

Corso di Oncologia Molecolare

AA 2020-2021

**ALTERAZIONI DELLE VIE DI SEGNALAZIONE DA GF
NEL CANCRO**



MY CANCER GENOME®
GENETICALLY INFORMED CANCER MEDICINE

What are you looking for?



Clinical Trials



Diseases



Biomarkers



Drugs



Pathways

[Query](#)
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 Please cite: [Cerami et al., 2012](#) & [Gao et al., 2013](#)
Select Studies for Visualization & Analysis:

0 studies selected (0 samples)

PanCancer Studies

7

Pediatric Cancer Studies

13

Immunogenomic Studies

8

Cell lines

3

Adrenal Gland

3

Ampulla of Vater

1

Biliary Tract

9

Bladder/Urinary Tract

17

Bone










2

Quick select:

PanCancer Studies

- MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017) 10945 samples   
- Metastatic Solid Cancers (UMich, Nature 2017) 500 samples   
- MSS Mixed Solid Tumors (Broad/Dana-Farber, Nat Genet 2018) 249 samples   
- SUMMIT - Neratinib Basket Study (Multi-Institute, Nature 2018) 141 samples   
- TMB and Immunotherapy (MSKCC, Nat Genet 2019) 1661 samples   
- Tumors with TRK fusions (MSK, Clin Cancer Res 2020) 106 samples   
- Cancer Therapy and Clonal Hematopoiesis (MSK, Nat Genet 2020) 24146 samples   

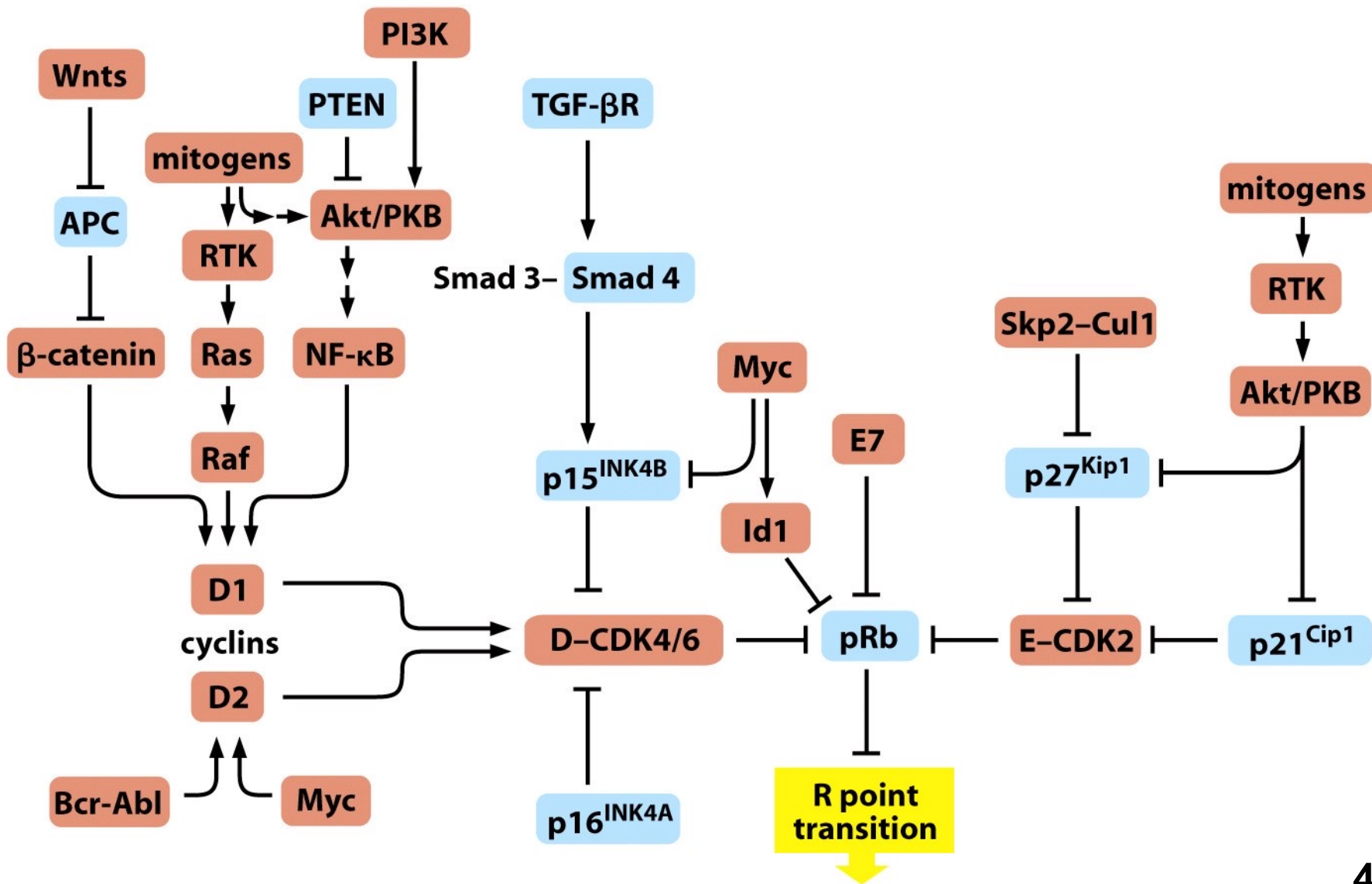
Pediatric Cancer Studies

- Pediatric Preclinical Testing Consortium (CHOP, Cell Rep 2019) 261 samples   
- Pediatric Acute Lymphoid Leukemia - Phase II (TARGET, 2018) 1978 samples   
- Pediatric Rhabdoid Tumor (TARGET, 2018) 72 samples   

