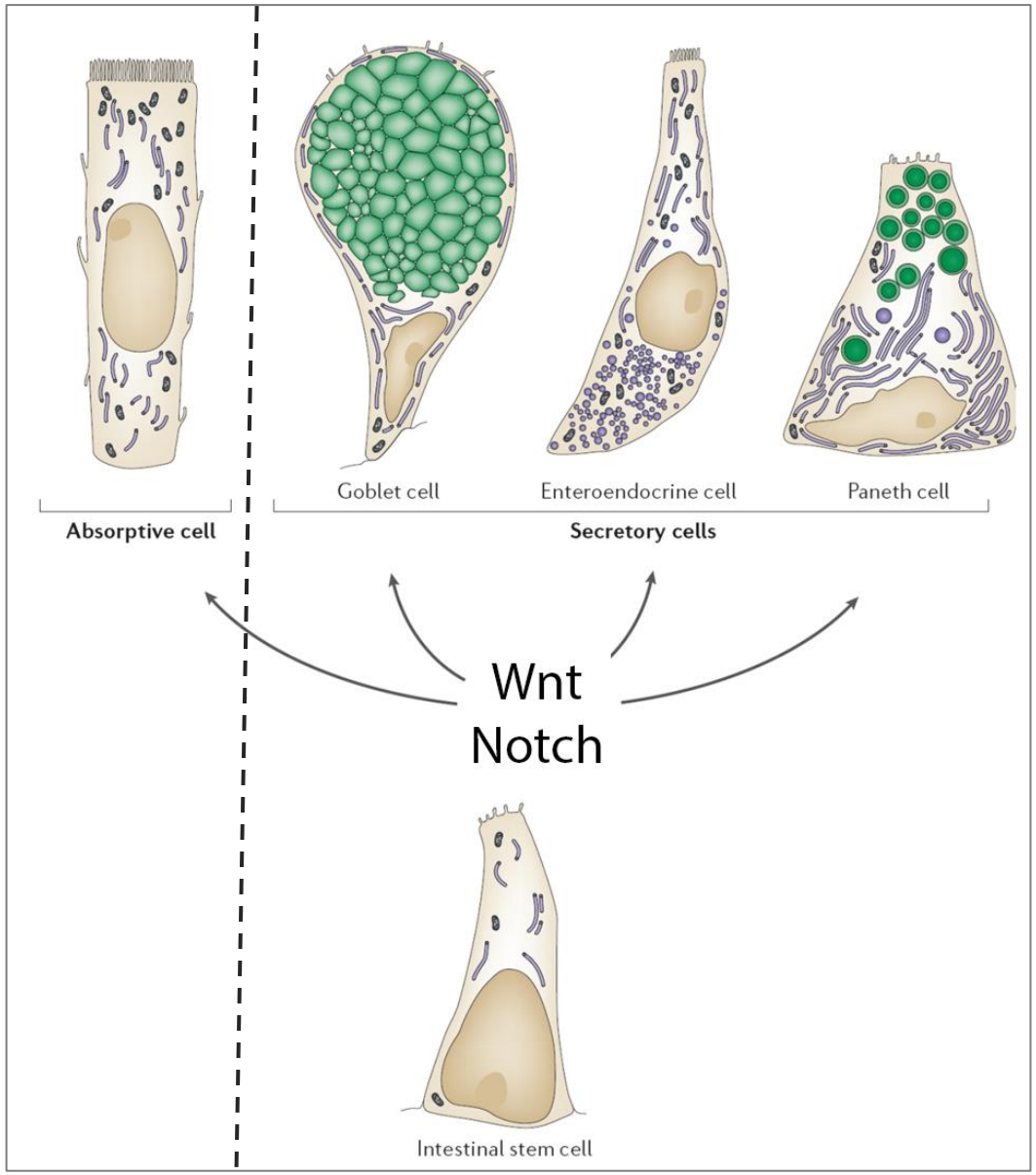


Question No.3

What is the main difference between the mucosal surface architecture between the small intestine and colon?

Stem cells differentiate in four major cell types



adopted from Crosnier et al., Nat Rev Genet. 2006

Physiological roles of intestinal tissue:

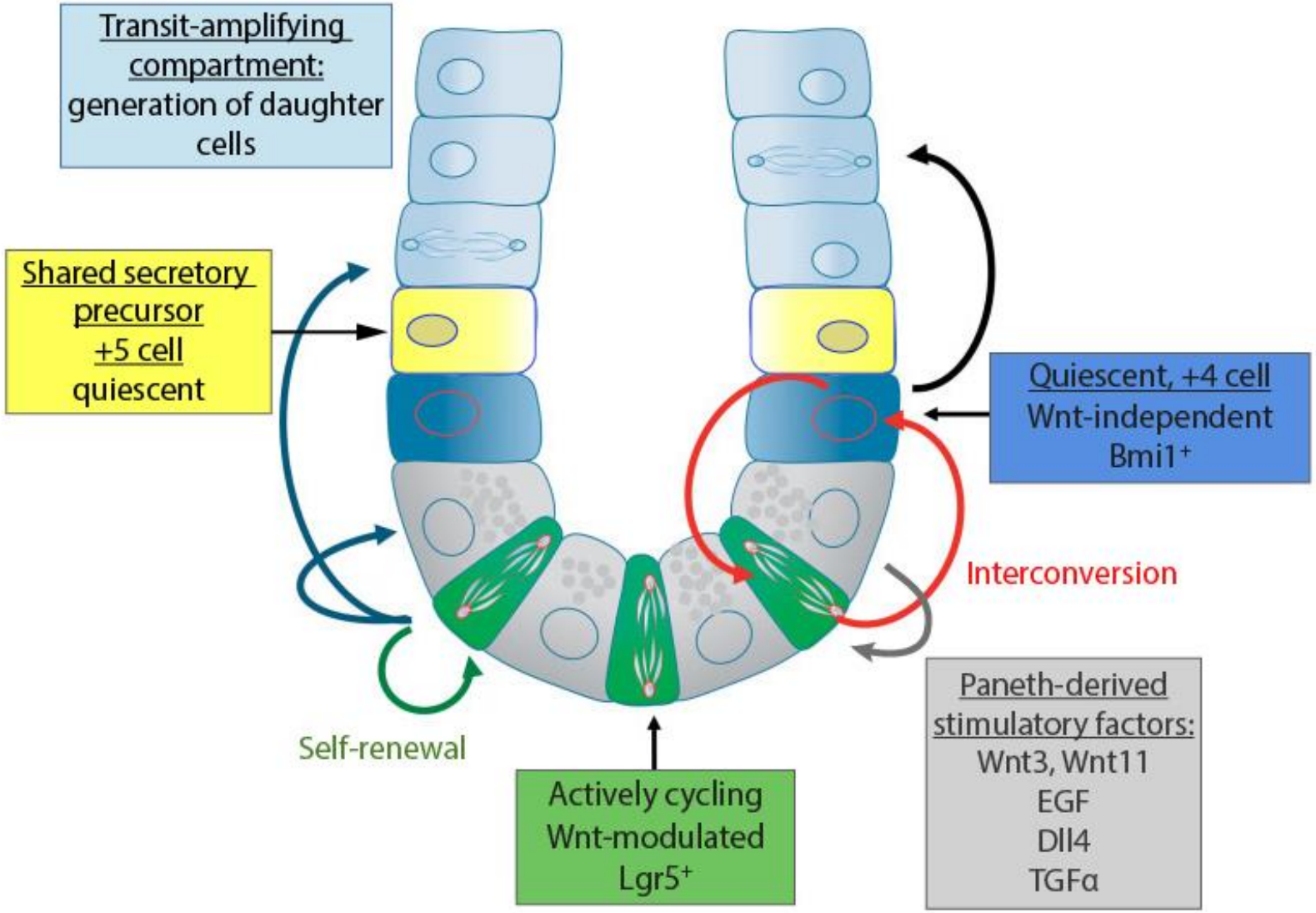
Absorptive: Enterocytes - transport processses

Secretory: Goblet cells - secrete mucus to lubricate the mucosal surface
Enteroendocrine cells - hormone releasing
Paneth cells - produce bacteriostatic compounds, niche for CBCs

Minor cell populations

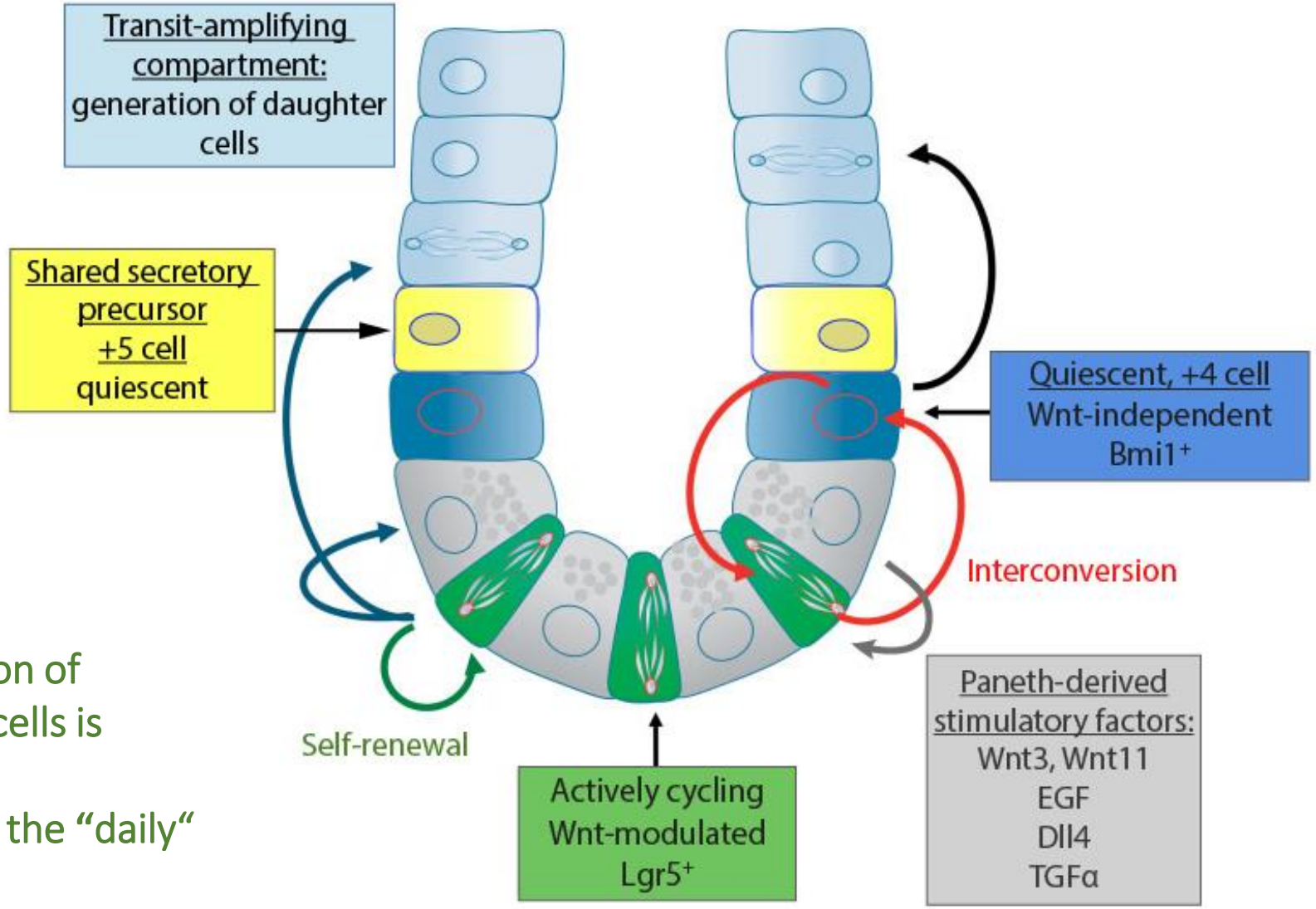
M-cells: transport of antigens from the intestinal lumen to underlying Peyer's patches
Tuft cells: producing opioids and enzymes involved in prostaglandin synthesis

Three plastic stem cell pools ensure proper intestinal homeostasis and self-renewal



adopted from Rizk & Barker, WIRE Syst Biol Med 2012

Three plastic stem cell pools ensure proper intestinal homeostasis and self-renewal

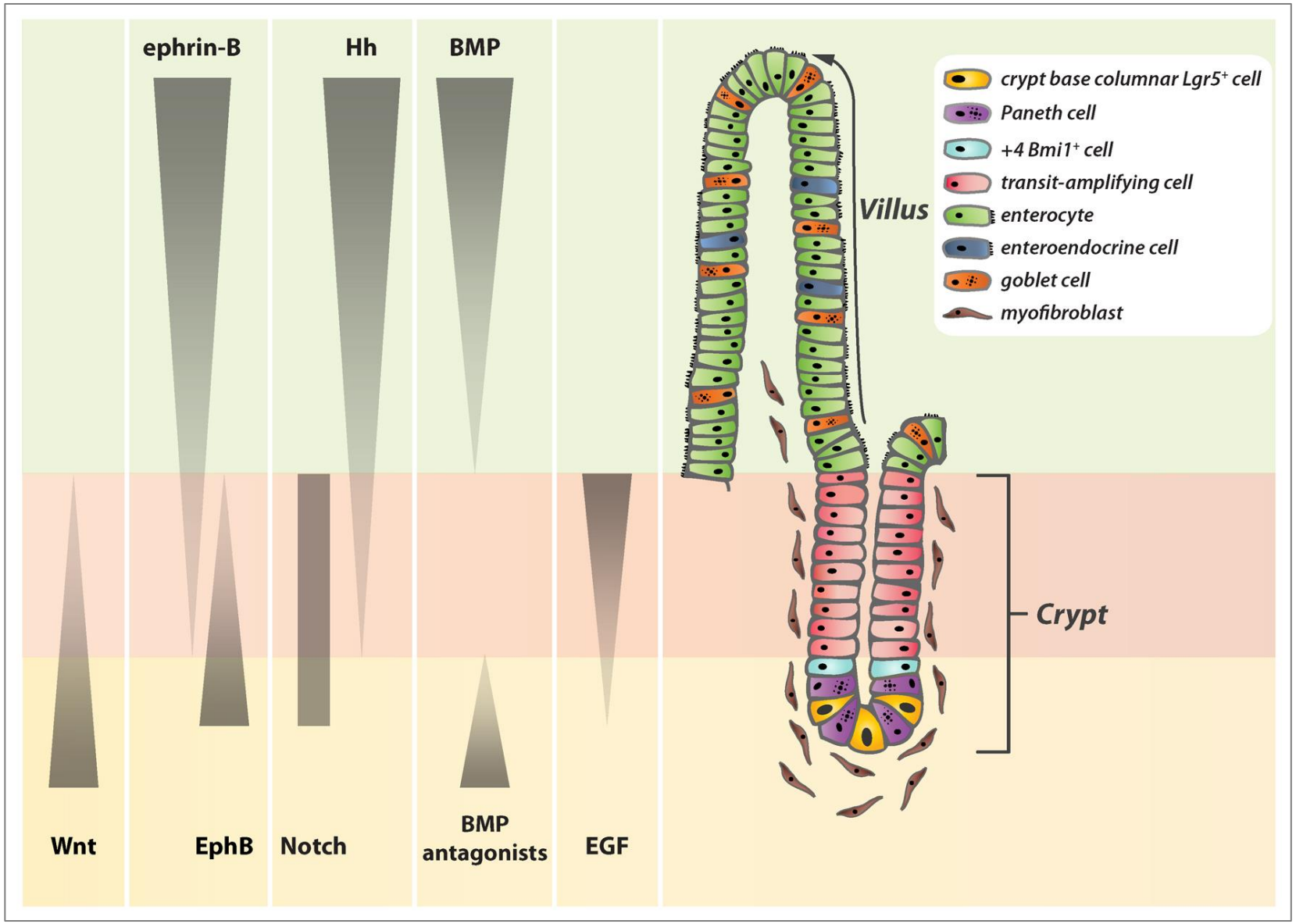


Question No.4

Which population of intestinal stem cells is responsible for maintenance of the "daily" homeostasis?

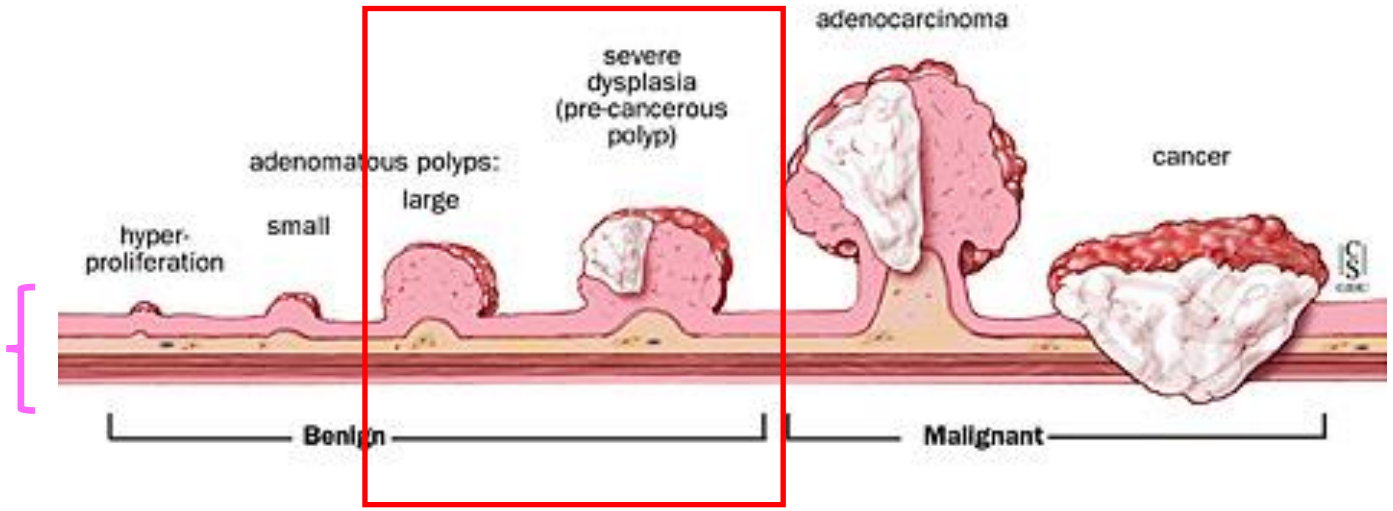
adopted from Rizk & Barker, WIRE Syst Biol Med 2012

Signaling pathways governing the architecture of intestinal epithelium



Krausova & Korinek, Neoplasma 2012

From polyp to cancer: initiation and progression of gastrointestinal neoplasia

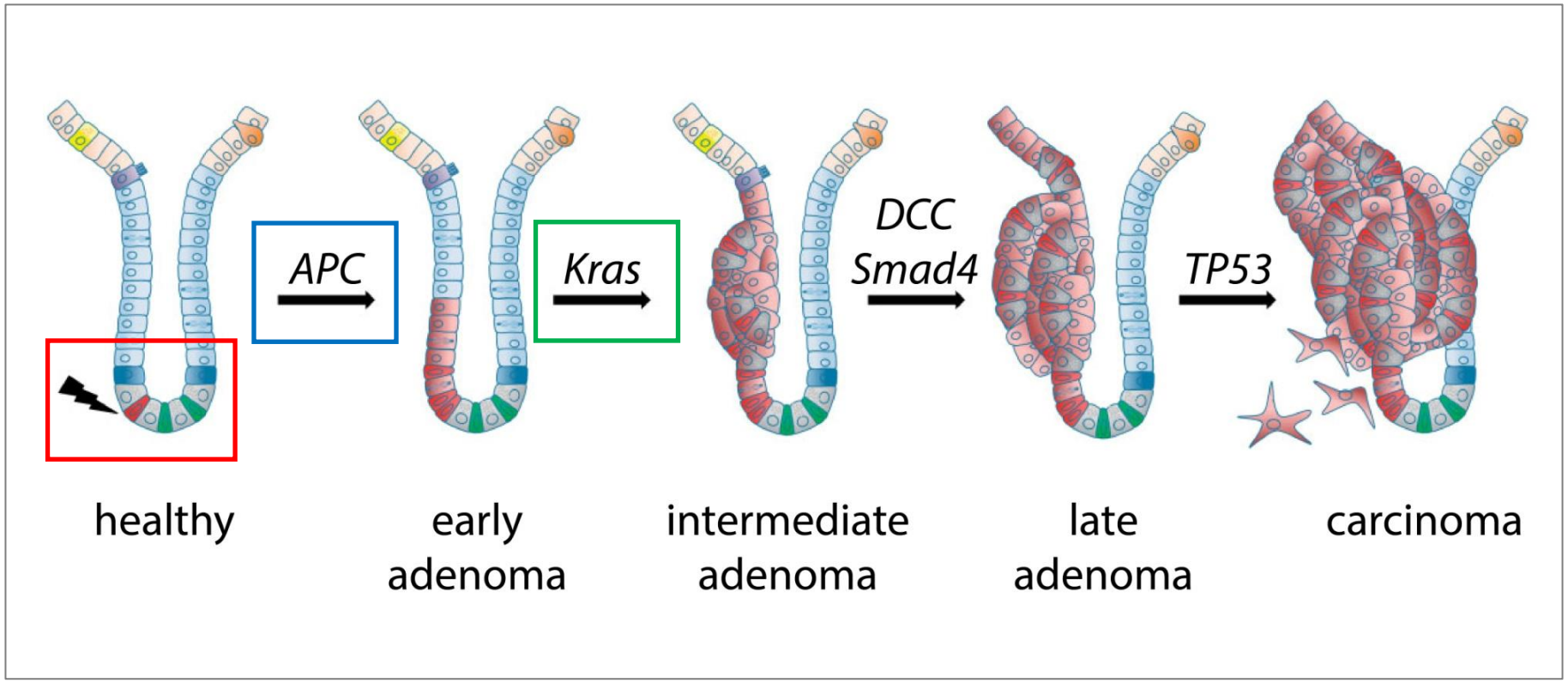


Layers of colonic tissue

CRC begins as benign polyps

John Hopkins Medicine

Genetic mutations driving malignant progression of intestinal/colonic epithelium

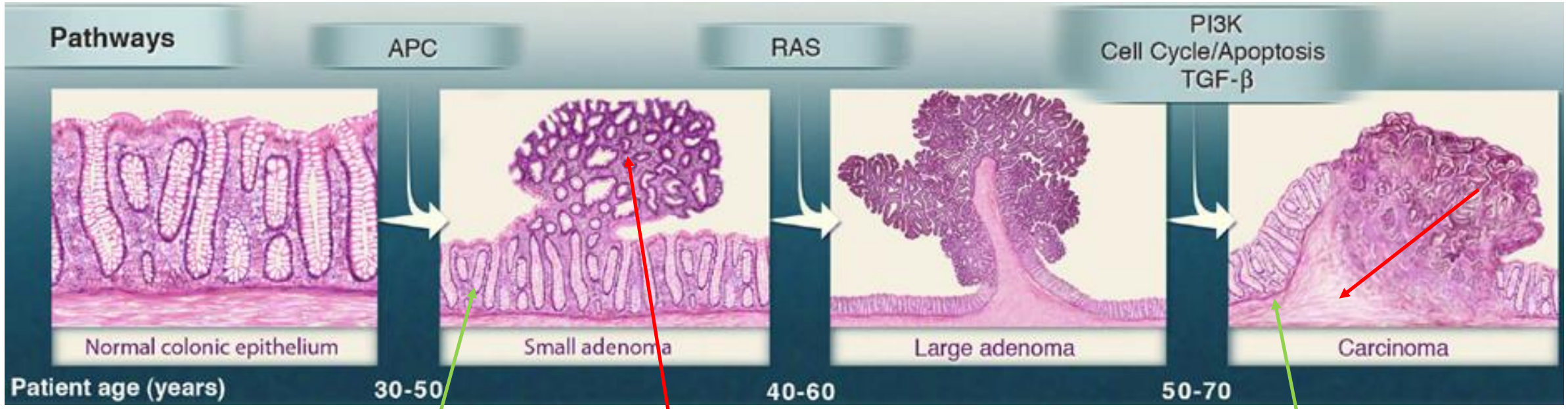


adopted from Rizk & Barker, WIRE Syst Biol Med 2012

"Vogelgram" (B.Vogestein) - malignant transformation occurs though stepwise accumulation of genetic alterations in tumor suppressor genes or activation of oncogenes

Mutations (predominantly) constrained to the stem cell compartment are further propagated

From polyp to cancer: stepwise progression towards malignancy



adopted from Vogelstein, B. et al.; Science 2013

healthy

Dysplastic = premalignant

Malignant invasion through the basal lamina

intact basal lamina

Signaling pathways governing the architecture of intestinal epithelium

Summary:

Three intercorvertible pools of intestinal stem cells maintain tissue homeostasis

Self-renewal is governed by principal developmental signaling pathways (Wnt, Notch, TGF-b *etc.*)

Mutations occuring in the stem cell compartment, that result in dysregulated signaling circuits, initiate onset of cancer

Question No.5

What makes the mutations occurring in the intestinal stem cells particularly dangerous?

Inherited colorectal cancer syndromes

Inherited colorectal cancer syndromes:

Inborn predisposition to development of colorectal cancer

Germinal mutations in genes executing control over developmental signaling pathways or DNA repair machinery

Inherited colorectal cancer syndromes

1. Developmental signaling pathways involved in germinal colorectal cancer syndromes:

Wnt pathway: Familial adenomatous polyposis (FAP) syndrome; disruption of *APC* tumor suppressor gene

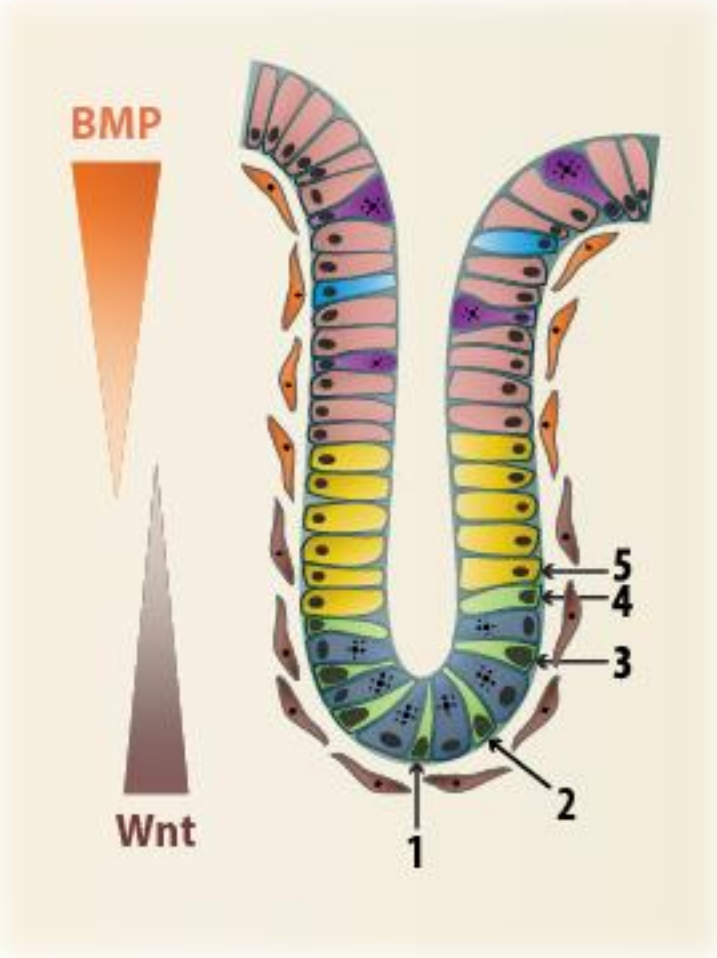
BMP pathway: Juvenile polyposis syndrome; inactivating mutations in the *BMPR1A* or *SMAD4* genes

EGF signaling: Cowden syndrome; germline mutations in *PTEN* (PI-3,4,5-triP phosphatase; negative regulator of AKT/PKB signaling pathway)

2. MMR (mismatch repair pathway):

Hereditary NonPolyposis Colorectal Cancer (HNPCC) or Lynch syndrome
MYH-Associated Polyposis (MAP)
Hyperplastic Polyposis Syndrome (HPS)

3. Peutz-Jeghers syndrome (hamartomatous polyps): *LKB1* tumor suppressor (regulation of epithelial cell polarity and metabolism)



Krausova & Korinek, Cellular Signaling 2014

Induced development of mouse intestinal neoplasia

Question No.6

What is the genetic difference between tumor initiation in inherited versus sporadic colorectal cancer?

Inherited colorectal cancer syndromes

Familial adenomatous polyposis (FAP) syndrome - disruption of the *APC* gene (Wnt pathway)

Hereditary colorectal cancer syndromes

<u>Familial adenomatous polyposis (FAP) syndrome</u> - disruption of the *APC* gene (Wnt pathway)

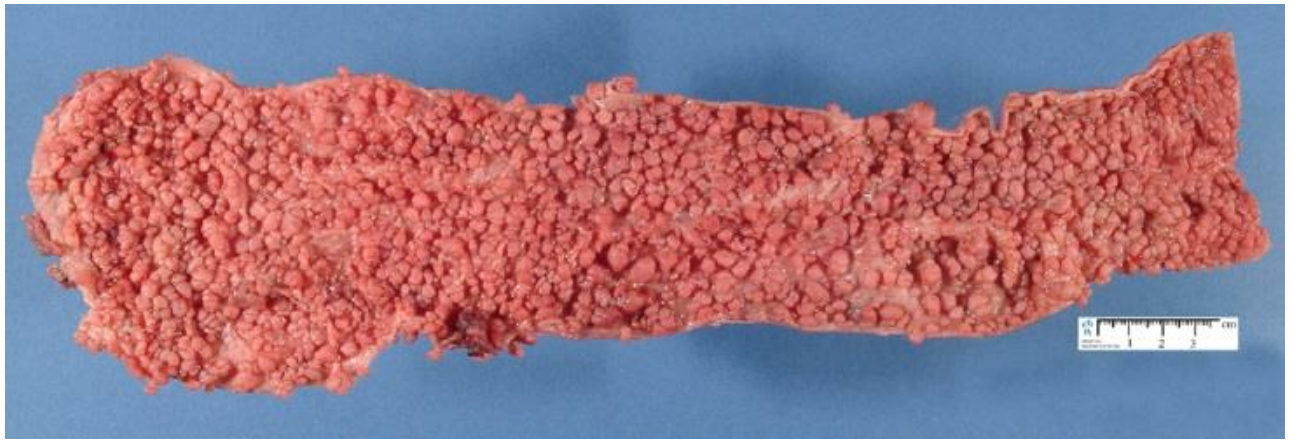
- an autosomal dominant disorder characterised by multiple colorectal polyps and a variety of extraintestinal manifestations

- affected individuals develop multiple adenomatous polyps in the colon and rectum, usually beginning in the teen years and increasing in number to the hundreds or even thousands at a young age (35y)

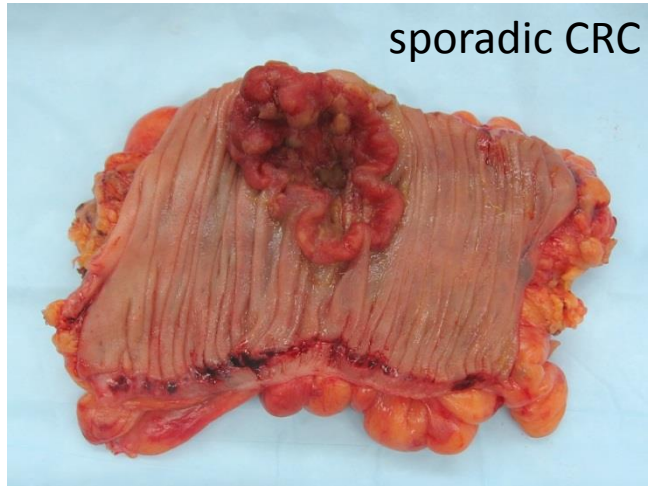
- accounting for less than 1 percent of all colorectal cancers (rare condition)

- nearly a third of the cases are the result of a spontaneous (newly-occurring) gene mutation, or abnormality

FAP-stricken colon



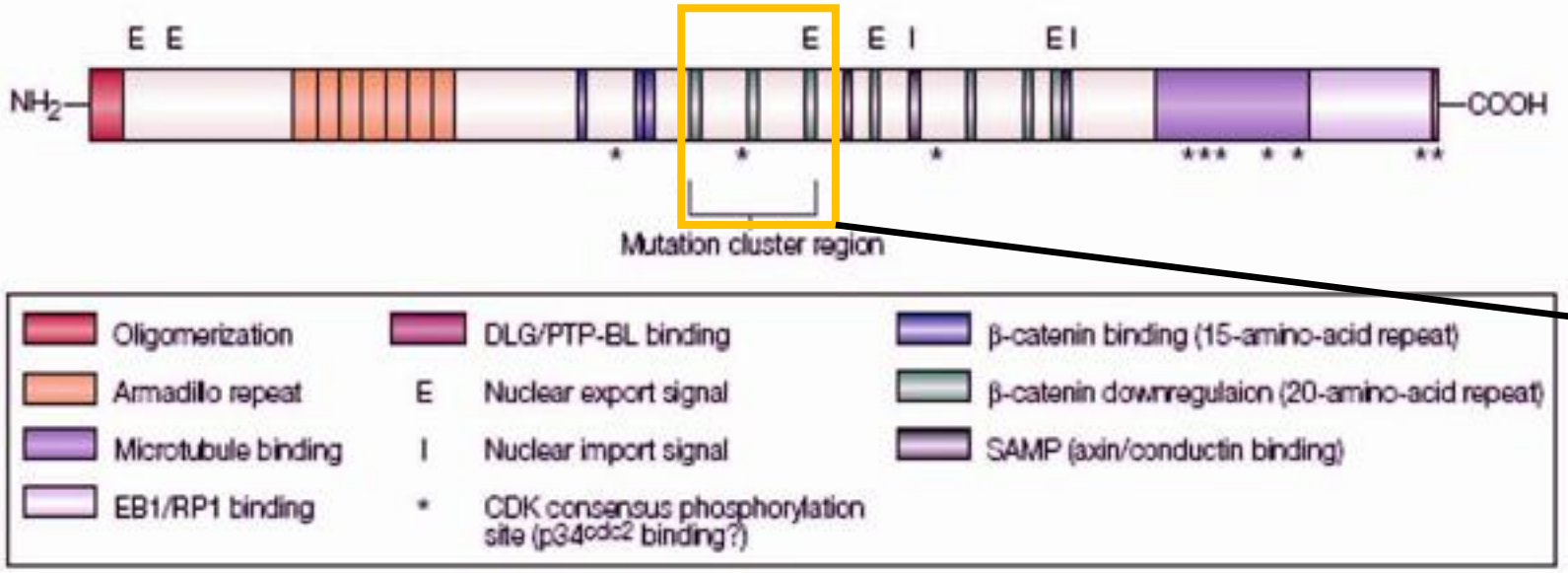
Humpath.com



commons.wikimedia.org

Mutational frequencies correlated to the structure of the APC protein

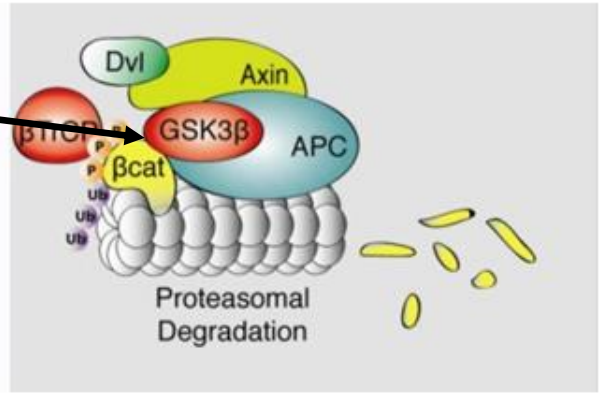
The APC protein and it´s functional domains