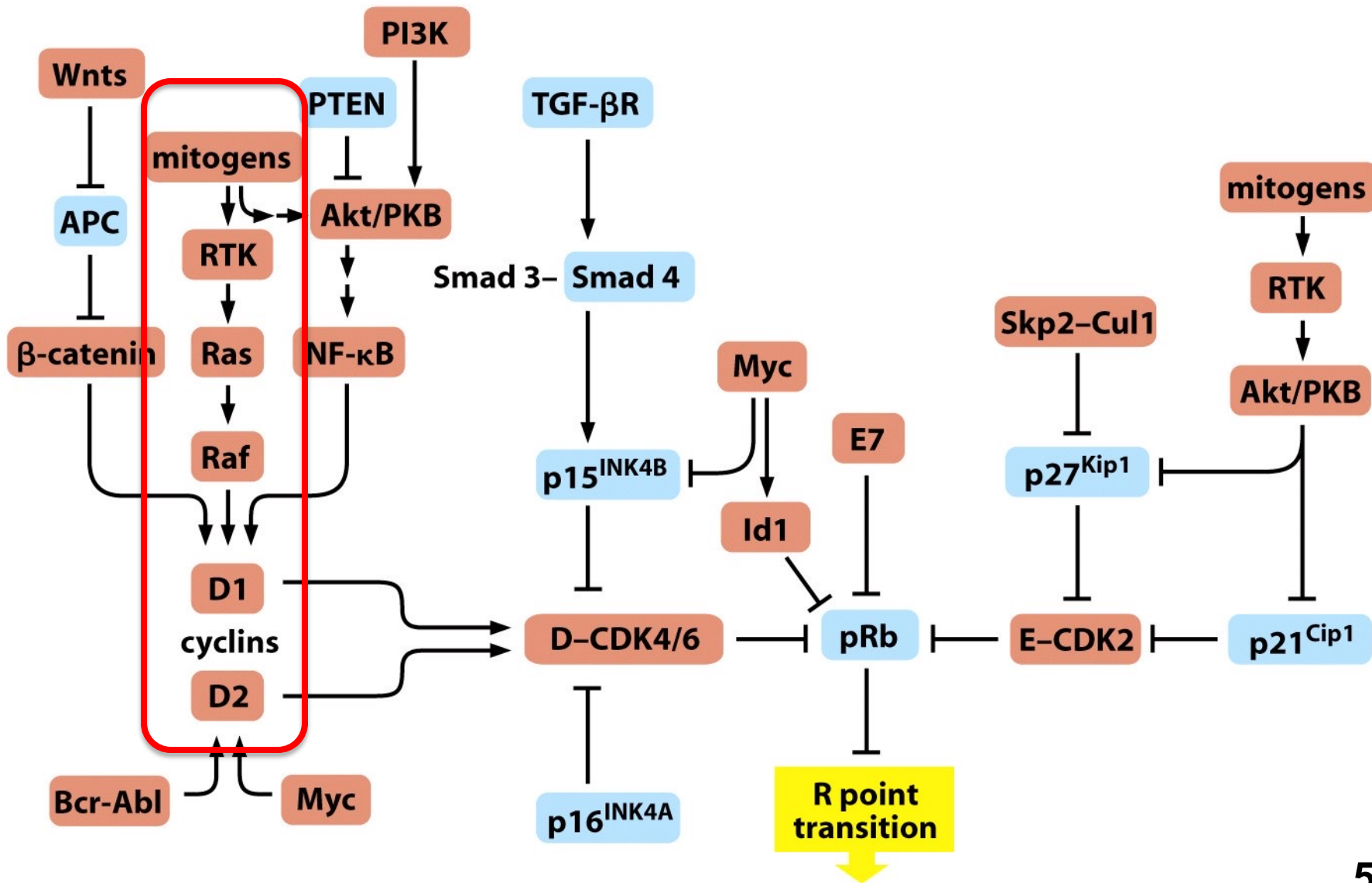
0 studies selected (0 samples)

OR

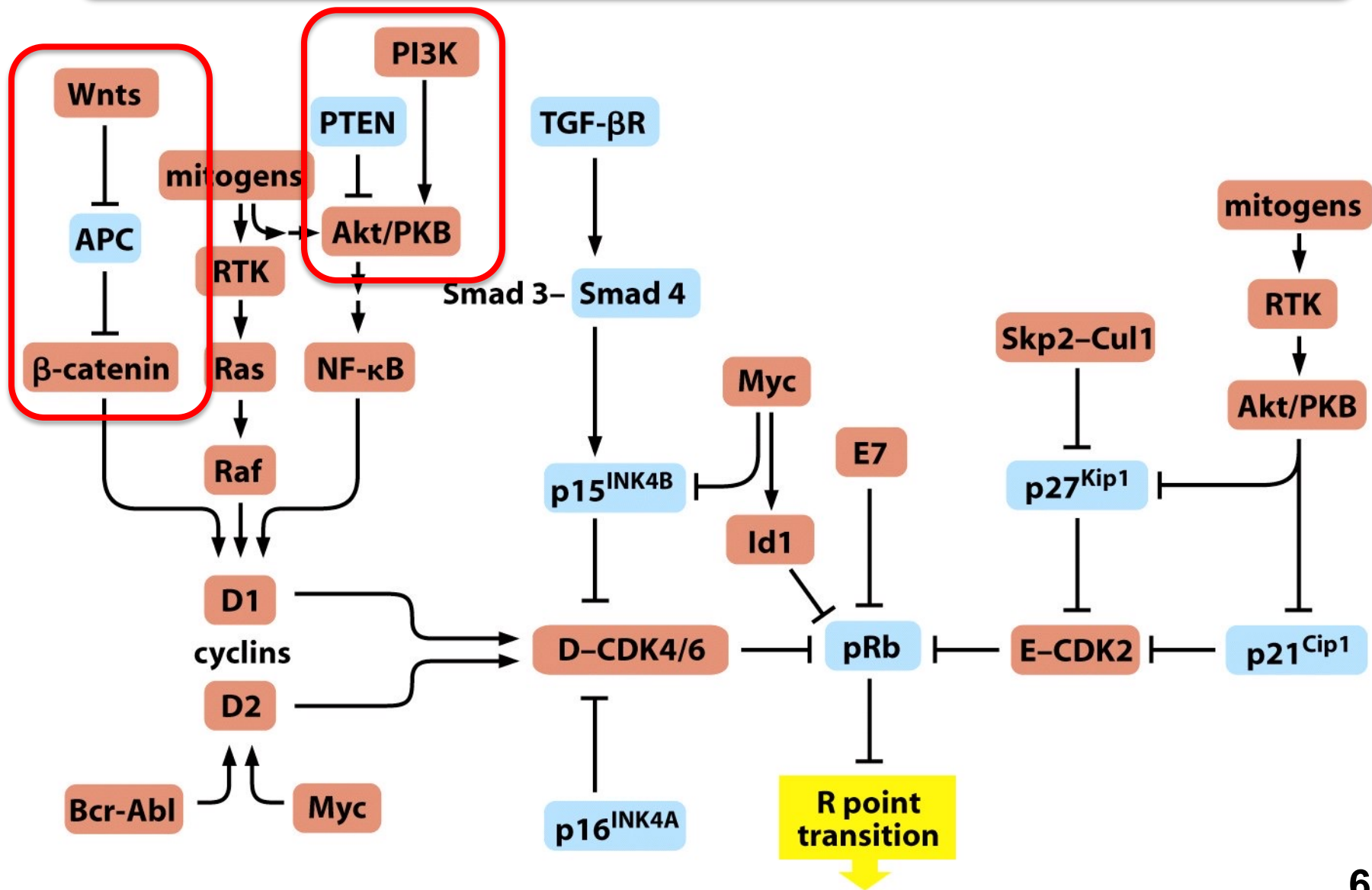
Acquisizione dell'indipendenza proliferativa nel cancro