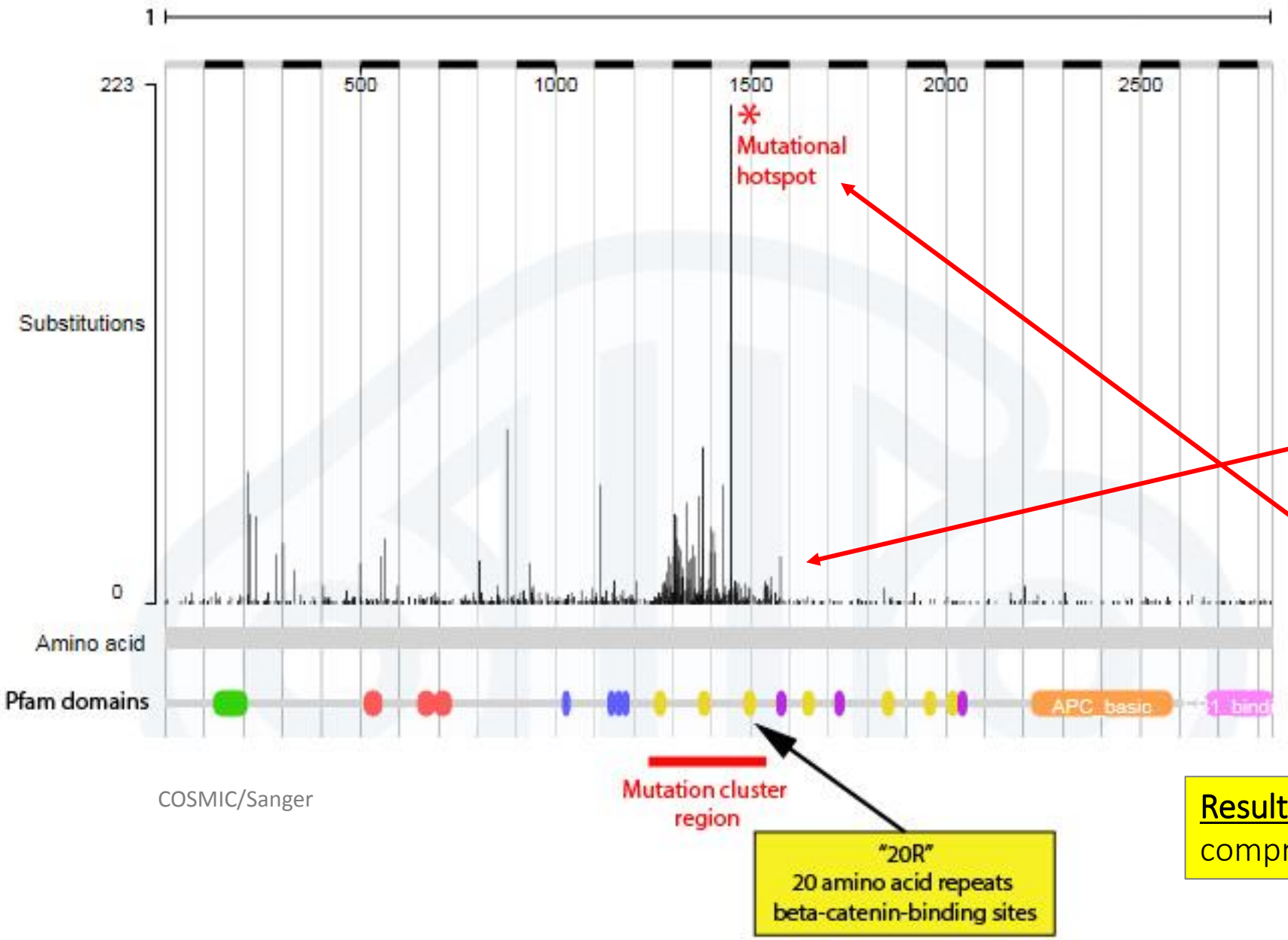
Familial adenomatous polyposis (FAP) syndrome

disruption of the *APC* gene (Wnt pathway)

Reminder



Mutational frequencies correlated to the structure of the *APC* gene



COSMIC/Sanger

Familial adenomatous polyposis (FAP) syndrome

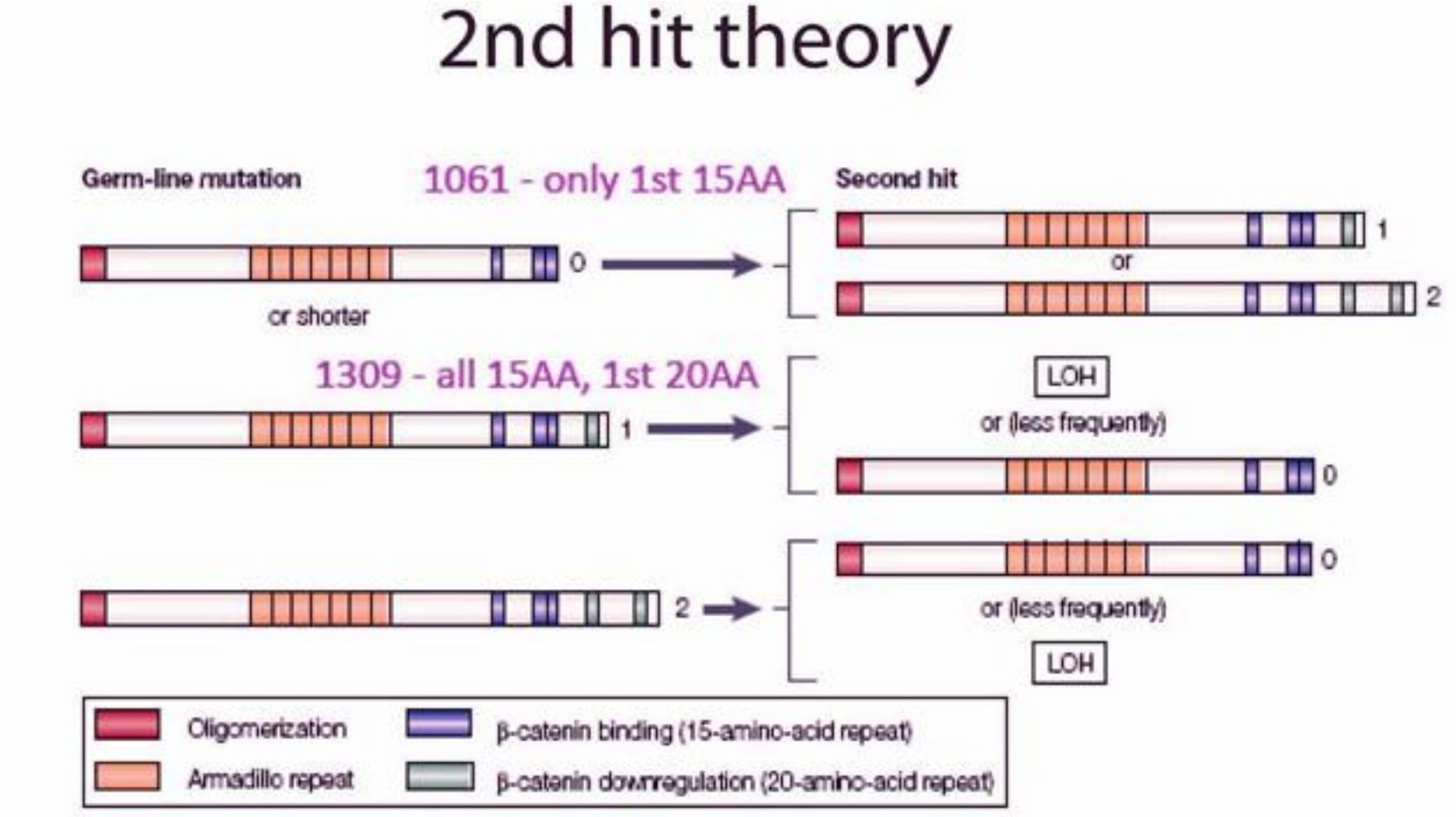
disruption of the *APC* gene (Wnt pathway)

Mutations cluster to a specific region of the *APC* gene = **MCR (Mutation Cluster region)**

Assorted residues are affected more frequently: **Mutational hotspots**

Result: truncated APC protein that is compromised in it´s ability to bind b-catenin

FAP: disruption of the *APC* gene



Familial adenomatous polyposis (FAP) syndrome

Site of *APC* germline mutations pre-determines the art of the remaining wt *APC* allele loss

↓

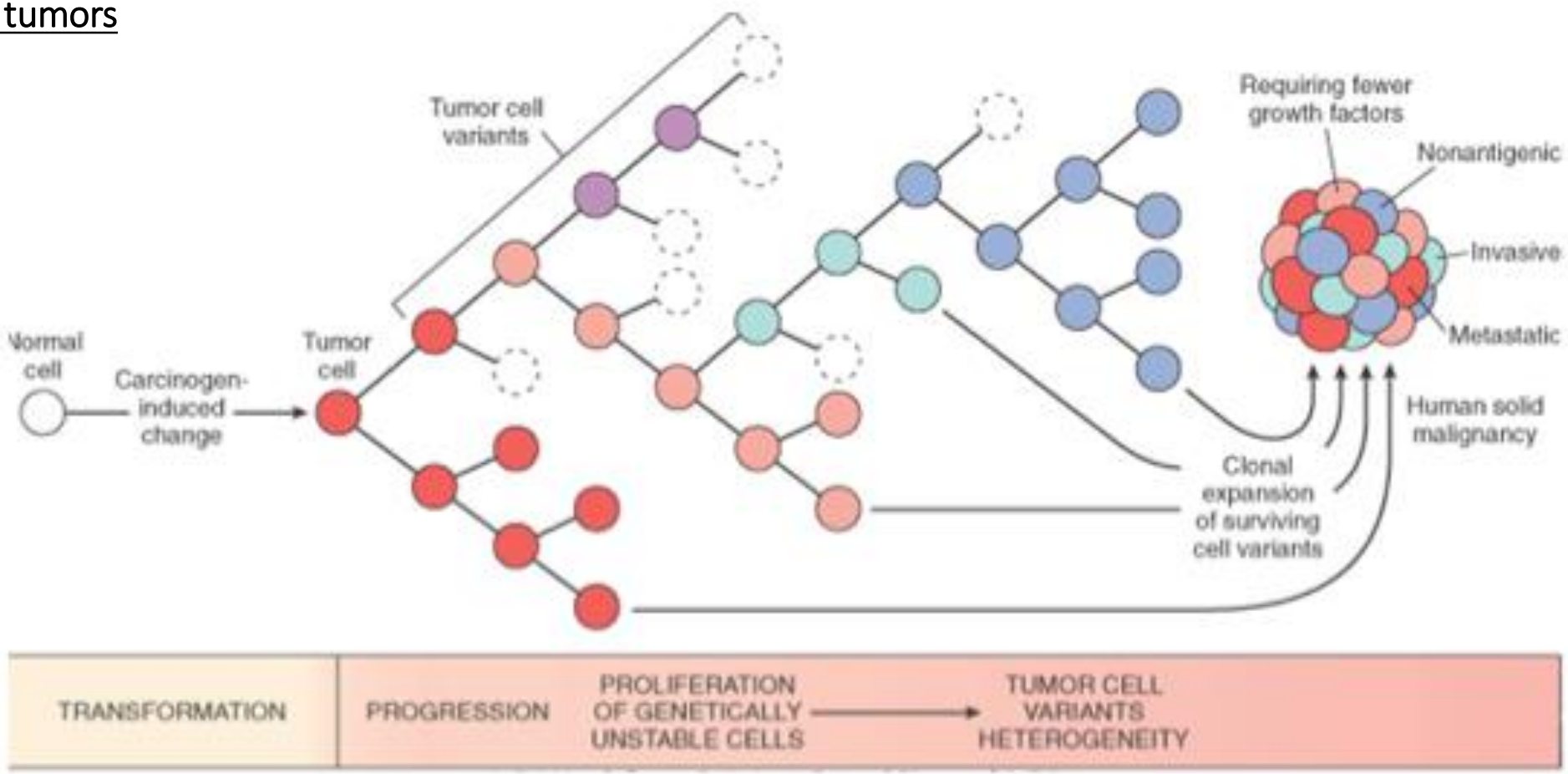
Controlled level of Wnt signaling confers a selective advantage and is required for an optimal tumor growth = phenotypic selection

Genotype/fenotype correlations:

site of germinal *APC* mutation dictates the severity of the disease (attenuated FAP; severe FAP)

Clonal features of solid tumors

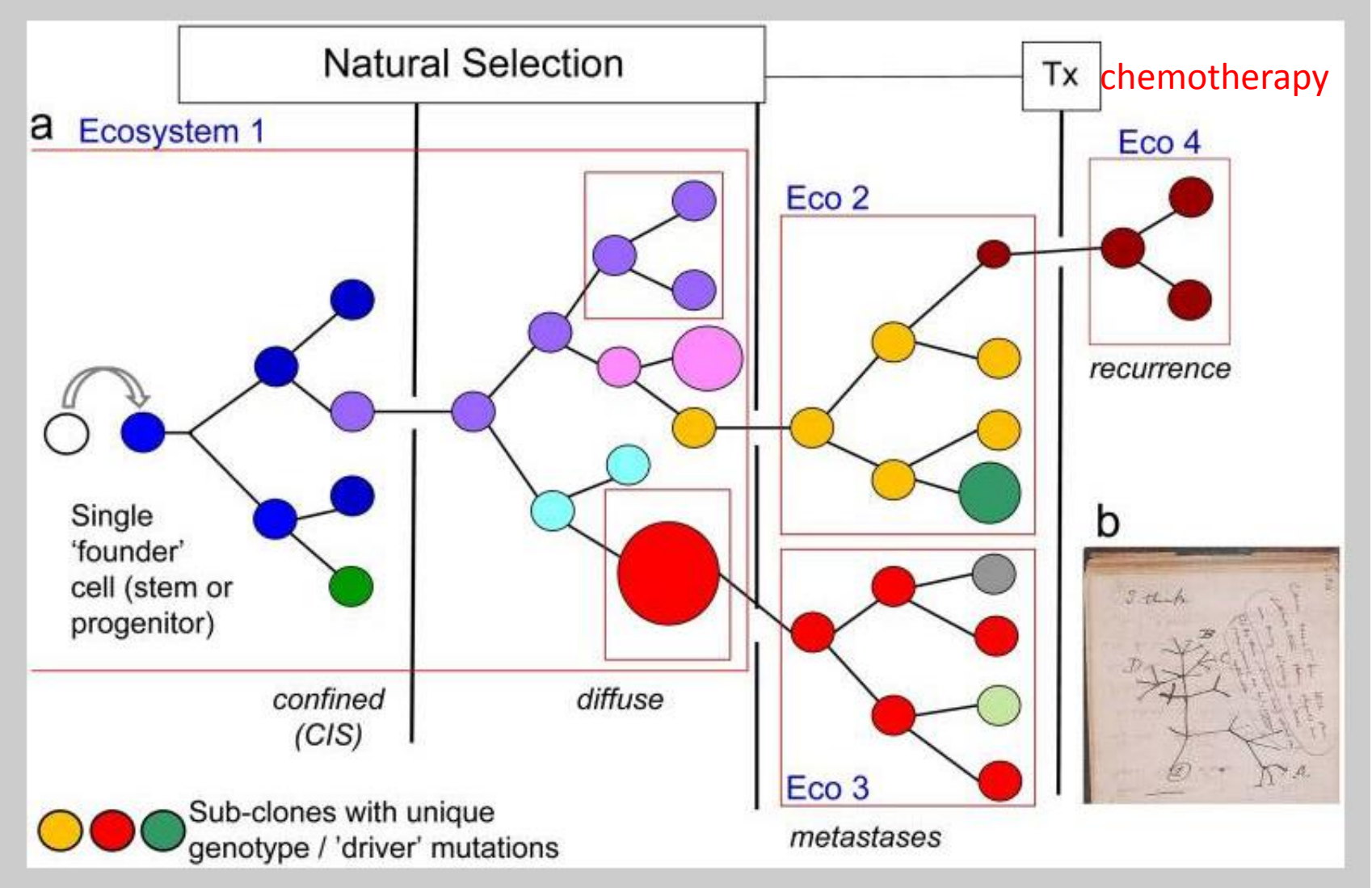
Phenotypic selection within solid tumors



Selective pressure concept

Phenotypic selection within solid tumors

Selective pressures allow some mutant subclones to expand while others become extinct or remain dormant. Vertical lines represents restraints or selective pressures.



Greaves & Maley, Nature 2012

Hereditary colorectal cancer syndromes

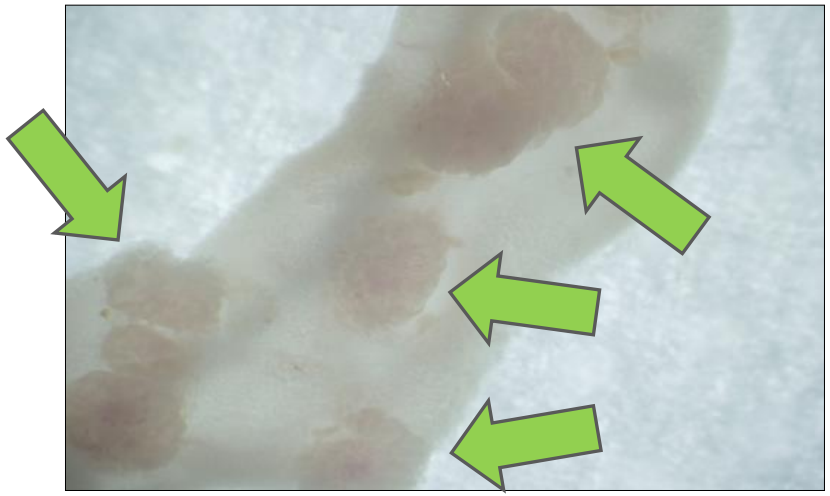
Familial adenomatous polyposis (FAP) syndrome - murine models: *Apc*^{Min} strain

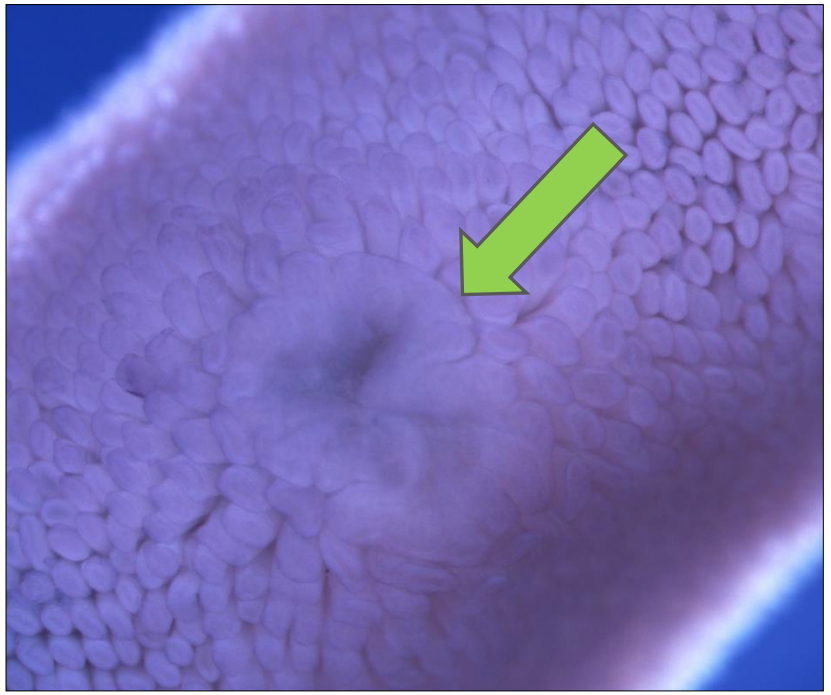
Apc^{Min} strain development: chemically induced mutagenesis (*N*-ethyl-*N*-nitrosourea (ENU)) to C57BL/6J mice; *Apc* c.2549T>A Apc p.L850* (nonsense mutation)

Heterozygous mice are highly susceptible to spontaneous intestinal adenoma formation. Mice suffer from adult onset anemia, females develop mammary tumors.

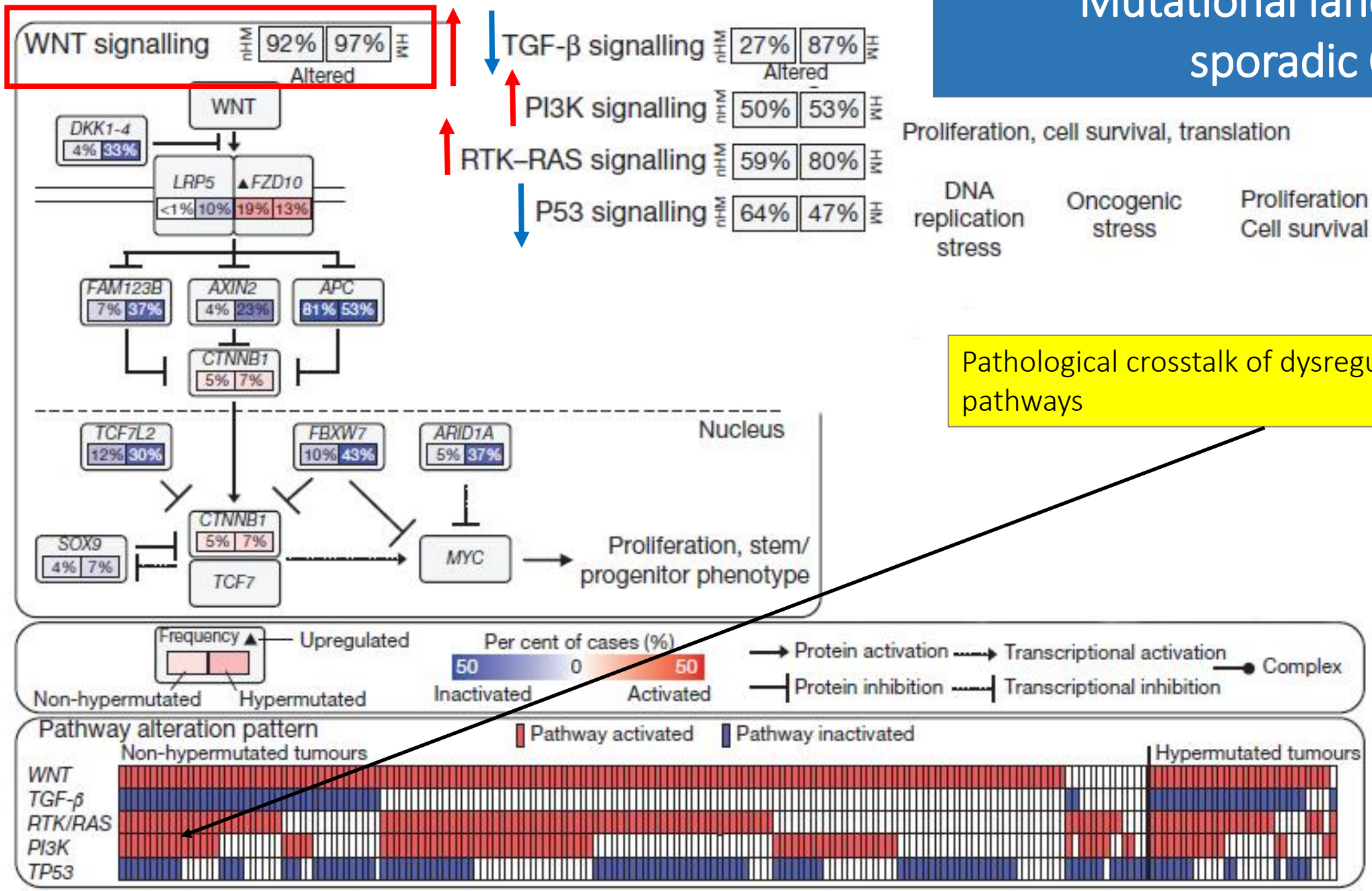
Tumor burden: small intestine; colon=ACF (aberrant crypt foci)

Tumors in the intestine of *Apc*^{Min} mice





Mutational landscape of sporadic CRC



Pathological crosstalk of dysregulated signaling pathways

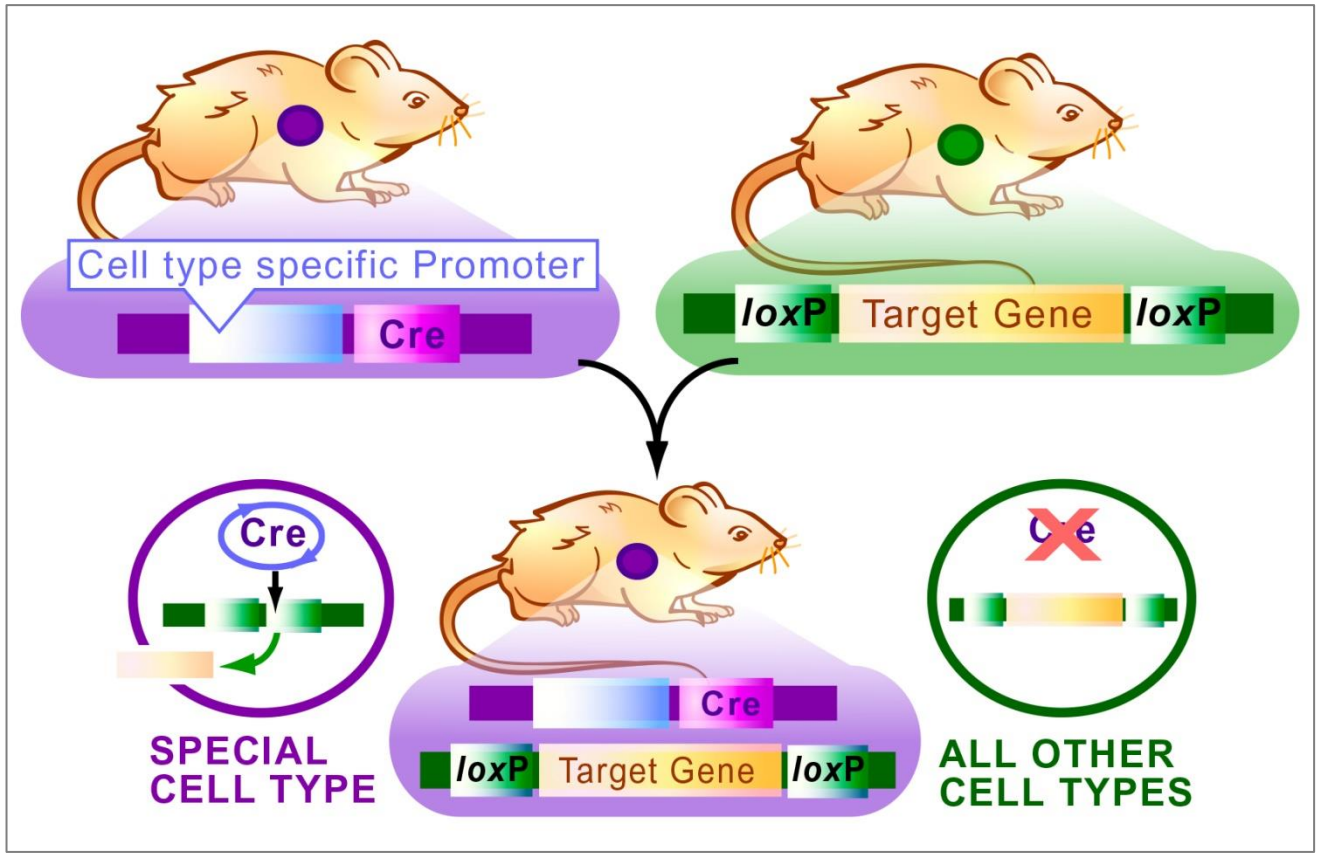
The Cancer Genome Atlas Network; Nature 2012

Sporadic colorectal cancer

Sporadic colorectal cancer - murine models of conditional *Apc* disruption: *Apc*^{cKO} strain

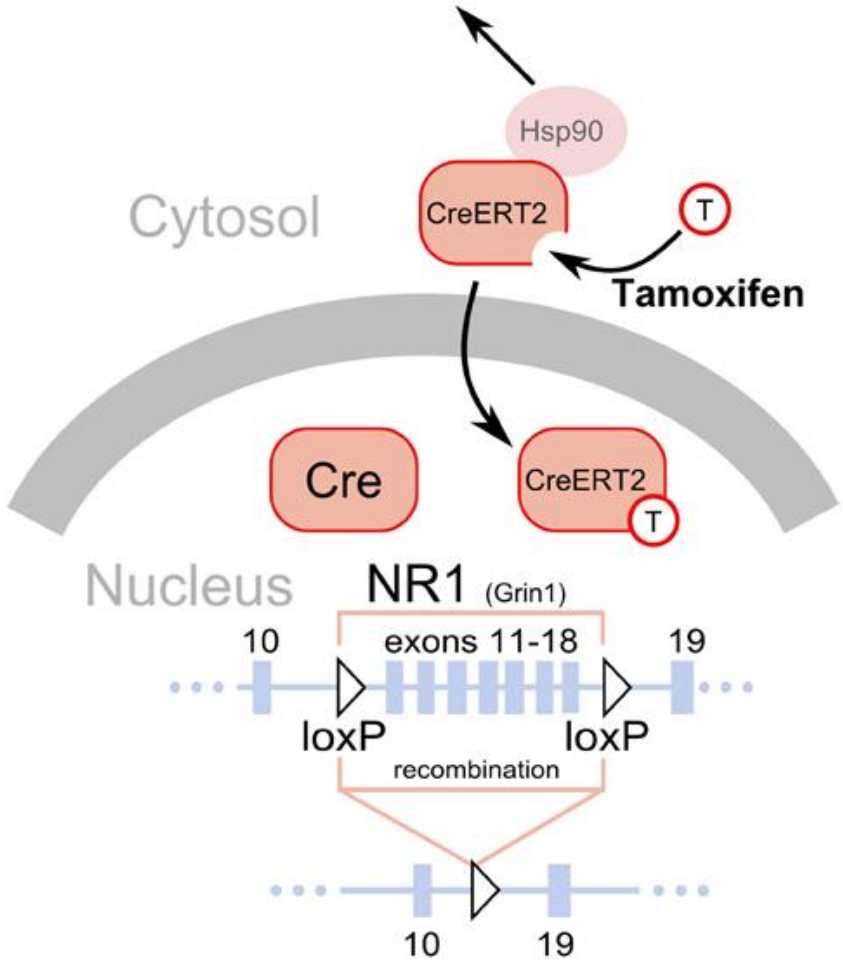
Apc^{cKO} strain development: floxed exon 15 of murine *Apc* gene

Cre loxP technology: spatial and temporal control over gene inactivation



Wang, J.

Induced development of mouse intestinal neoplasia

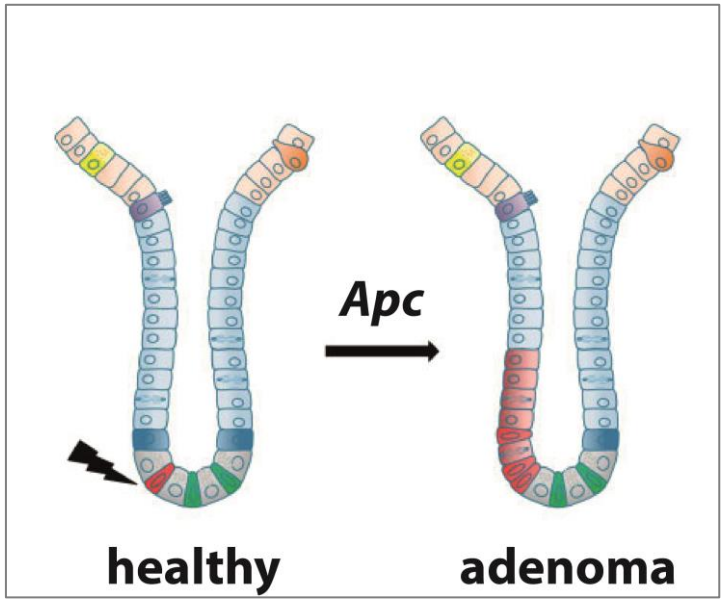


- Lgr5-EGFP-IRES-CreER^{T2} mice

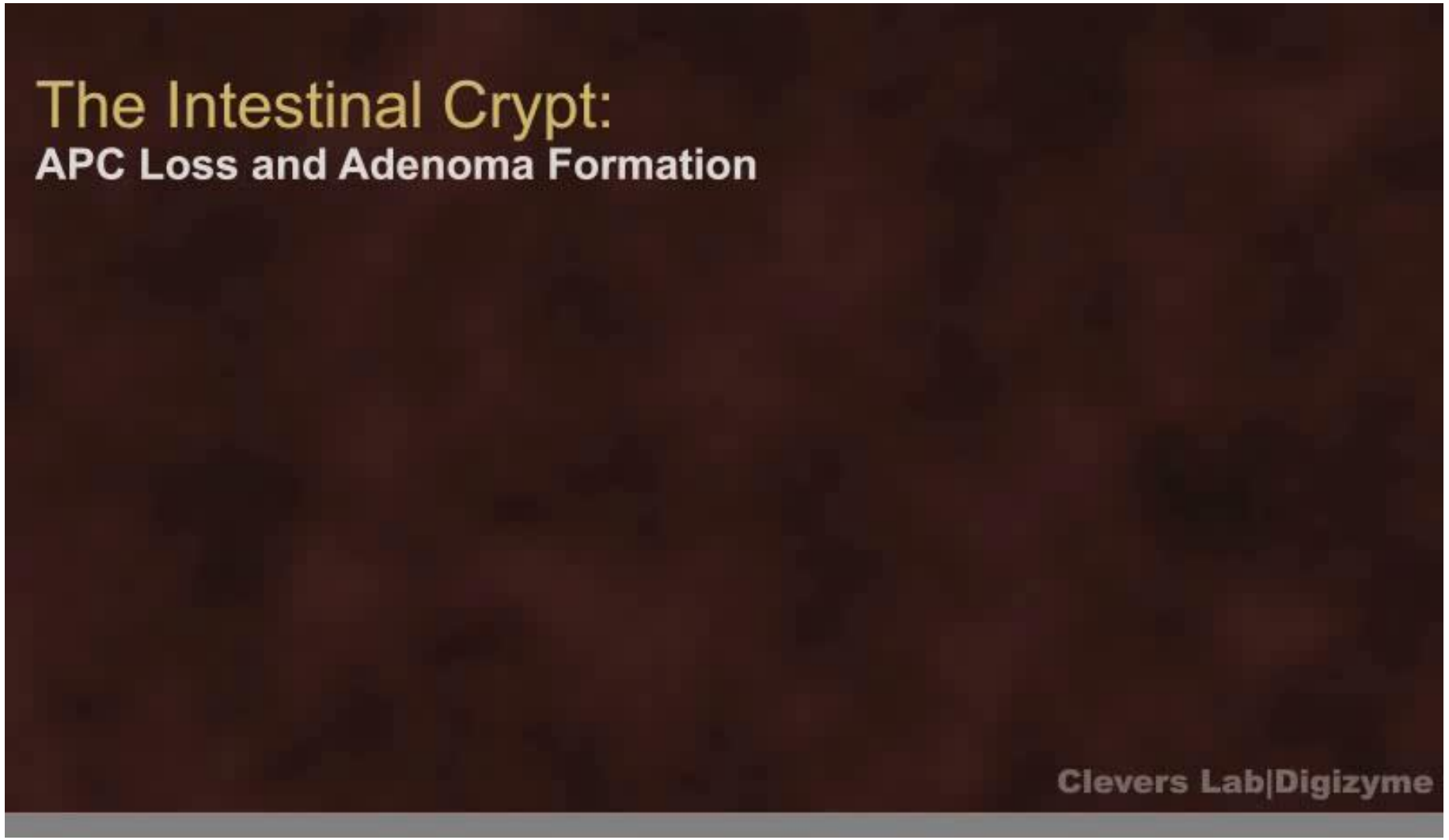
- Apc$^{cKO/cKO}$ - floxed exon 14 (15); truncation of the protein after 580AA (605AA)

- temporal inducibility: ER^{T2}: regulation of Cre nuclear shuttling (uninduced: association with Hsp90 in cytoplasm/dissociation upon binding of oestrogen analog 4-OH tamoxifen)

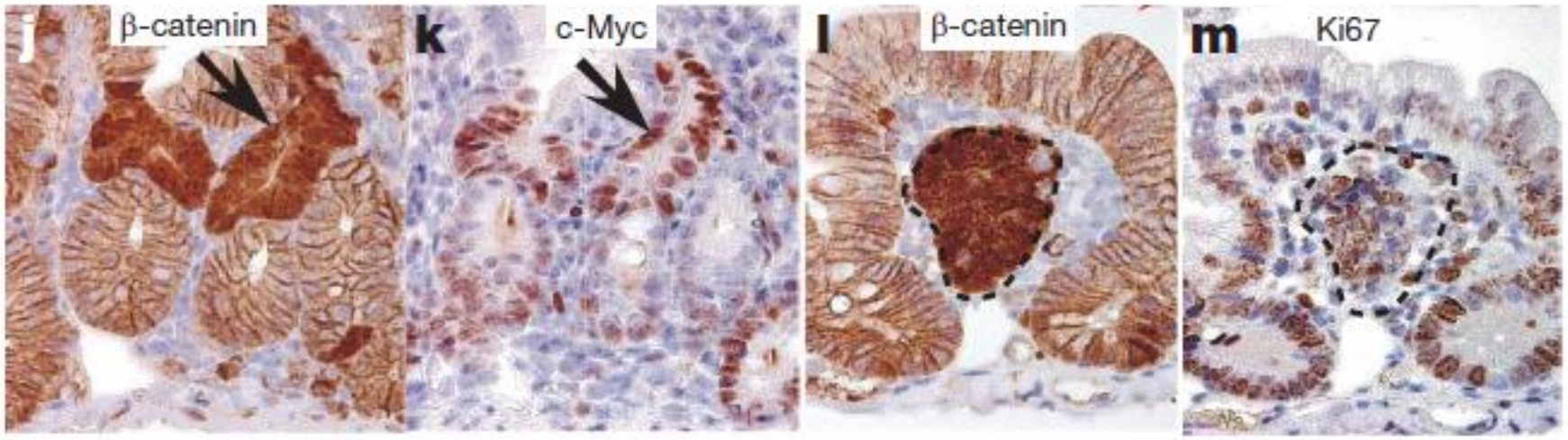
→ initiation of tumors restricted to the stem cell compartment



The cancer stem cell niche



Induced development of mouse intestinal neoplasia



Barker, N.; Cell Stem Cell 2009

Lgr5-EGFP-IRES-CreER^{T2} x Apc$^{cKO/cKO}$: 8 days following tamoxifen administration (induction of CreER^{T2} activity)

beta-catenin: strong cytoplasmic staining - aberrantly stabilized molecules
c-Myc: Wnt signaling target gene; transcriptional amplifier
Ki-67: general marker of proliferating cells

Induced development of mouse intestinal neoplasia

Question No.7

What is the genetic difference between tumor development in Apc^{Min} versus Apc^{cKO} mice?