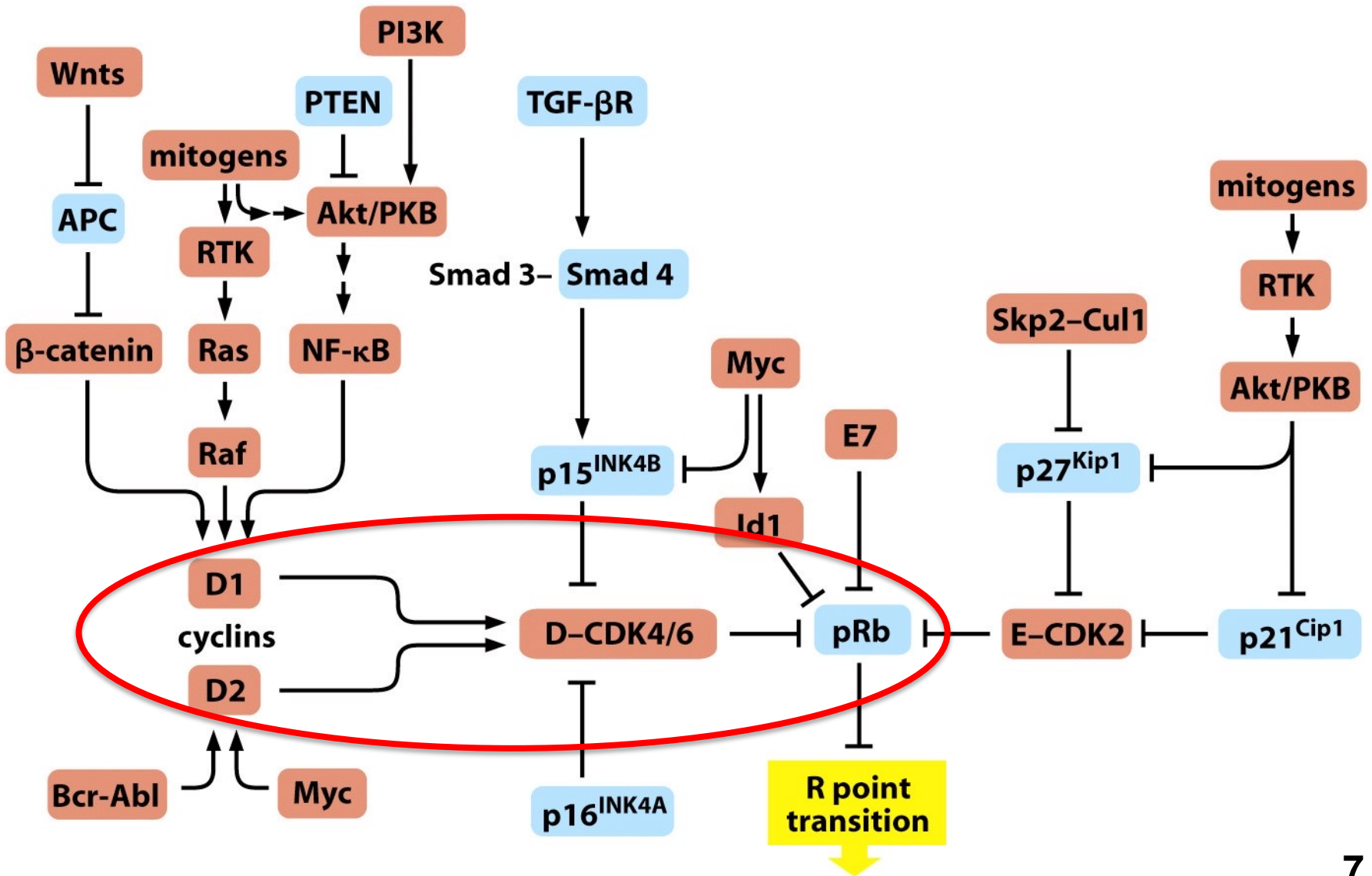
Acquisizione dell'indipendenza proliferativa nel cancro



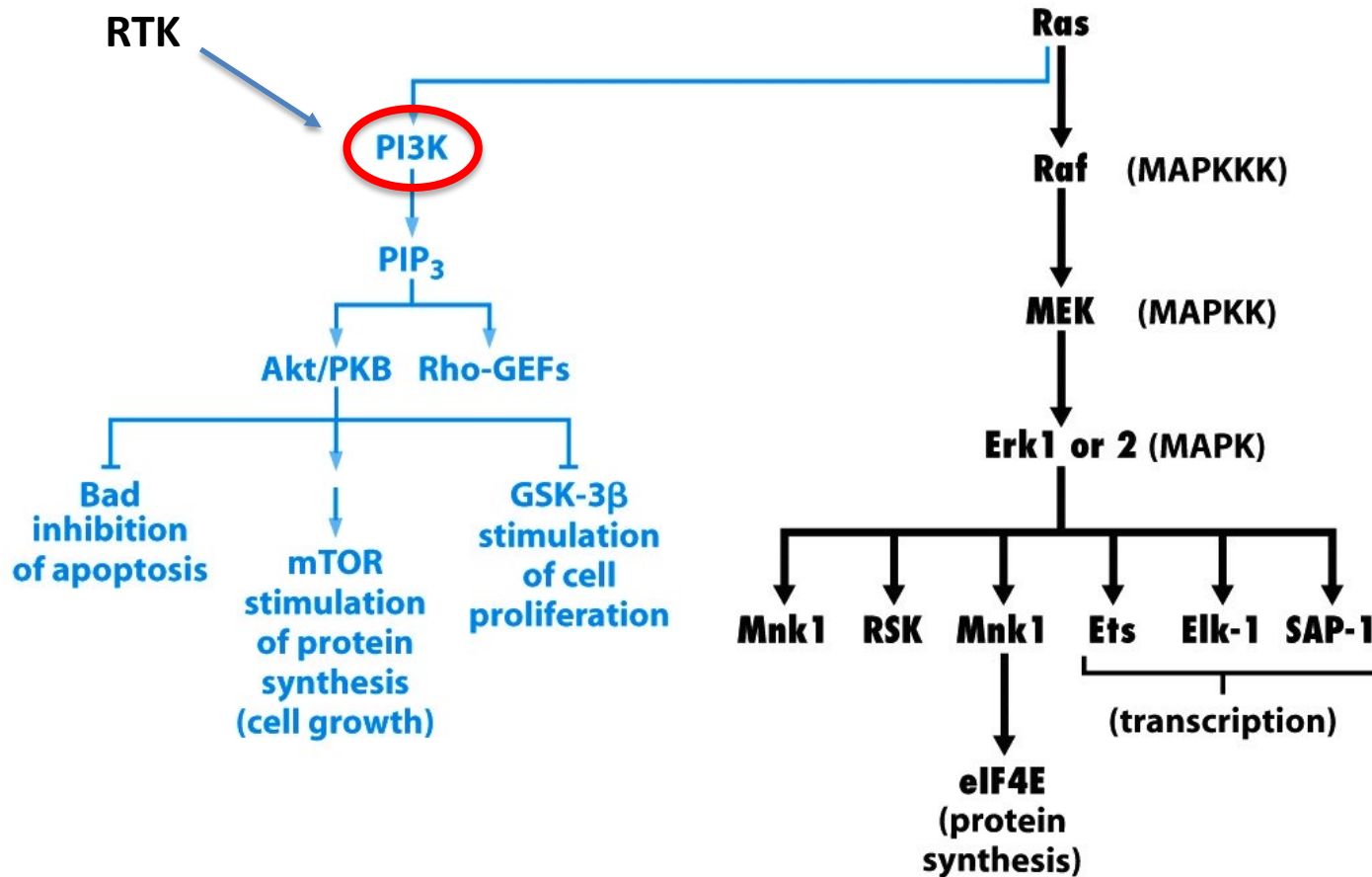
Acquisizione dell'indipendenza proliferativa nel cancro