Hereditary colorectal cancer syndromes

Lynch syndrome (Hereditary nonpolyposis colorectal cancer; HNPCC): defective DNA mismatch repair (MMR)

Hereditary colorectal cancer syndromes

Lynch syndrome (Hereditary nonpolyposis colorectal cancer; HNPCC) - inherited condition of defective DNA mismatch repair (MMR) - the post-replicative proofreading and editing system that ensures genome integrity

- autosomal dominant heterozygous germline mutations in one of the four key MMR genes - mutL homologue 1 (*MLH1*), mutS homologue 2 (*MSH2*), *MSH6* or postmeiotic segregation increased 2 (*PMS2*)
- somatic loss of the remaining wild-type MMR gene allele: accumulation of downstream genetic mutations = **MSI** (microsatellite instability)

Microsatellites:

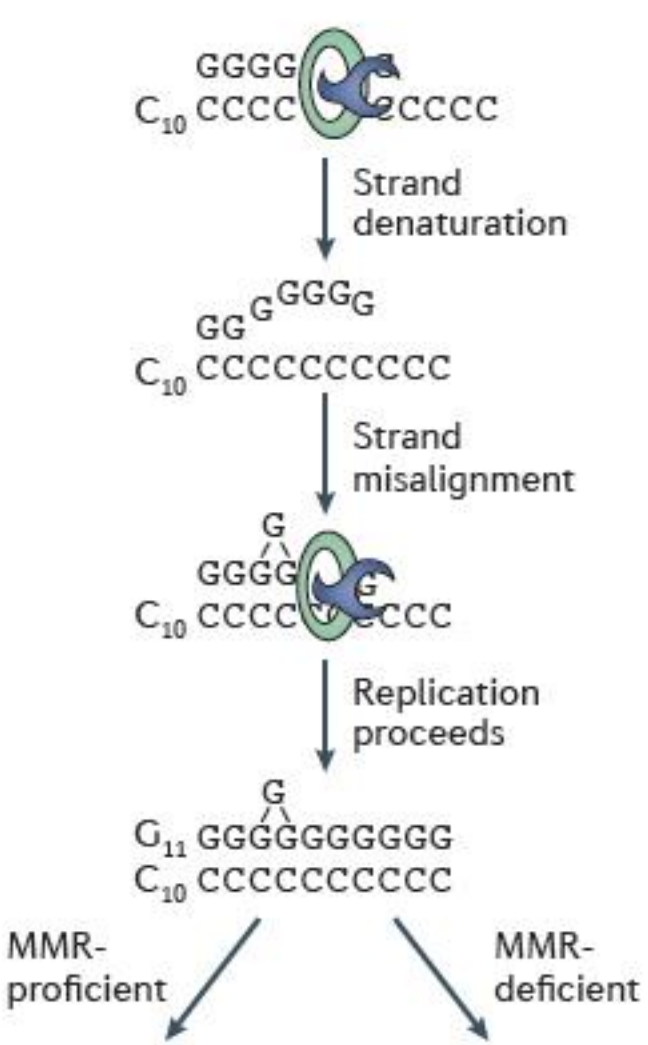
Synonyms: SSR (Simple Sequence Repeat); STR (Short Tandem Repeat)

sections of DNA composed of mono-, di-, tri-, and tetranucleotide repeats (e.g. C_{10}, CA, GTG, TGCT etc.)

……CCCCCCCCCC……

……CACACACACACACACA……

Molecular mechanisms of microsatellite instability (MSI)

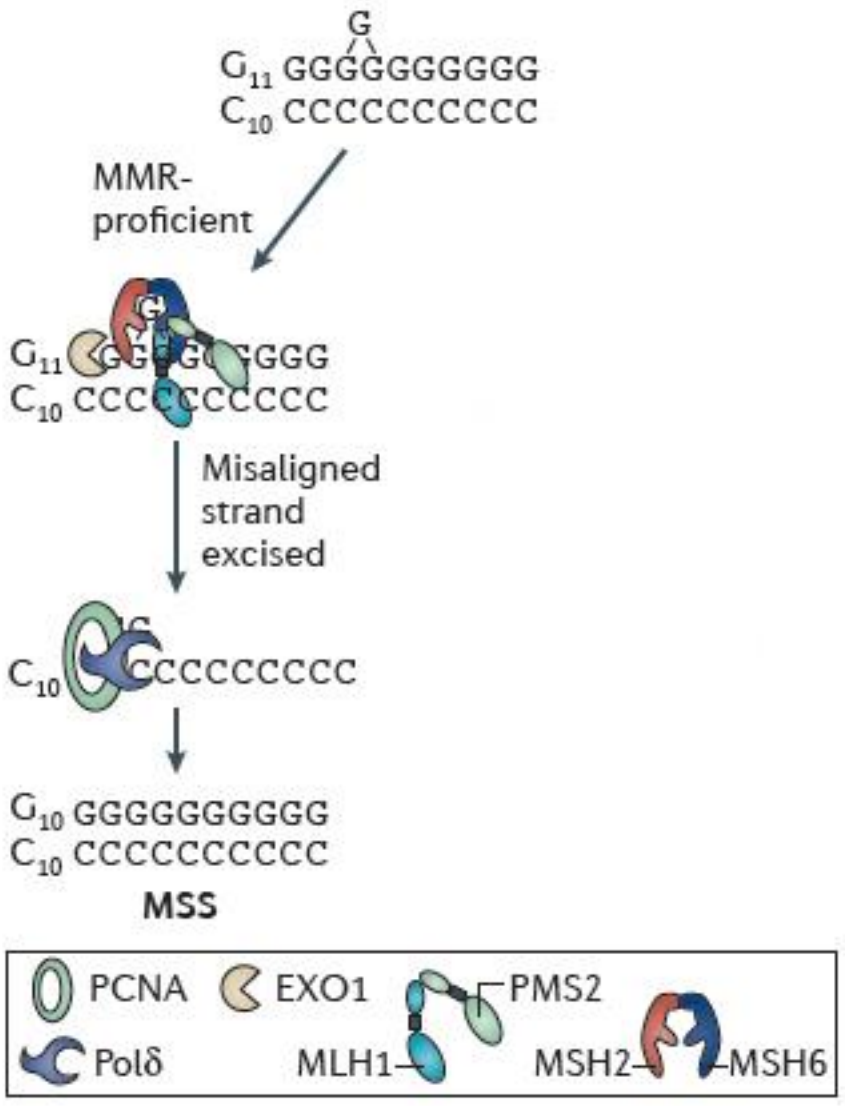


Lynch, HT; Nat Rev Can 2015

Replication of homopolymer stretches (C_{10}):

denaturation of DNA strands: strands can re-anneal "out-of register" → addition/subtraction of nucleotides.

Molecular mechanisms of microsatellite instability (MSI)

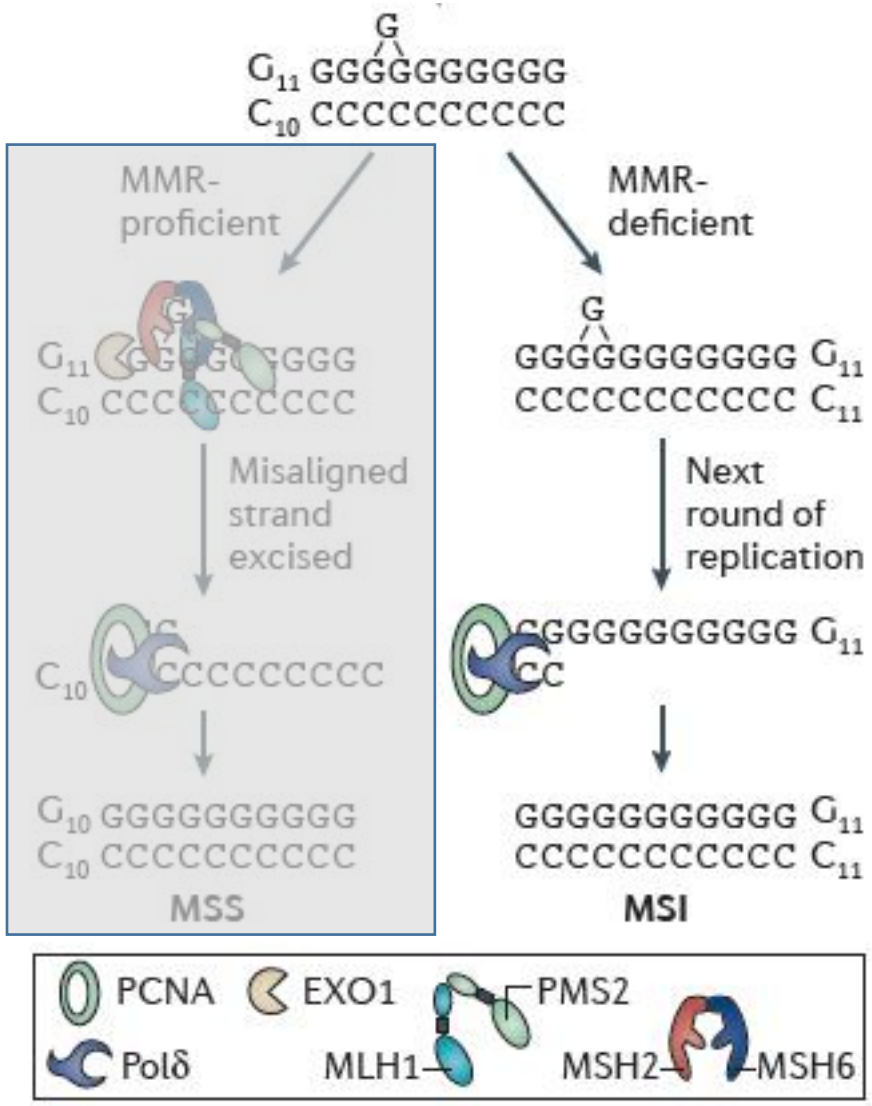


Lynch, HT; Nat Rev Can 2015

Replication of homopolymer stretches (C_{10}):

MMR proficient cells: extra nucleotide bulge is recognized by the MMR heterodimer MSH2-MSH6, which work together with MLH1/PMS2 to promote excision of the errant daughter strand.

Molecular mechanisms of microsatellite instability (MSI)



Lynch, HT; Nat Rev Can 2015

Replication of homopolymer stretches (C_{10}):

MMR deficient cells: in the absence of MMR activity, the extra nucleotide remains. During the next round of DNA replication, the G11 strand becomes the template strand. Successful replication of this errant strand results in permanent fixation of the additional nucleotide and the generation of a new allele (C11).

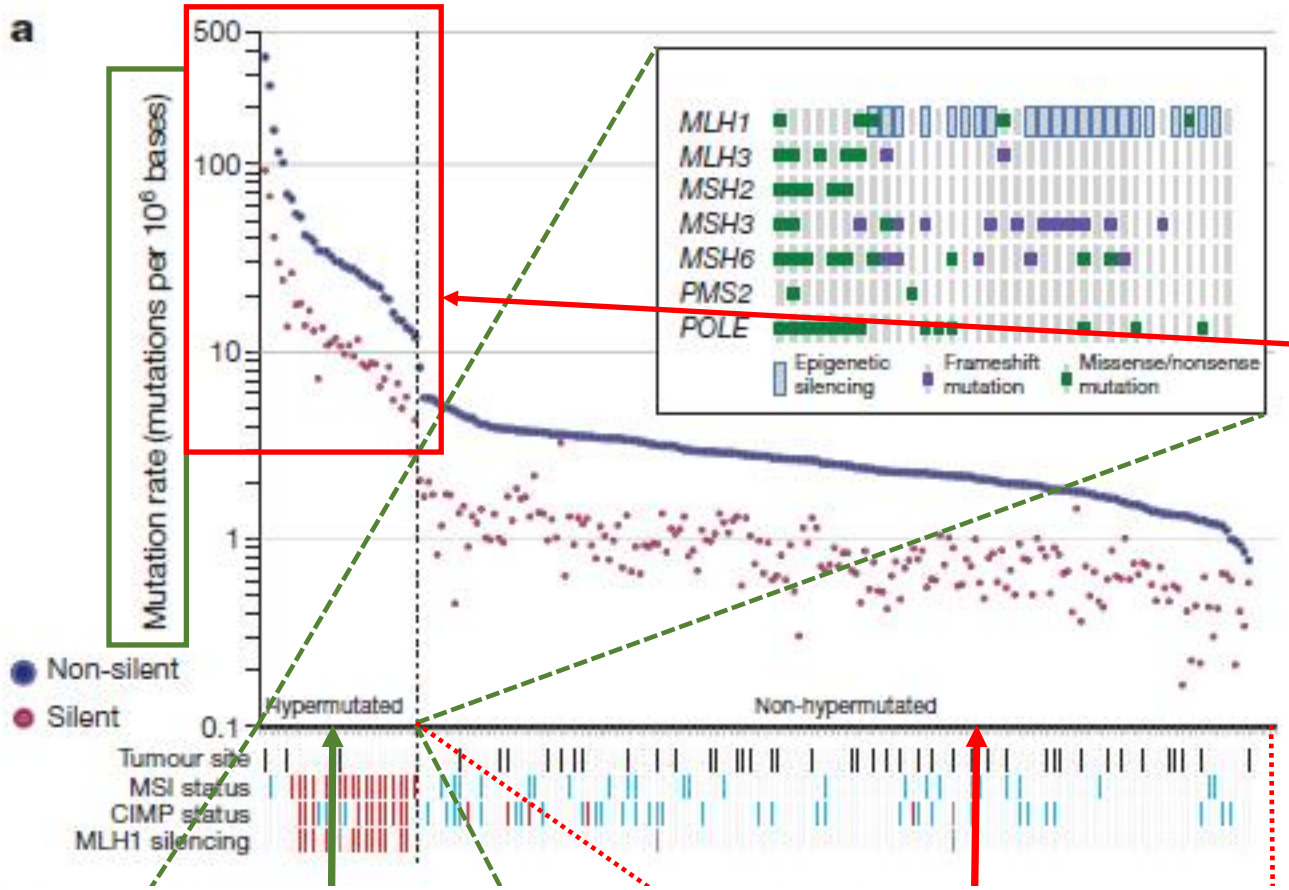
↓

Why does this constitute a problem?

Homopolymer/dinucleotide stretches in ORF of genes

C_{10} can be a coding sequence

Outcomes of microsatellite instability (MSI): Hypermutated vs. microsatellite-stable tumors



Mutation frequencies in human CRC:

a. Tumour samples from 224 patients. MSI lesions clearly separate from non-hypermutated samples

Red, MSI high, CIMP high or MLH1 silenced
Light blue, MSI low, or CIMP low;
black, rectum; white, colon;

Inset, mutations in mismatch-repair genes and POLE among the hypermutated samples.

b. Significantly mutated genes in hypermutated and non-hypermutated tumours.

Hereditary colorectal cancer syndromes

Question No.8

What is the molecular mechanism underlying hypermutation observed in tumors developed by Lynch patients?

Hereditary colorectal cancer syndromes

Lynch syndrome (Hereditary nonpolyposis colorectal cancer; HNPCC)

- accounts for about 3% of all colorectal cancer diagnoses each year

- disorder typically manifests later in life than FAP but produces a fast-growing cancer that occurs at an average age of 45. People with Lynch syndrome have an 80 percent lifetime risk of developing colorectal cancer, and they are also at much higher risk for endometrial, ovarian, stomach, urinary tract, and other cancers.

Determination of "HNPCC families":

evaluation of pattern of colorectal cancers in relatives throughout generations. Amstrerodam Criteria I & II, Bethesda guidelines

Hereditary colorectal cancer syndromes

Determination of "HNPCC families":

Amsterdam I Criteria

For a diagnosis of Lynch syndrome (LS), the Amsterdam I Criteria require at least three relatives with histologically verified colorectal cancer (CRC):

1. One is a first-degree relative of the other two;
2. At least two successive generations are affected;
3. At least one of the relatives with CRC is diagnosed at <50 years of age;
4. Familial adenomatous polyposis (FAP) has been excluded.

Amsterdam II Criteria

For a diagnosis of LS the Amsterdam II Criteria require at least three relatives with an LS-associated cancer (that is, CRC and cancers of the endometrium, stomach, ovary, ureter or renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumours)):

1. One is a first-degree relative of the other two;
2. At least two successive generations are affected;
3. At least one of the LS-associated cancers should be diagnosed at <50 years of age;
4. FAP should be excluded in any CRC cases;
5. Tumours should be verified by pathology whenever possible.

Hereditary colorectal cancer syndromes

Determination of "HNPCC families": continued

To justify MSI testing, the Bethesda Guidelines require:

1. CRC diagnosed in a patient who is <50 years of age;
2. Presence of synchronous or metachronous colorectal or other LS-associated tumours*, regardless of age;
3. CRC with MSI-high (MSI-H)‡ histology§ diagnosed in a patient who is <60 years of age||;
4. CRC or LS-associated tumour* diagnosed <50 years of age in at least one first-degree relative¶;
5. CRC or LS-associated tumour* diagnosed at any age in two first- or second-degree relatives¶.

*LS-associated tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract and brain (usually glioblastoma) tumours, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel. ‡MSI-H in tumours refers to changes in two or more of the five US National Cancer Institute-recommended panels of microsatellite markers. §MSI-H histology refers to the presence of tumour-infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern. ||There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3; participants voted to keep <60 years of age in the guidelines. ¶Criteria 4 and 5 have been reworded to clarify the Revised Bethesda Guidelines.

Further hereditary colorectal cancer syndromes

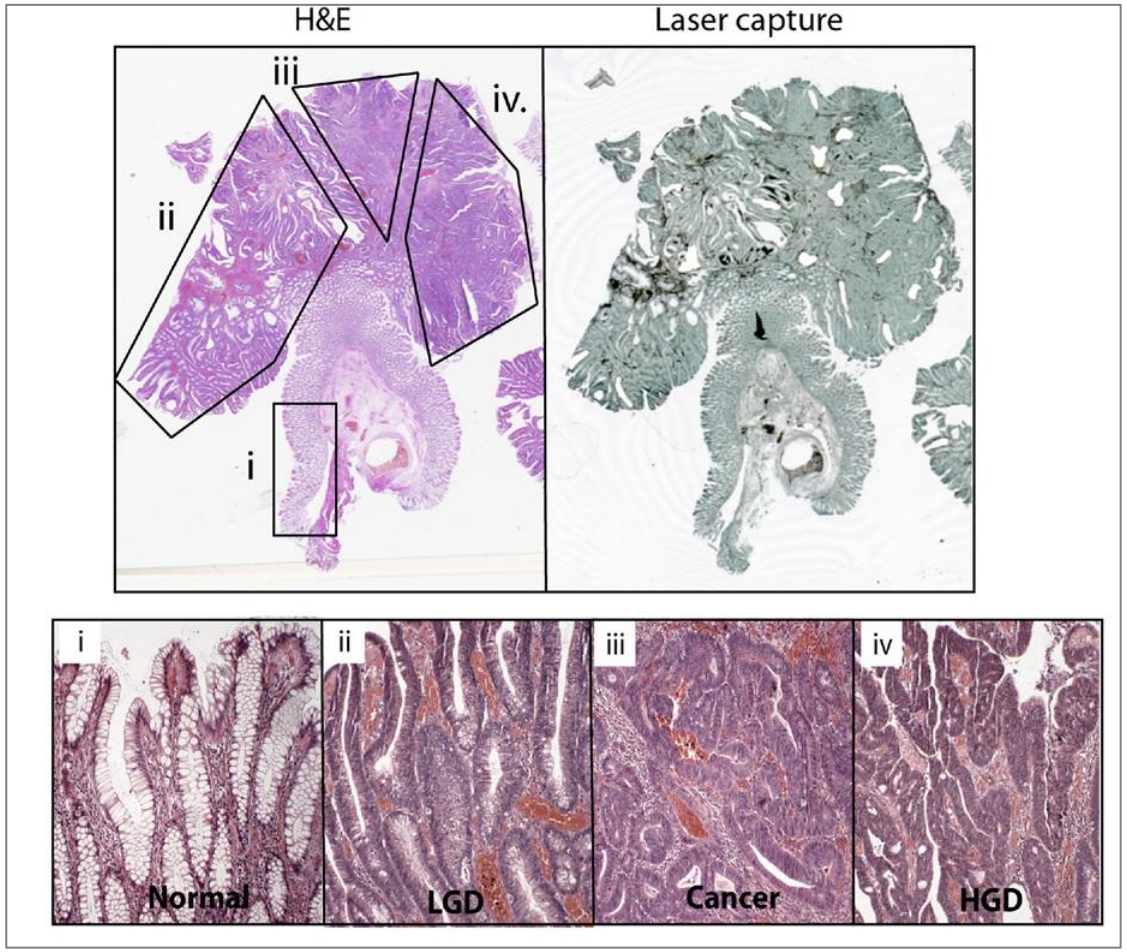
MYH-Associated Polyposis (MAP)

- caused by mutations in the ***MUTYH* gene**: encodes a **DNA glycosylase involved in oxidative DNA damage repair**. The enzyme excises adenine bases from the DNA backbone at sites where adenine is inappropriately paired with guanine, cytosine, or 8-oxo-7,8-dihydroguanine, a major oxidatively damaged DNA lesion.
- MAP follows an autosomal recessive inheritance pattern (i.e., both maternal and paternal alleles have to be affected)
- MAP is usually suspected if a person has multiple adenomatous colon polyps but does not have a mutation in the *APC* gene, or has brothers or sisters with multiple colon polyps but there is no history of colon problems in previous generations.

Hyperplastic Polyposis Syndrome (HPS)

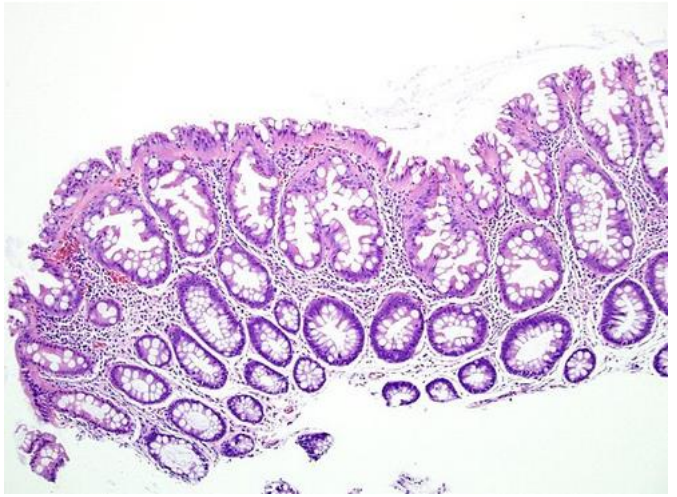
- several genetic mutations that might cause HPS have been described, but none has been conclusively identified
- a rare condition characterized by the development of multiple hyperplastic polyps in the colon and rectum

Cellular dysplasia versus hyperplasia



Thirlwell, C., Gastroenterology 2010

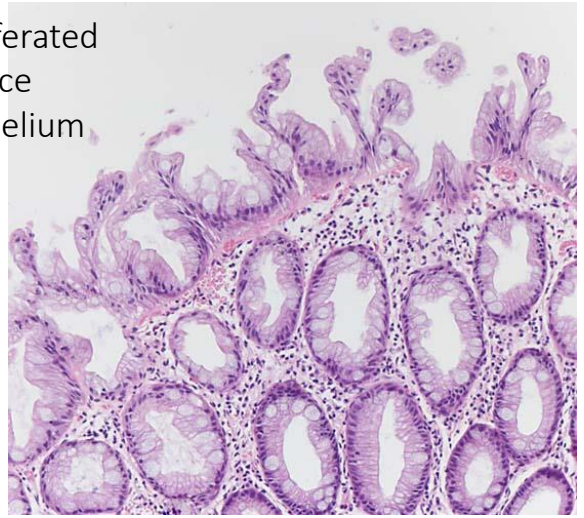
Dysplastic cells:
- hyperchromatic, cigar shaped enlarged nuclei
- according to maintenance of basal orientation and architectural disarray - Low/High Grade Dysplasia



vSlides, Pathorama

Hyperplastic cells:
dilated with serrated (saw tooth) appearance

proliferated surface epithelium



PathoPic

Colorectal cancerogenesis traits

Colon carcinomas develop via various histologically definable routes → individual subtypes od colon cancer are biologically highly distinct

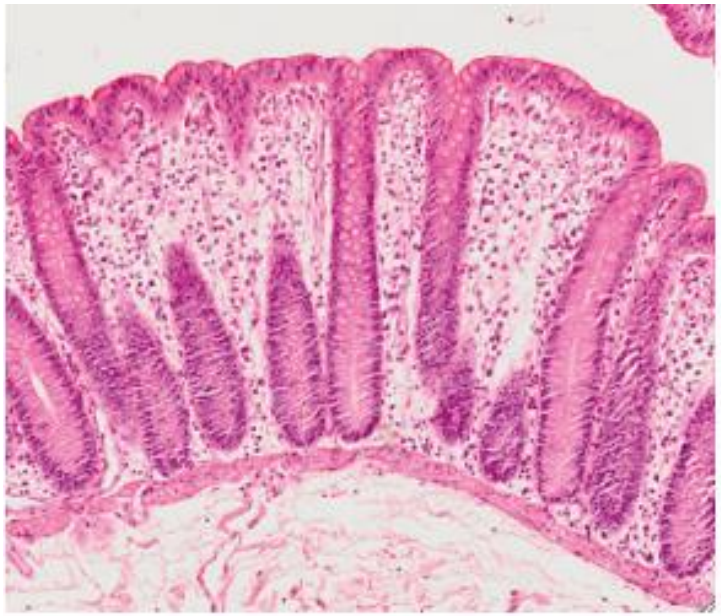
Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

1. Chromosomal instable cancers (CIN)
2. Microsatellite instable cancers (MSI)
3. Sessile-serrated pathway

Chromosomal instable cancers (CIN)

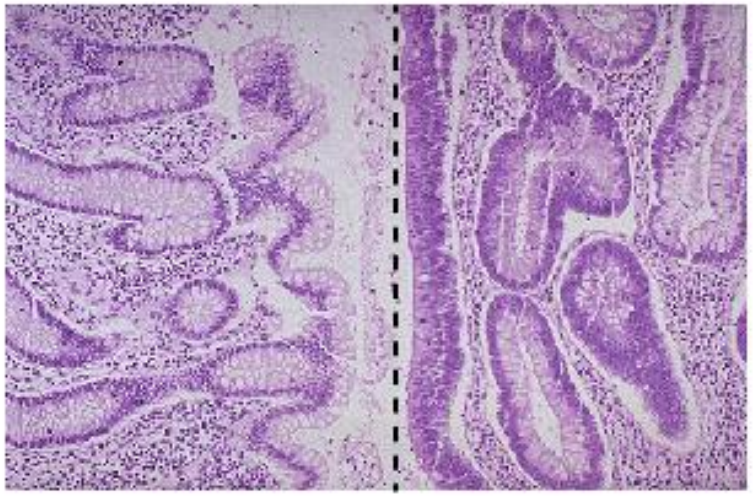
Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

1. Chromosomal instable cancers (CIN): non-hypermutated tumors: *APC-KRAS-TP53* pathway; tubovillous adeno/carcinomas developing from dysplastic lesions. Left-sided (i.e. affecting distal colonic regions (aboral)).



vSlides, Pathorama

Healthy colonic epithelium



Healthy colonic epithelium

Tubular adenomatous polyp

Dysplastic glands (cells): Irregular, with hyperchromatic and more crowded nuclei

Benign, well-differentiated neoplasm (still closely resembles normal colonic architecture)

library.med.utah.edu

Chromosomal instable cancers (CIN)

Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

1. Chromosomal instable cancers (CIN):

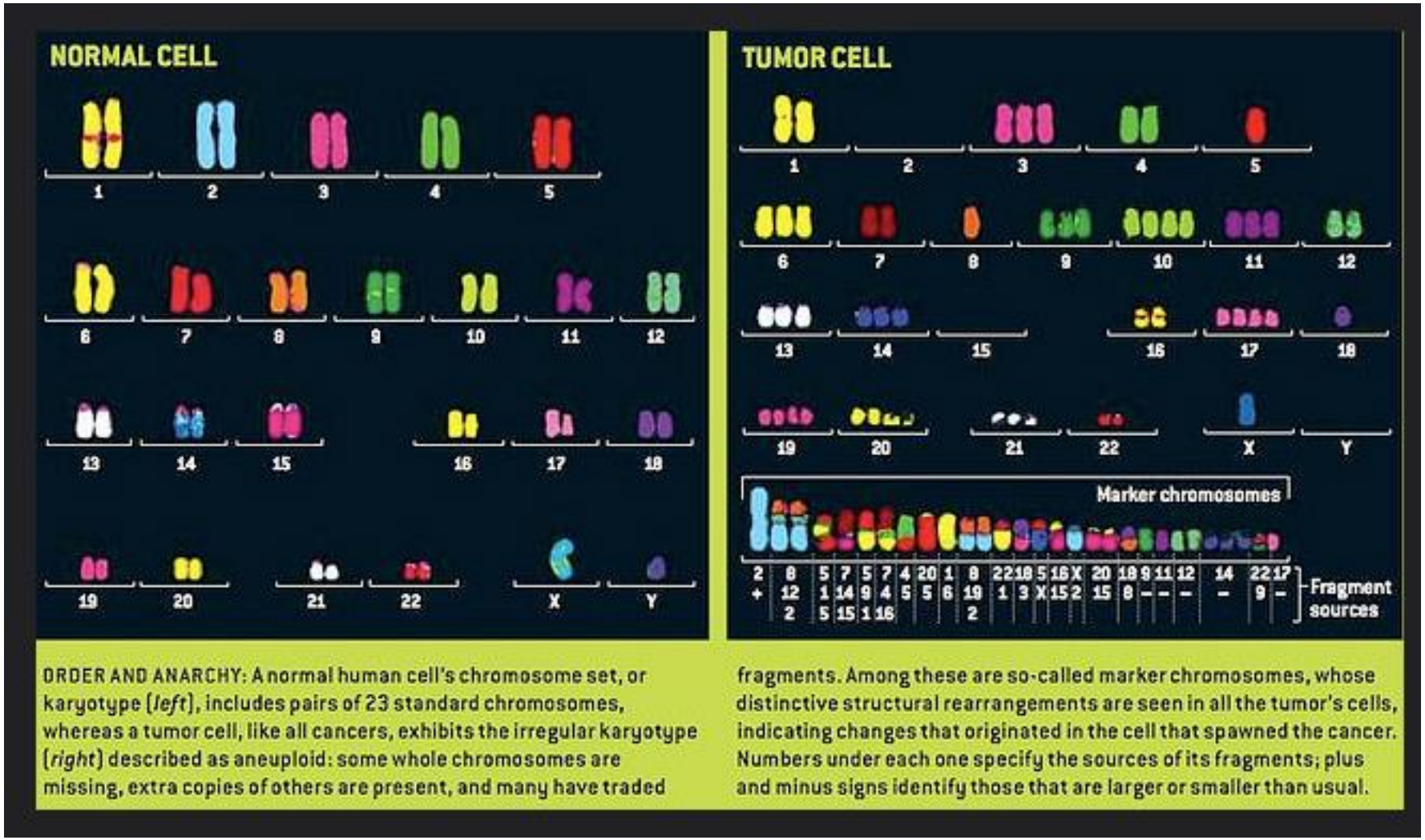
Chromosomal instability (CIN): type of genomic instability in which chromosomes are unstable, such that either whole chromosomes or parts of chromosomes are duplicated or deleted. The unequal distribution of DNA to daughter cells upon mitosis results in a failure to maintain euploidy leading to aneuploidy (i.e. incorrect number of chromosomes).

Segmental aneuploidy: breaks in DNA: gives rise to deletions, amplifications or translocations

Gross chromosomal rearrangements (GCR): errors during mitosis: loss and gain of whole chromosomes

Chromosomal instable cancers (CIN)

Healthy cell:
diploid

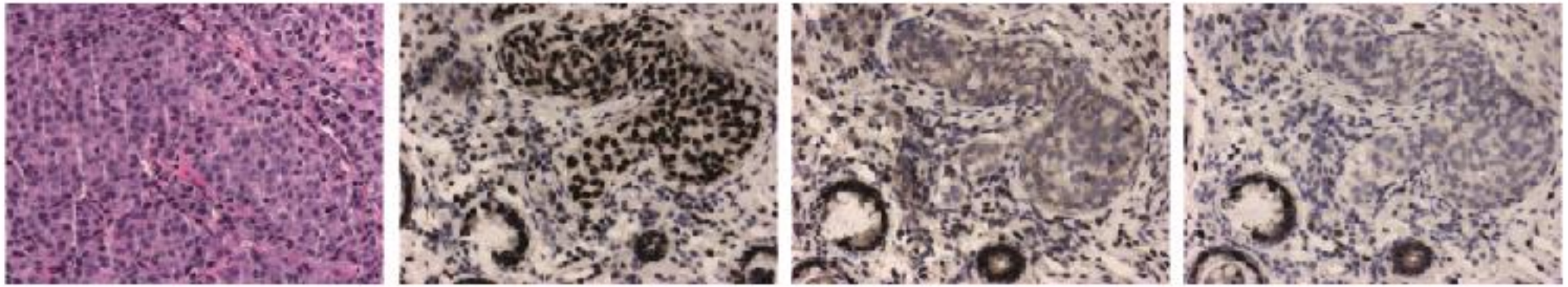


Cancerous cell:
aneuploid
i.e. irregular karyotype

Microsatellite instable cancers (MSI)

Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

1. Chromosomal instable cancers (CIN)
2. Microsatellite instable cancers (MSI): hypermutated tumors, CIMP^{+}; inactivation (mutational, epigenetic) of MMR genes; characteristic pathomorphology. Right-sided (proximal colon (oral)).

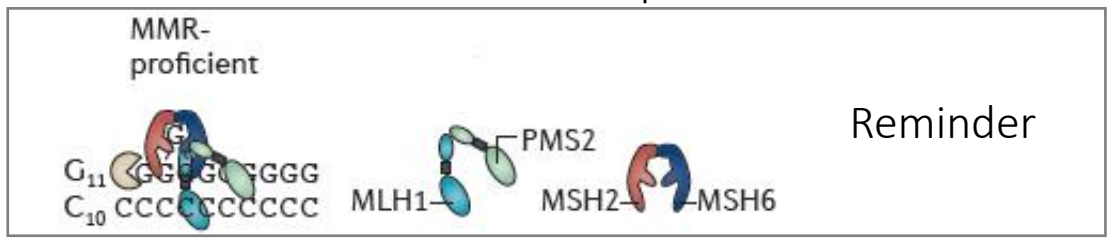


PathoPic

Poorly differentiated colorectal carcinoma in HNPCC (*MSH2* germline); ascending colon; MSI-high.

IHC of the tumor: MLH1 and PMS2 positive (preserved), MSH2 and MSH6 negative (lost).

When MSH2 expression is lost, MSH6 is also lost because MSH6 requires MSH2 for stabilization through heterodimerization.