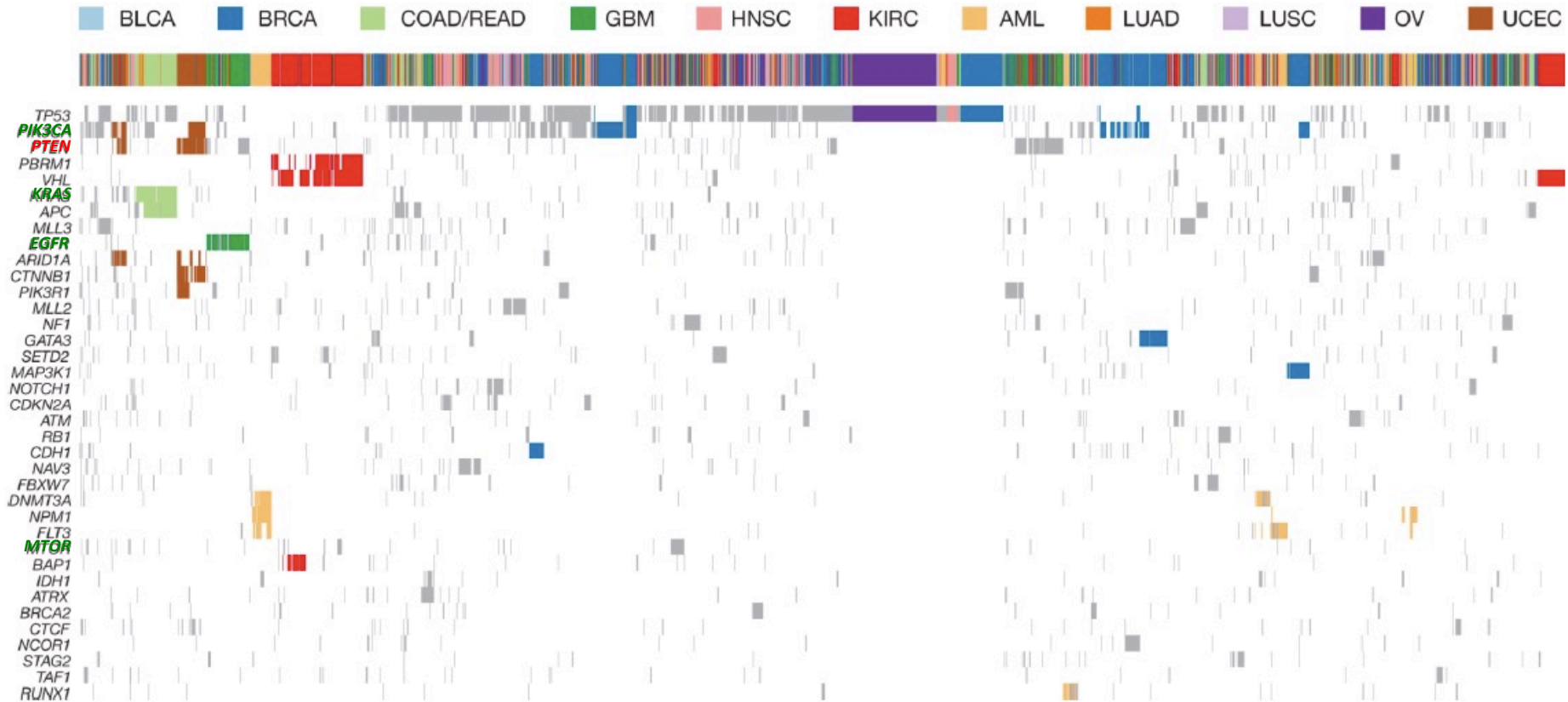
Fattori che influenzano la transizione G1/S nel cancro