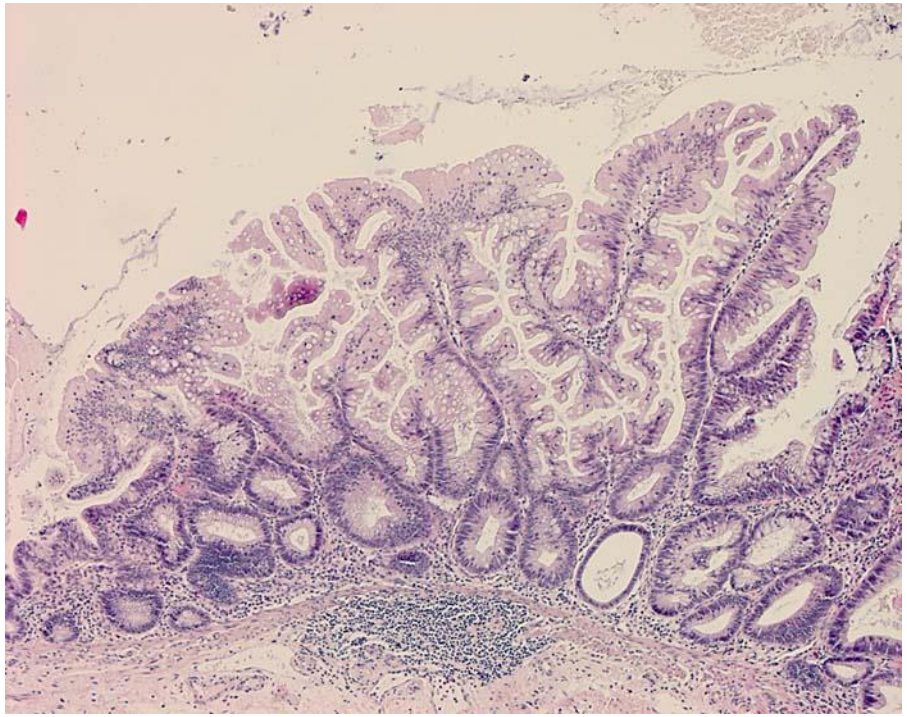


Reminder

Sessile-serrated cancerogenesis trait

Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

1. Chromosomal instable cancers (CIN)
2. Microsatellite instable cancers (MSI)
3. Sessile-serrated pathway



PathoPic

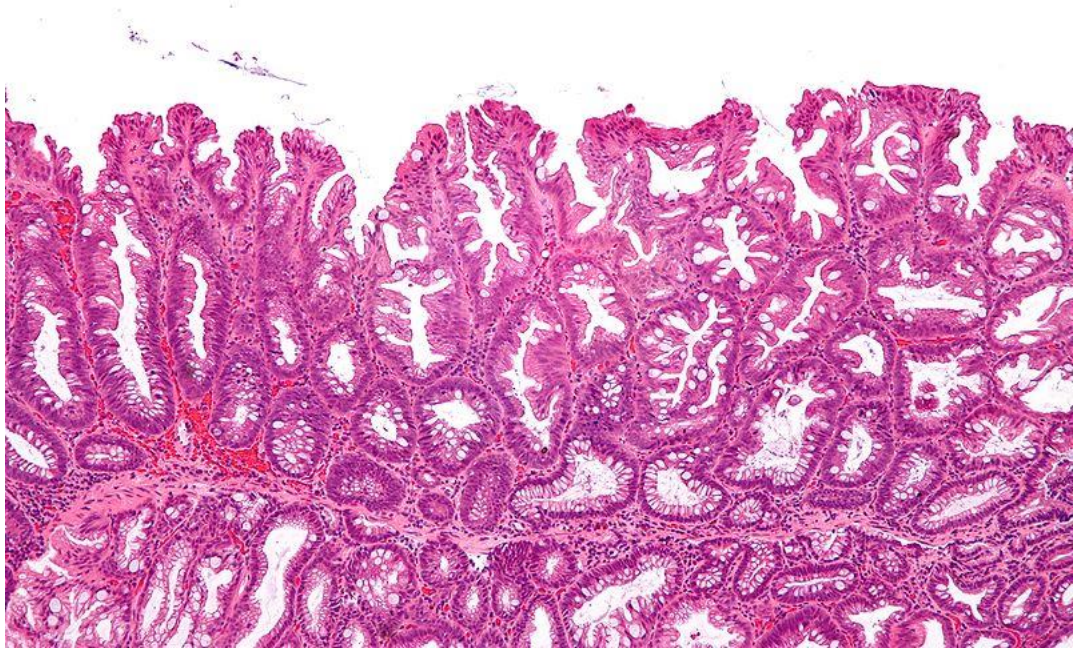
Serrated adenoma

saw tooth configuration of hyperplastic polyp with dysplasia of the epithelial lining of the upper portion of the crypts and the luminal surface

Sessile-serrated cancerogenesis trait

Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

3. Sessile-serrated pathway:



commons.wikimedia.org

Sessile-serrated adenoma (cecum)

SSAs are characterized by:

- basal dilation of the crypts,
- basal crypt serration,
- crypts that run horizontal to the basement membrane (horizontal crypts),
and crypt branching.

Unlike traditional colonic adenomas (e.g. tubular adenoma, villous adenoma), they do not typically have nuclear changes (nuclear hyperchromatism, nuclear crowding, elliptical/cigar-shaped nuclei).

Sessile-serrated cancerogenesis trait

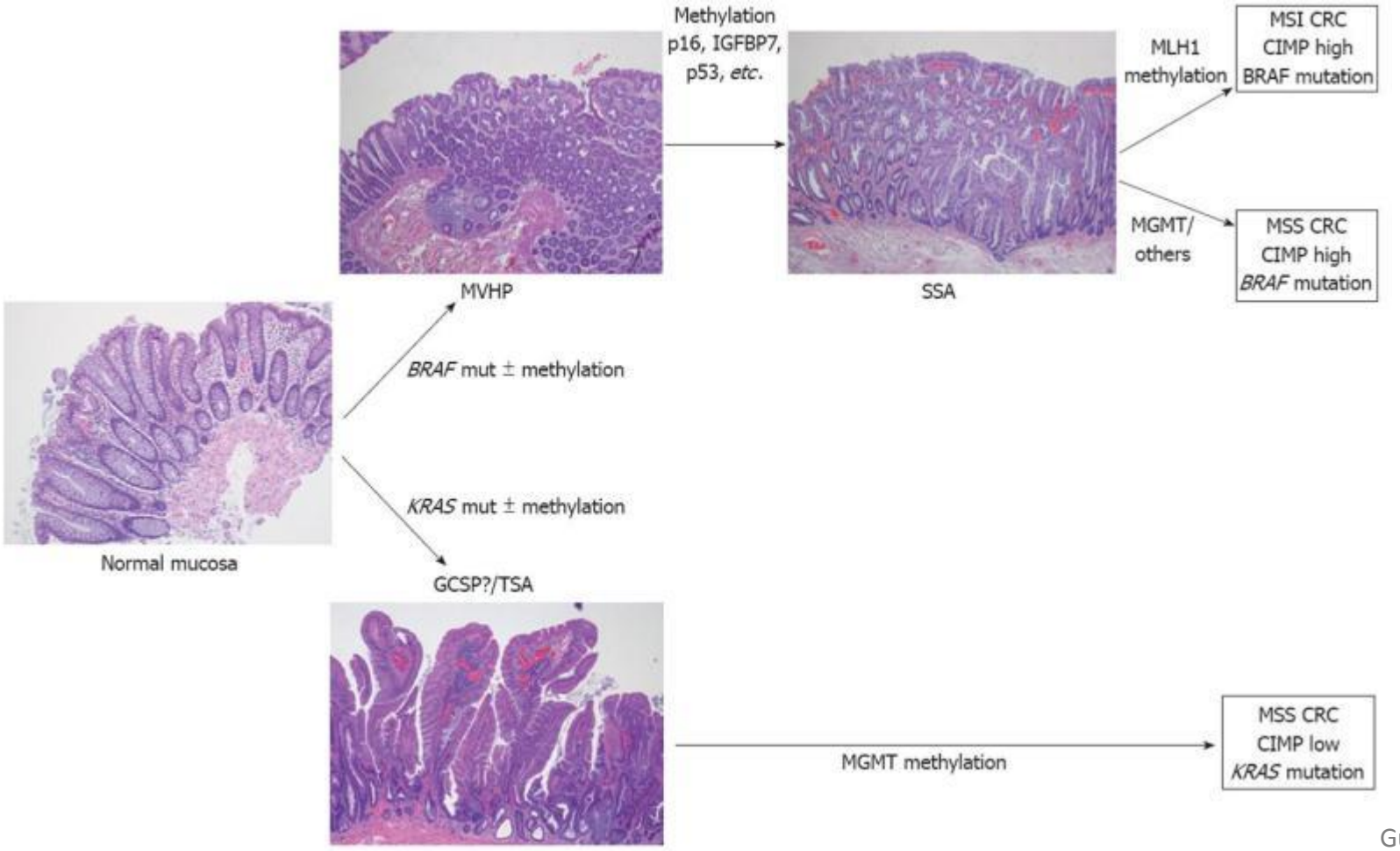
Colorectal cancerogenesis traits: classification of colorectal lesions to three main molecularly distinct subtypes

3. Sessile-serrated pathway:

Sessile-serrated adenomas: considered pre-malignant lesions, i.e. precursors to cancer, and tend to be found in the right colon

Serrated tumors: largely microsatellite stable and contain relatively more CpG island methylator phenotype–positive ($CIMP^+$) carcinomas but cannot be identified on the basis of characteristic mutations.

Sessile-serrated cancerogenesis trait



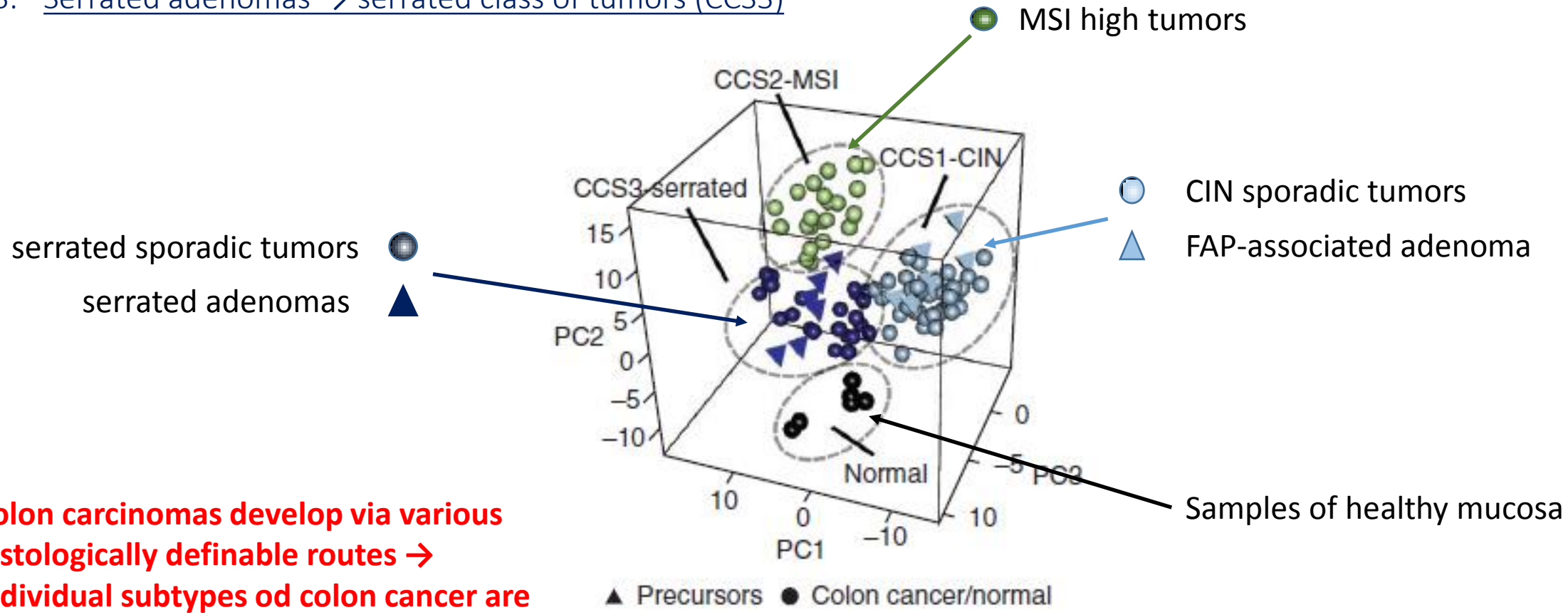
Guarinos, World J Gastroenterology 2012

Model of serrated pathway of colorectal carcinogenesis. MVHP: Microvesicular hyperplastic polyp; SSA: Sessile serrated adenoma; MGMT: Methylguanine methyltransferase; CIMP: CpG island methylator phenotype; GCSP: Goblet cell serrated polyp; TSA: Traditional sessile adenomas.

Classification of CRC into clusters

Principal component analysis of precursor lesions in relation to colon cancer samples (expression profiling clustering)

1. Dysplastic polyps (*APC*) → Chromosomal instable cancers (CIN)
2. Microsatellite instable cancers (MSI)
3. Serrated adenomas → serrated class of tumors (CCS3)



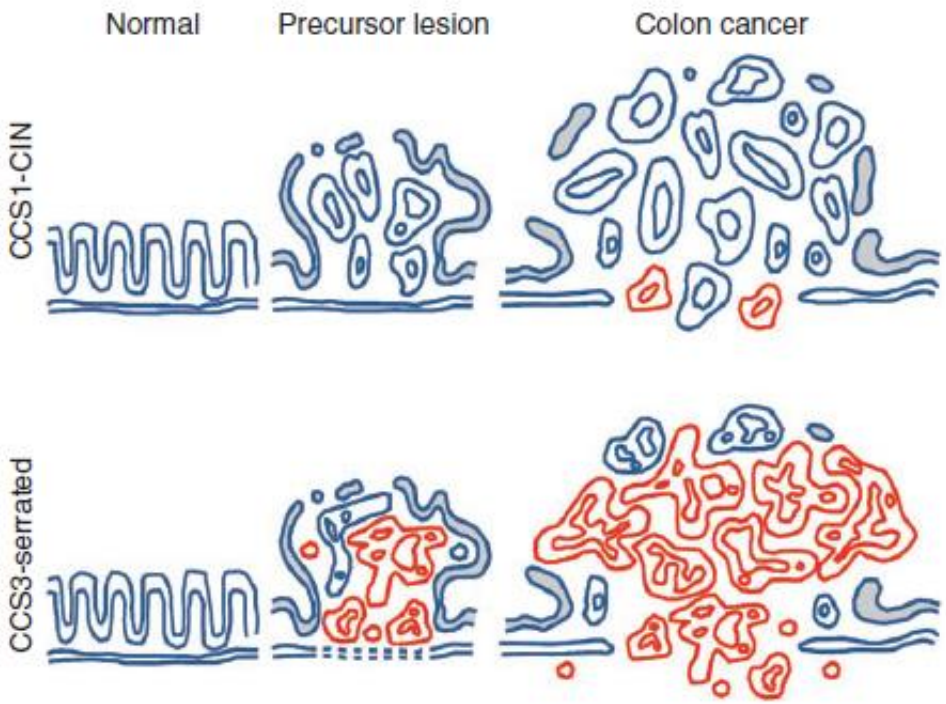
Colon carcinomas develop via various histologically definable routes → individual subtypes od colon cancer are biologically highly distinct

de Sousa E Melo, Nature Medicine 2013

Sessile-serrated route to colon cancer

Sessile-serrated pathway: largely microsatellite stable and contains relatively more CpG island methylator phenotype–positive ($CIMP^+$) carcinomas but cannot be identified on the basis of characteristic mutations.

- relates to sessile-serrated adenomas: upregulation of genes involved in matrix remodeling, epithelial-mesenchymal transition, cell migration and transforming growth factor-β (TGF-β) signaling
- has a very unfavorable prognosis and, moreover, is refractory to epidermal growth factor receptor (EGFR)-targeted therapy (Cetuximab).
- large proportion of patients with *BRAF* and *KRAS* mutations
- enriched with histologically poorly differentiated cancers



Serrated precursor lesions are “primed“ to invade and metastasize (indicated by the interrupted basement membrane) and presence of glandular structures containing cells of high invasive potential (depicted in red).