PI3K signaling pathway

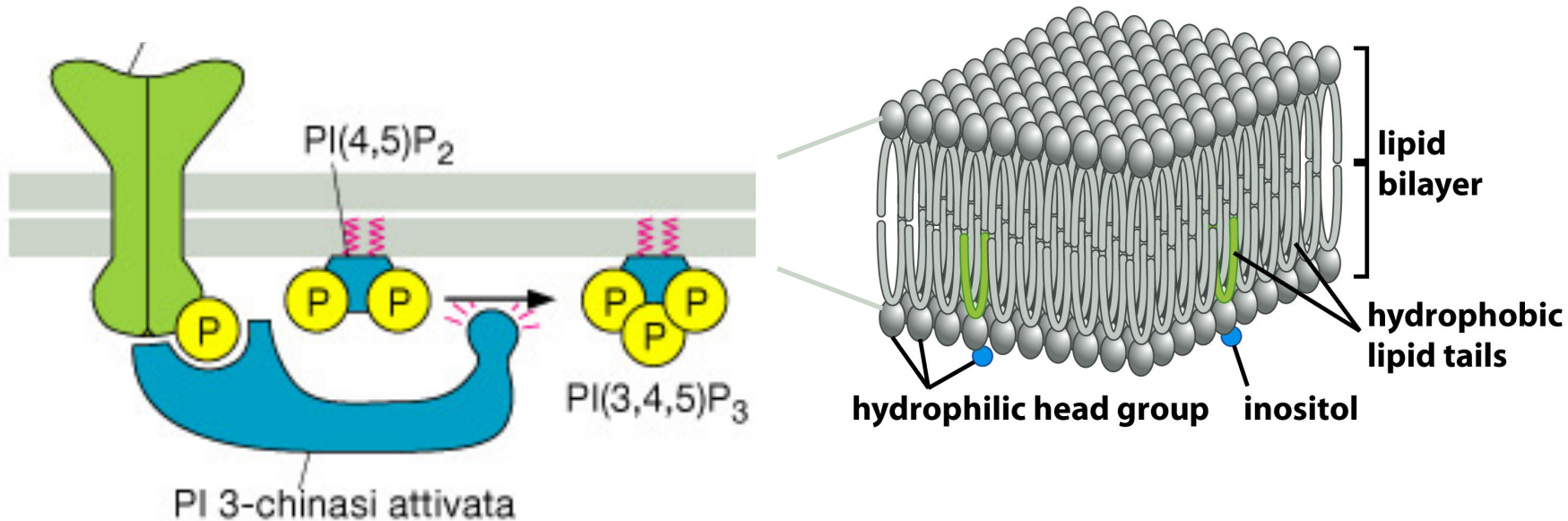


Principali geni mutati in diversi tumori umani

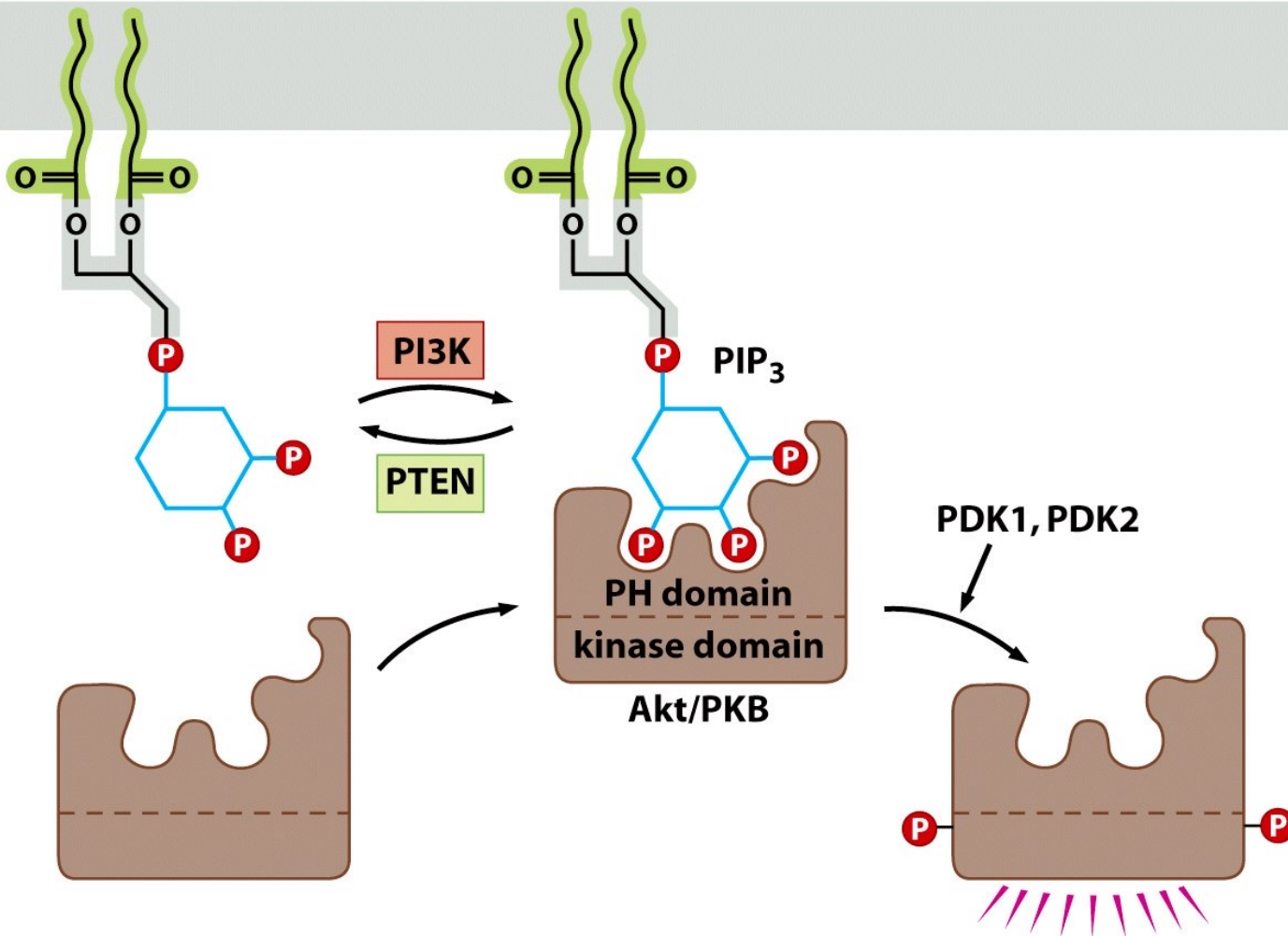


PI3K: PI 3-kinase

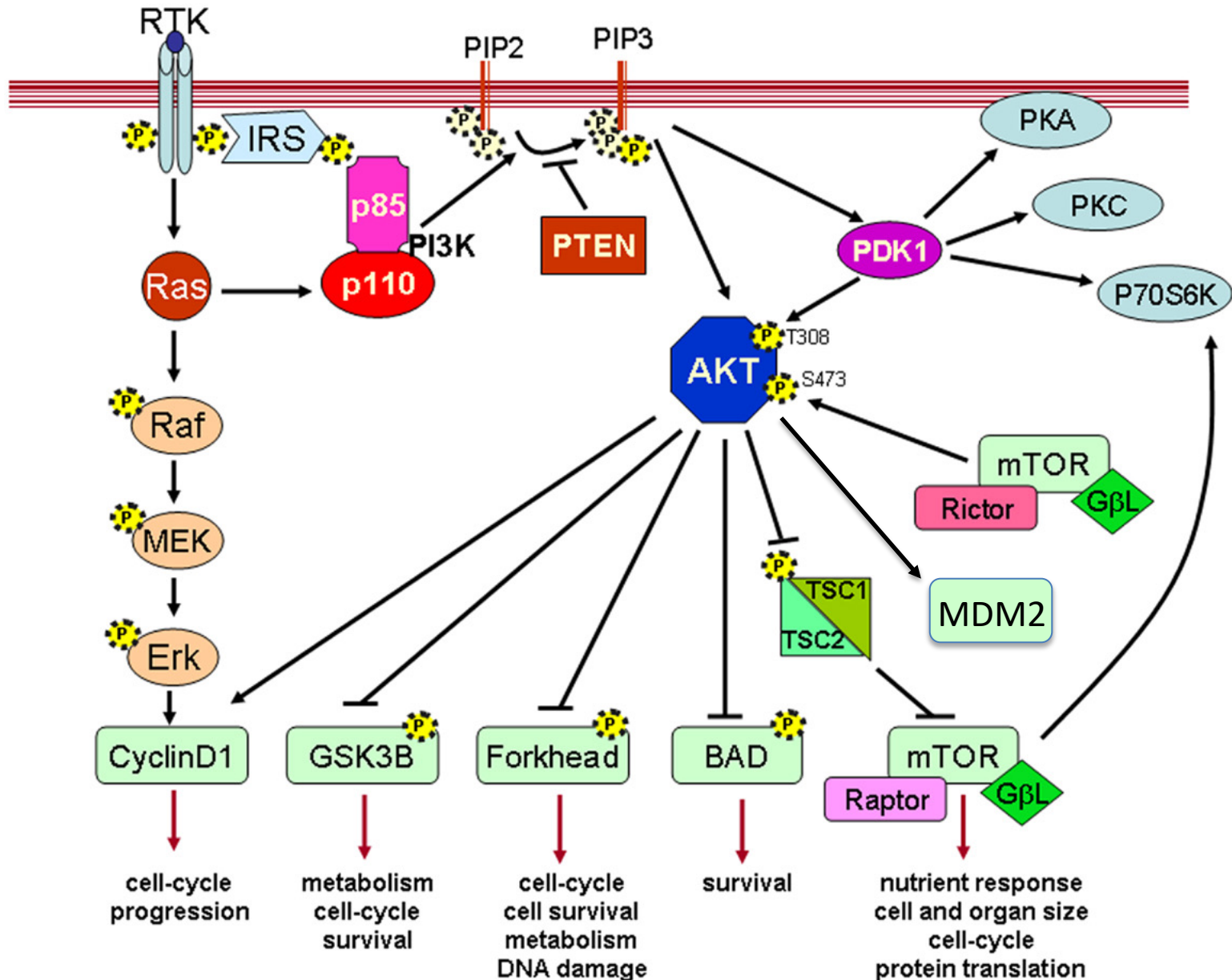
La **fosfatidil-inositolo 3 kinasi** (PI 3-kinase) genera glicofosfolipidi che sono riconosciuti da proteine di segnalazione (tramite i loro domini PH)



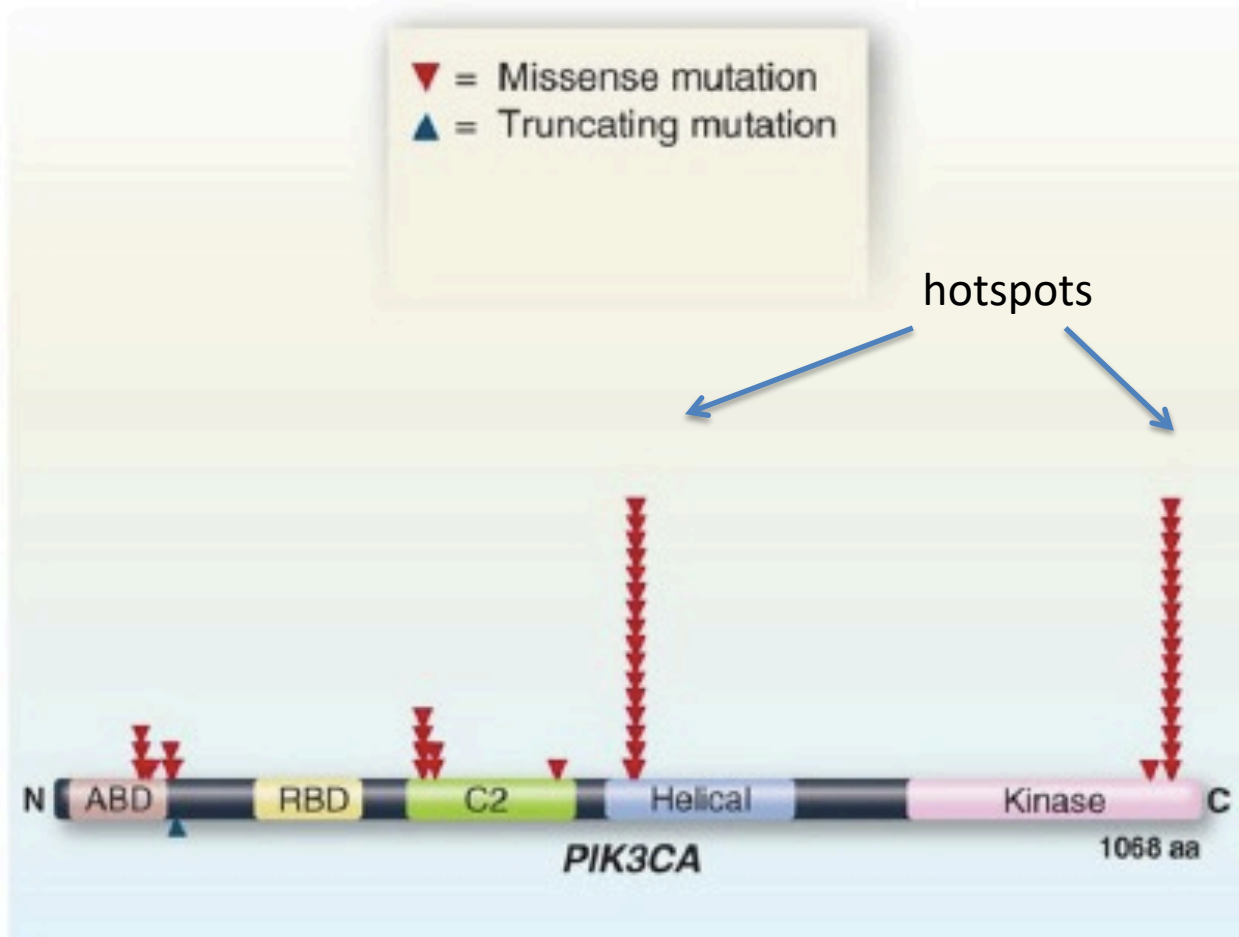
PI3K promuove l'attivazione di Akt/PKB



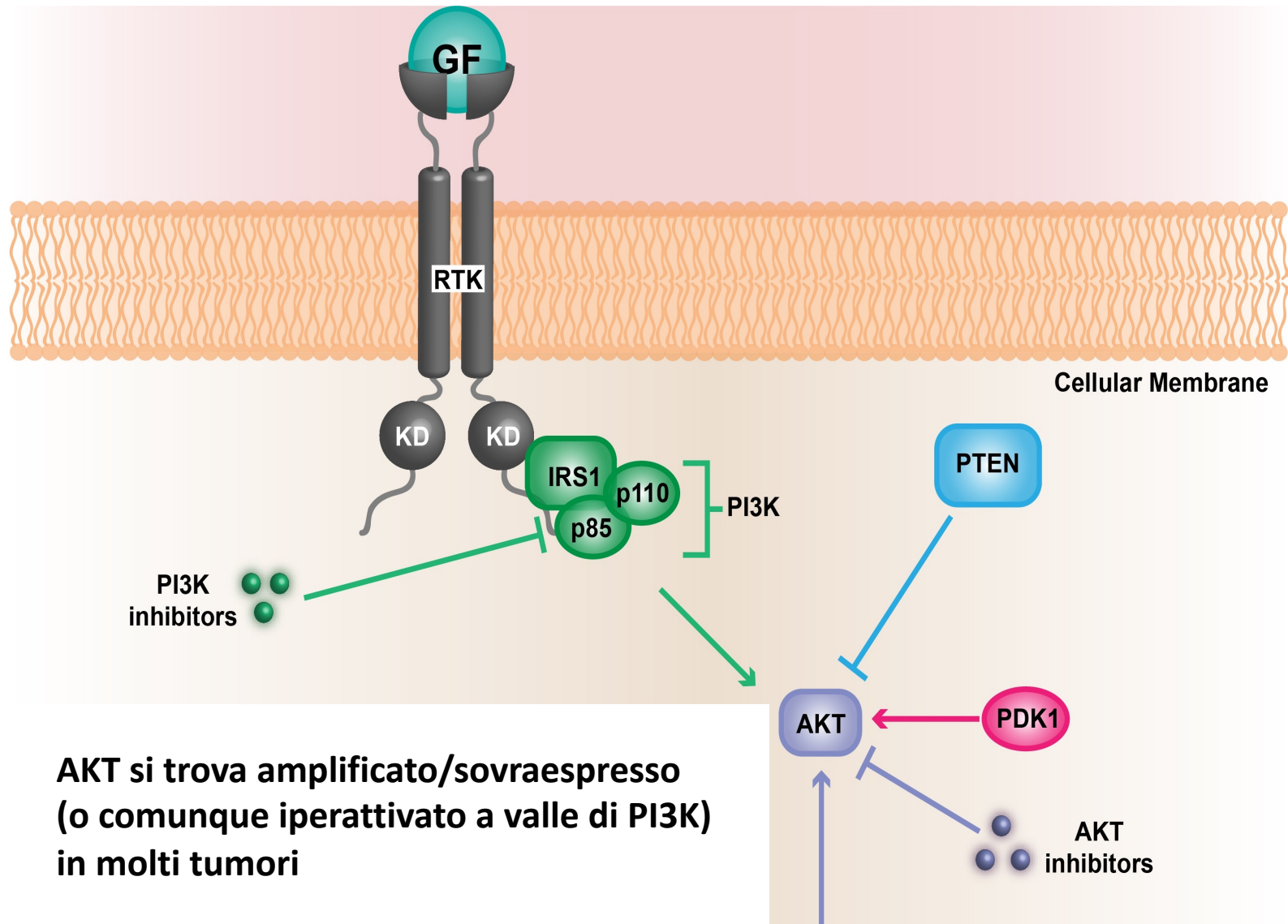
Regulation and pleiotropic activities of Akt/PKB