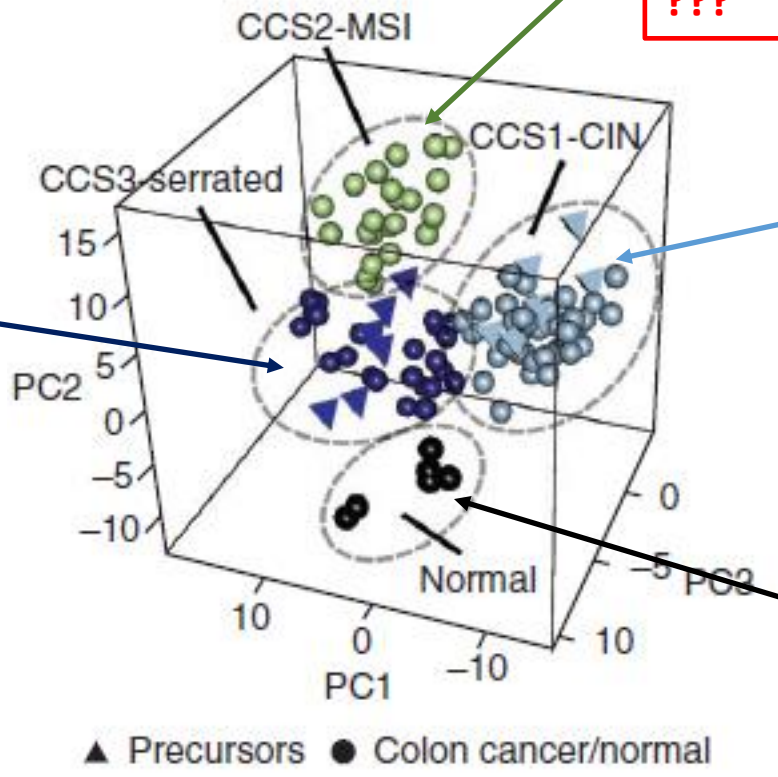
de Sousa E Melo, Nature Medicine 2013

Classification of CRC into clusters

Principal component analysis of precursor lesions in relation to colon cancer samples (expression profiling clustering)

1. Dysplastic polyps (*APC*) → Chromosomal instable cancers (CIN)
2. Microsatellite instable cancers (MSI)
3. Serrated adenomas → serrated class of tumors (CCS3)

MSI high tumors
???



serrated sporadic tumors

serrated adenomas

CIN sporadic tumors

FAP-associated adenoma

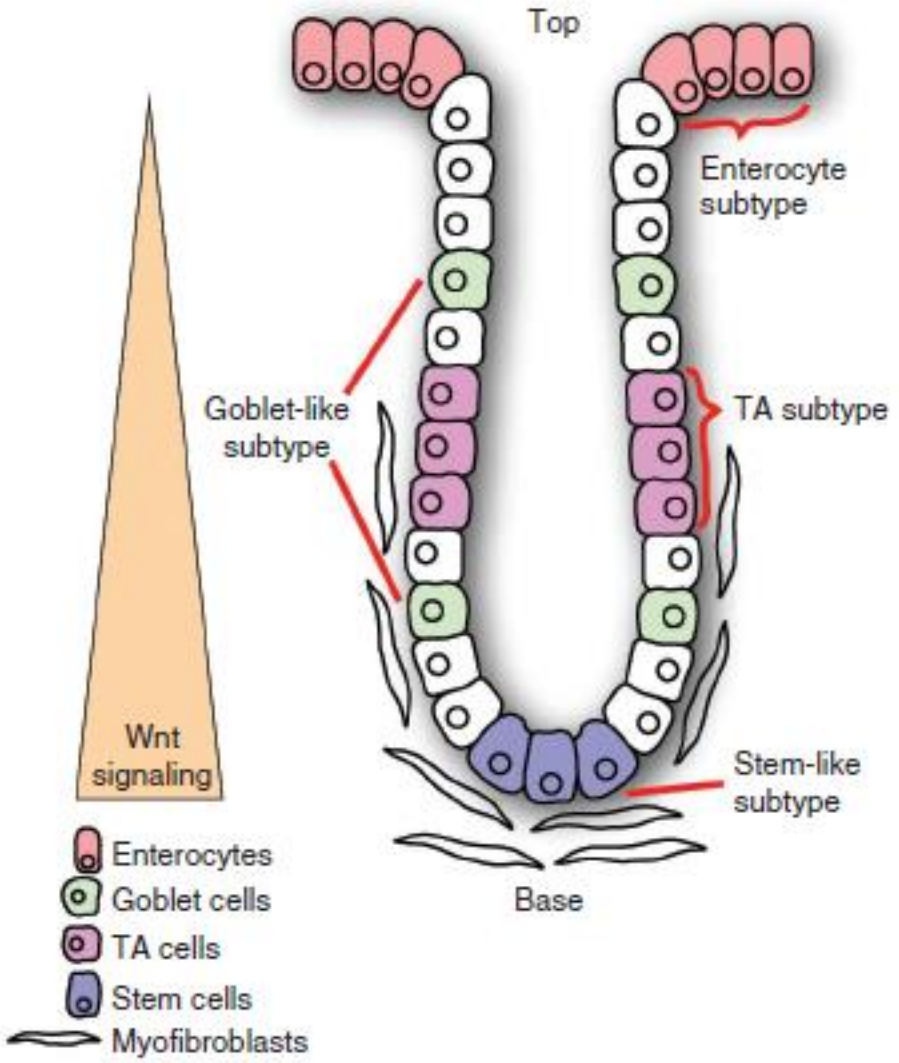
Samples of healthy mucosa

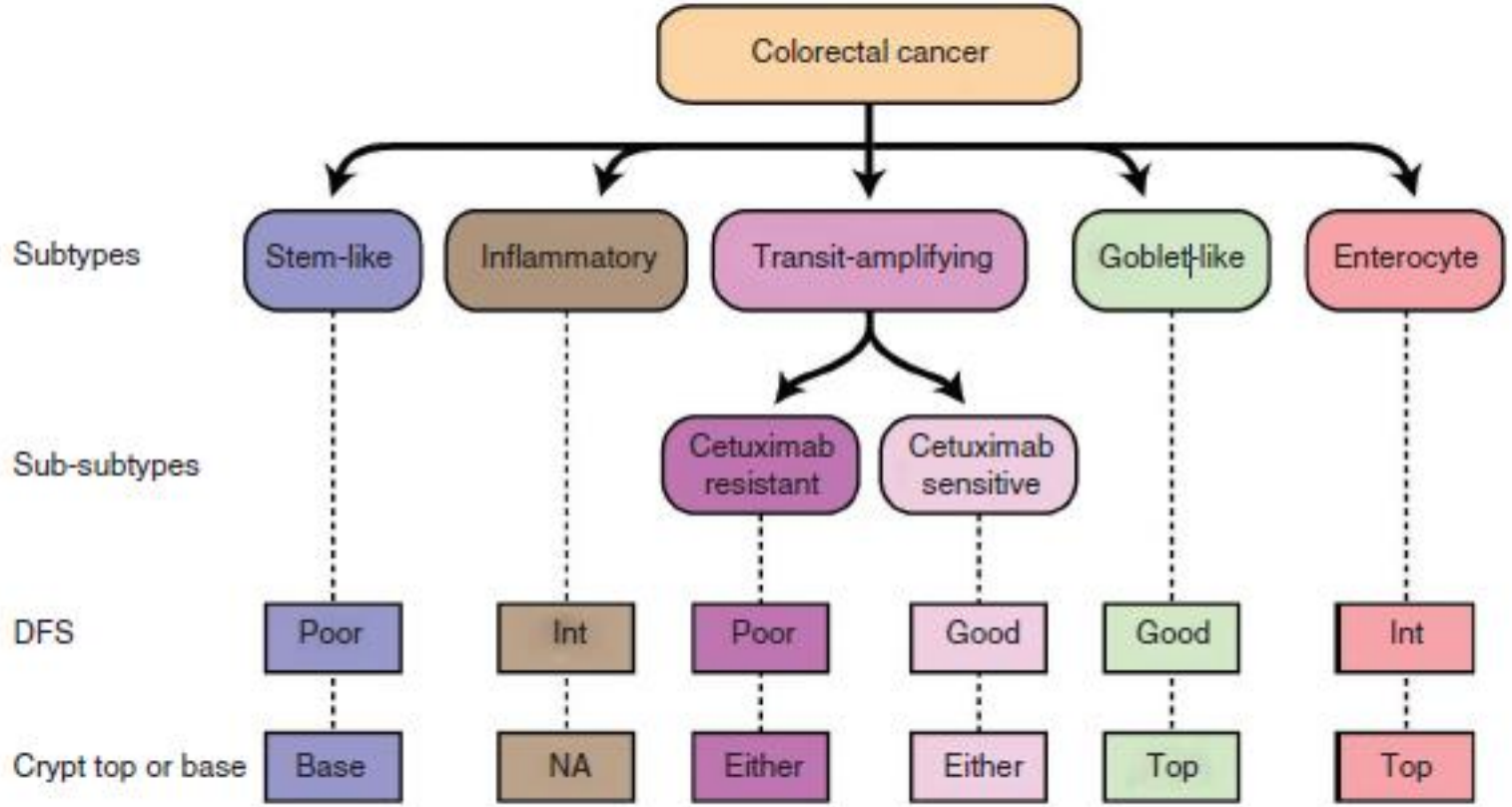
Question No.9

Where (and what) are the precursors for MSI high tumors?

de Sousa E Melo, Nature Medicine 2013

Molecular stratification of colorectal cancer II.

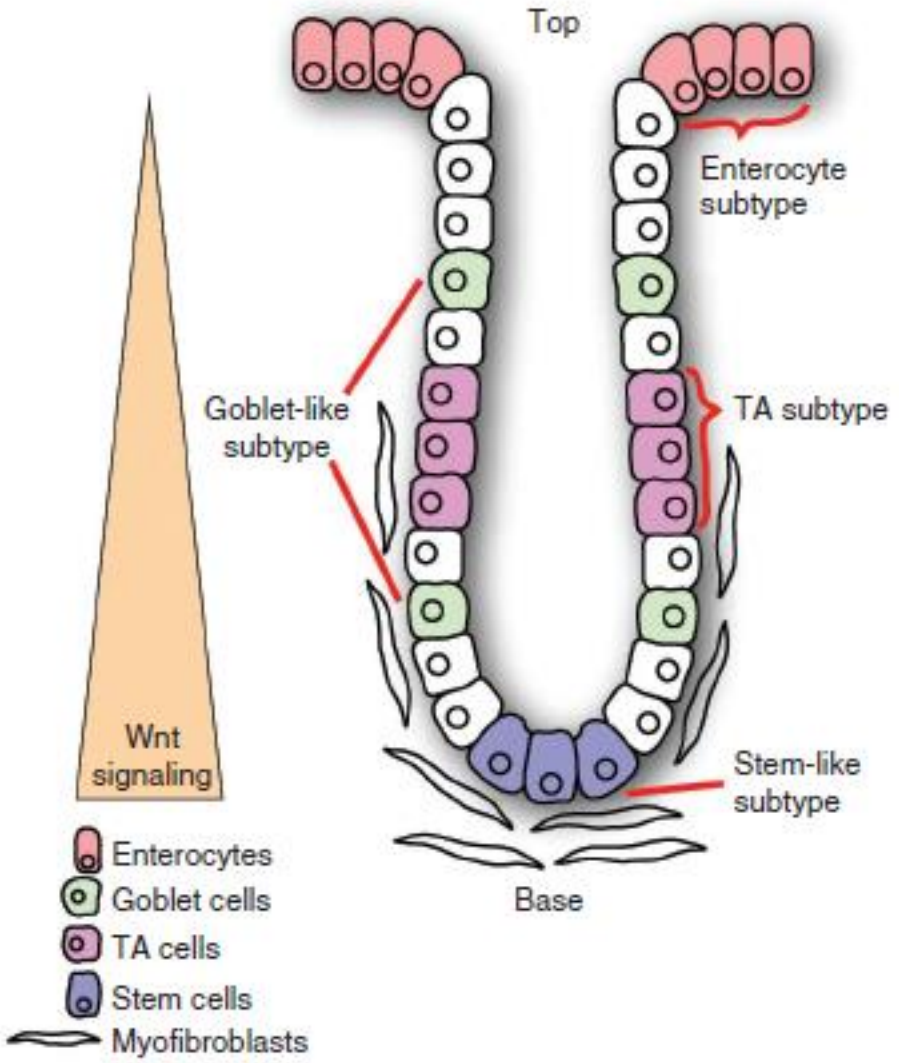


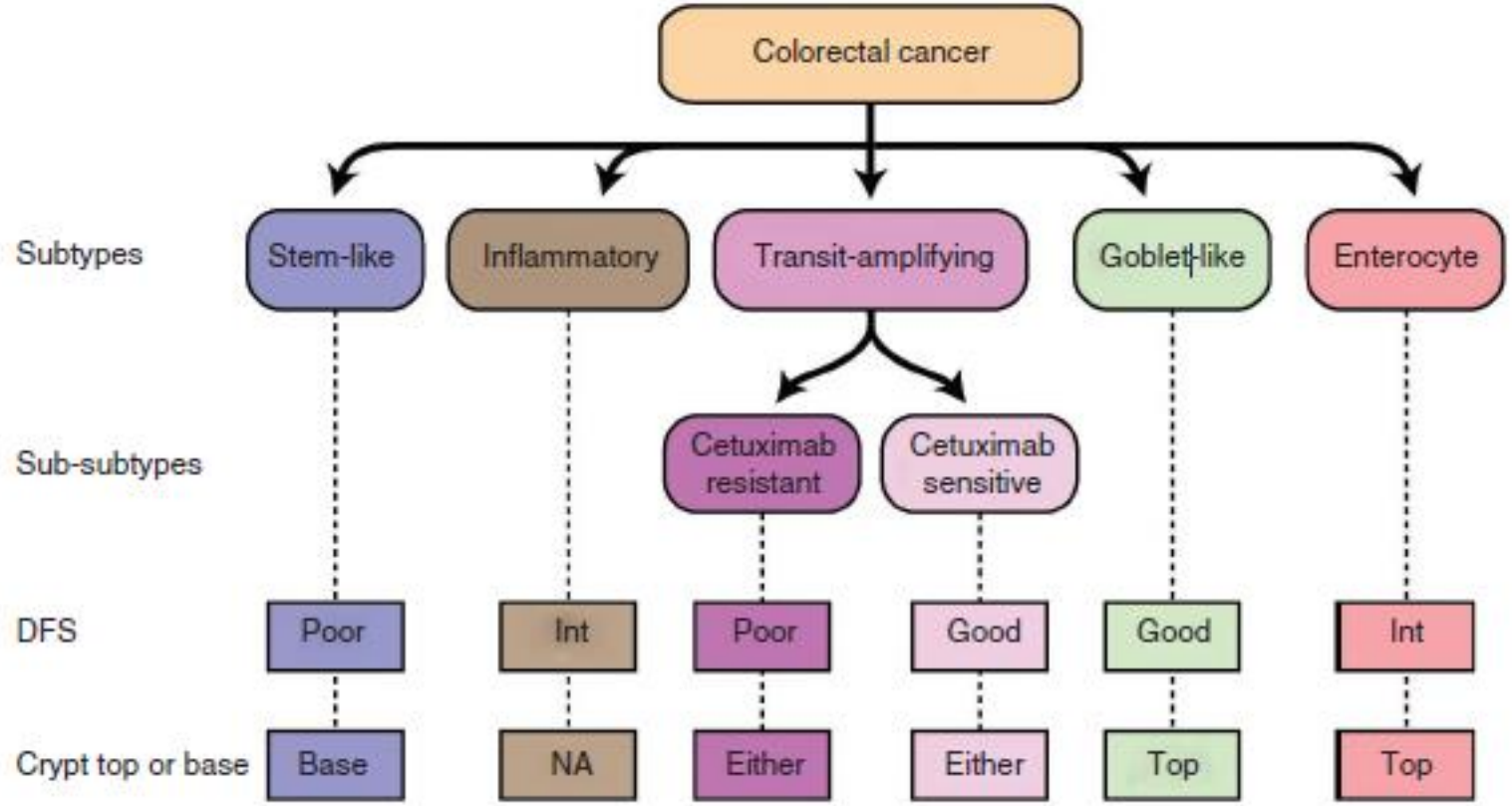


Gene expression profiles of large CRC cohorts define clinically relevant molecular subtypes to the disease

Sadanandam, A. *et al.*; Nature Medicine 2013

Molecular stratification of colorectal cancer II.

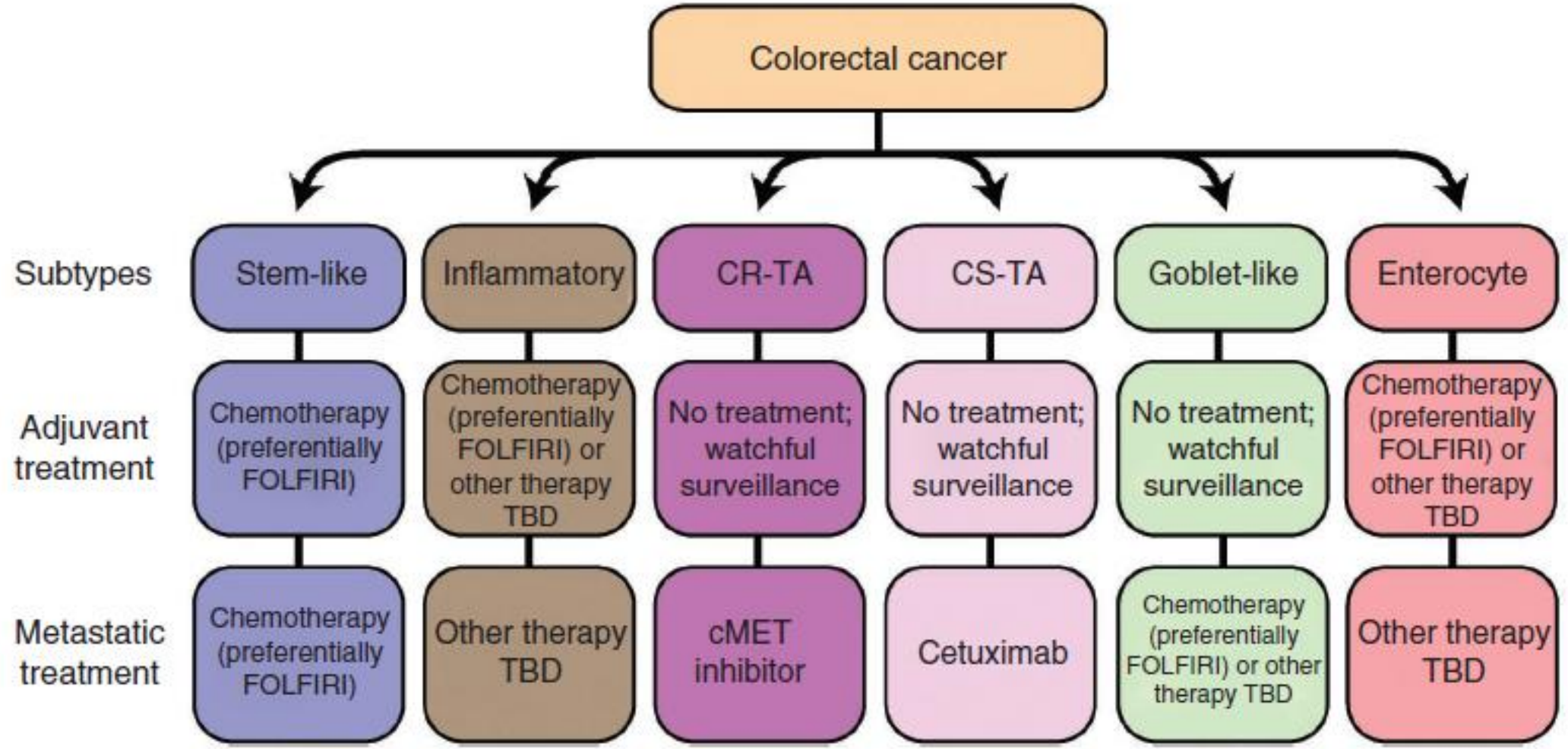




Question No.10

Why is the “Crypt“ phenotype correlated to poorer prognosis?

Transcriptome-based classification may promote optimization of CRC subtype-guided regimens to the disease



Sadanandam, A. *et al.*; Nature Medicine 2013

Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

Take-home messages

1. Three intercorvertible pools of intestinal stem cells maintain tissue homeostasis
2. Intestinal self-renewal is governed by principal developmental signaling pathways (Wnt, Notch, TGF-b *etc.*)
3. The same signaling circuits are hijacked in cancer to drive malignant progression

4. Inherited colorectal cancer syndromes reveal genes esential to sporadic cancerogenesis

5. Colorectal cancer encompasses clinically heterogenous disease: stratification according to mutational landscape or expression profiling

Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

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esf european social fund in the czech republic

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Malignant transformation of the gastrointestinal tissue; with a special focus on the Wnt signaling pathway

Thank you for your attention

Michaela Krausová

Institute of Molecular Genetics of the ASCR, v.v.i.

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"Founding the Centre of Transgenic Technologies"

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