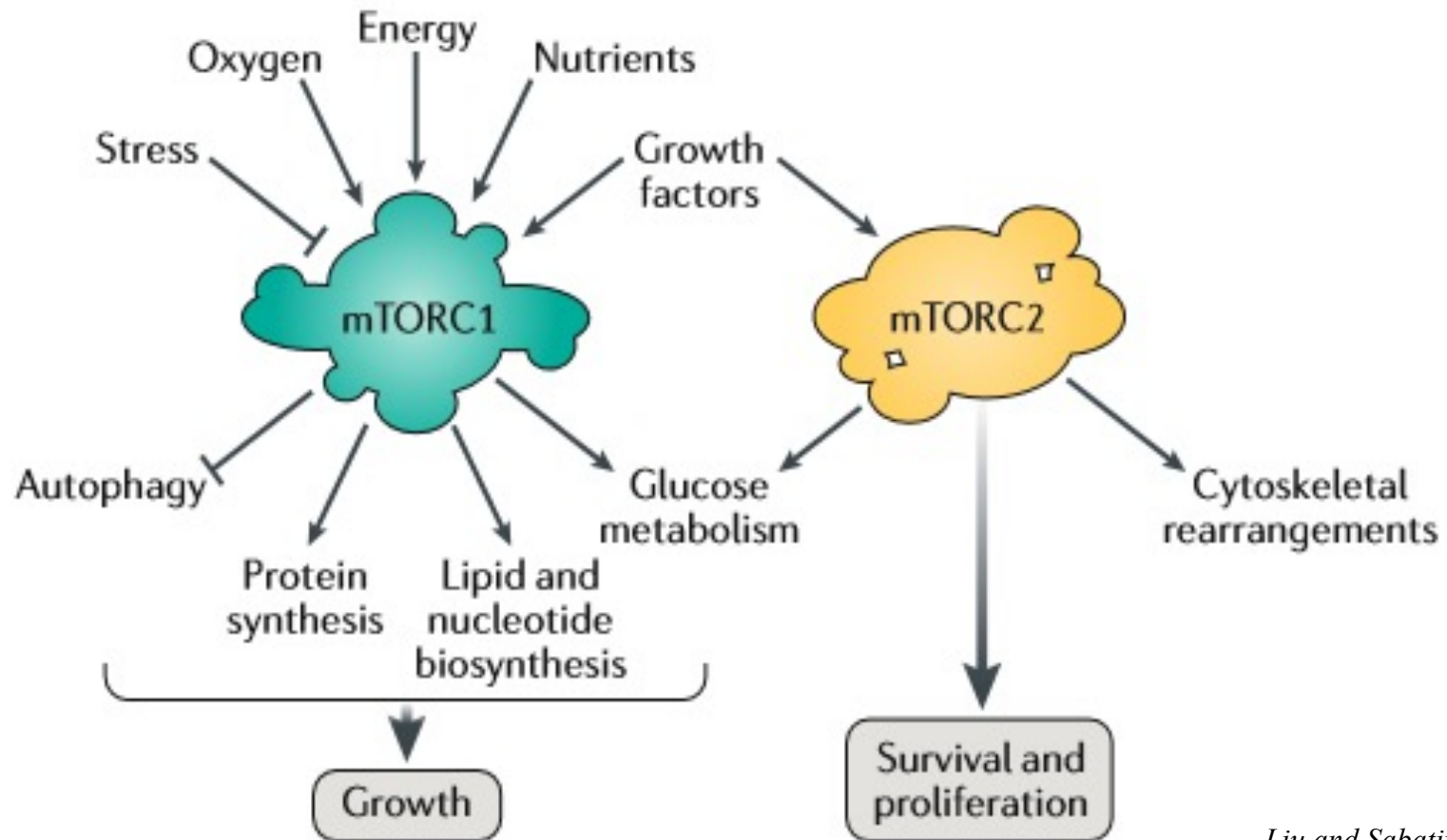
Mutazioni nel gene per la subunità catalitica di PI3K p110 α causano iperattivazione dell'oncogene in 1/3 dei carcinomi coloretali



PI3K: PI 3-kinase

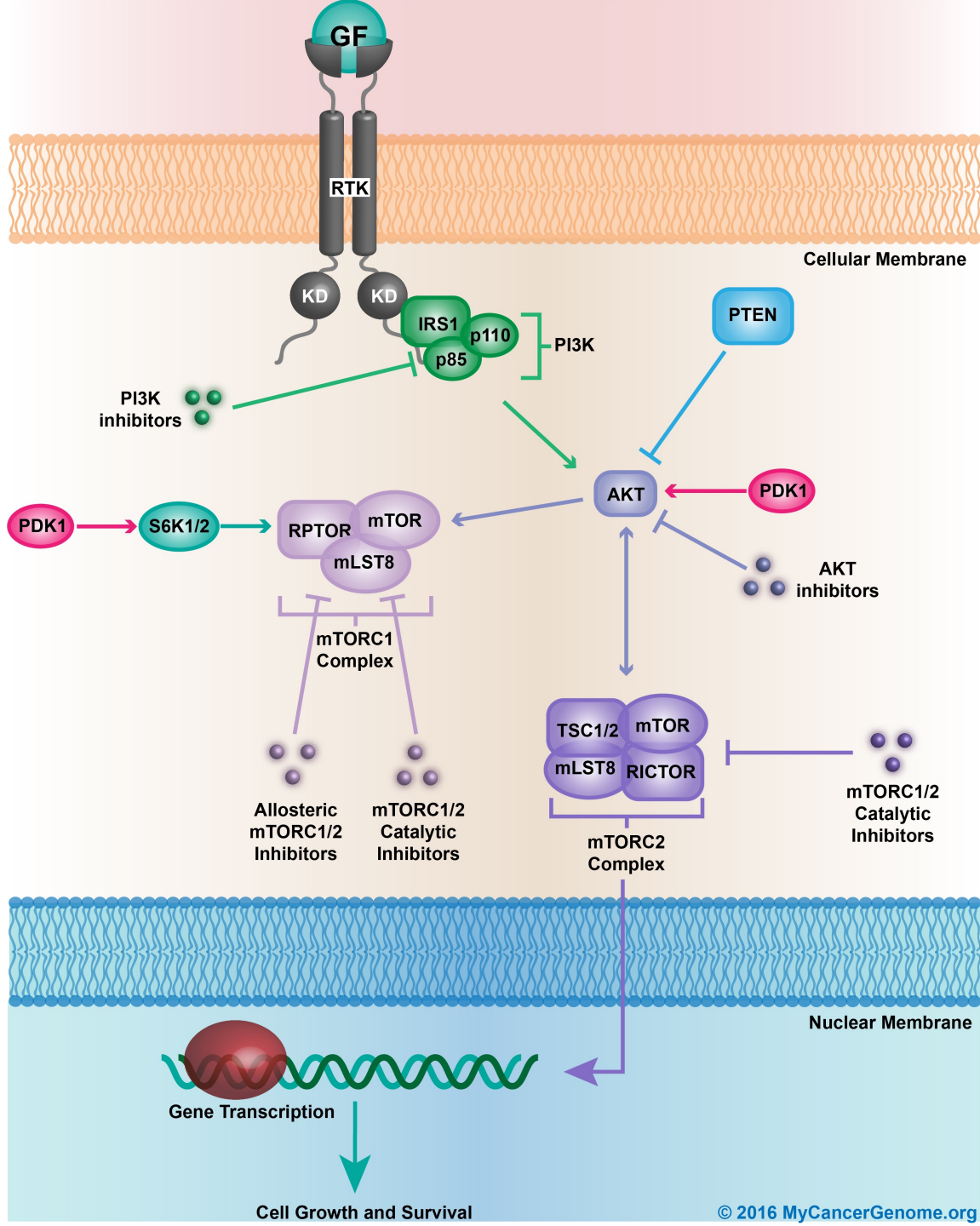


Roles of mTOR kinase in cell growth and survival



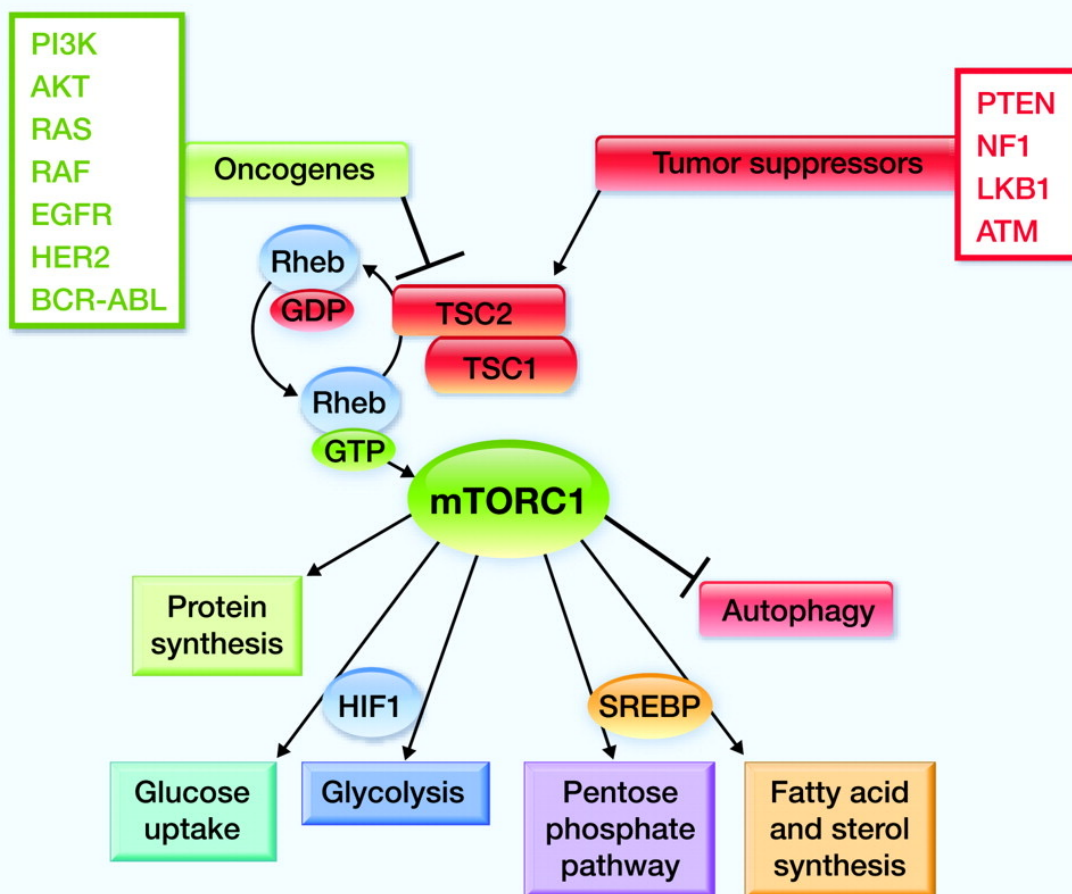
Liu and Sabatini, 2020

- mTOR è una serin/treonin chinasi presente in due complessi: **mTORC1** e mTORC2.
- mTORC1 è il principale **sensore di stimoli nutrizionali** ed energetici e attiva **processi di biosintesi** per la crescita cellulare.

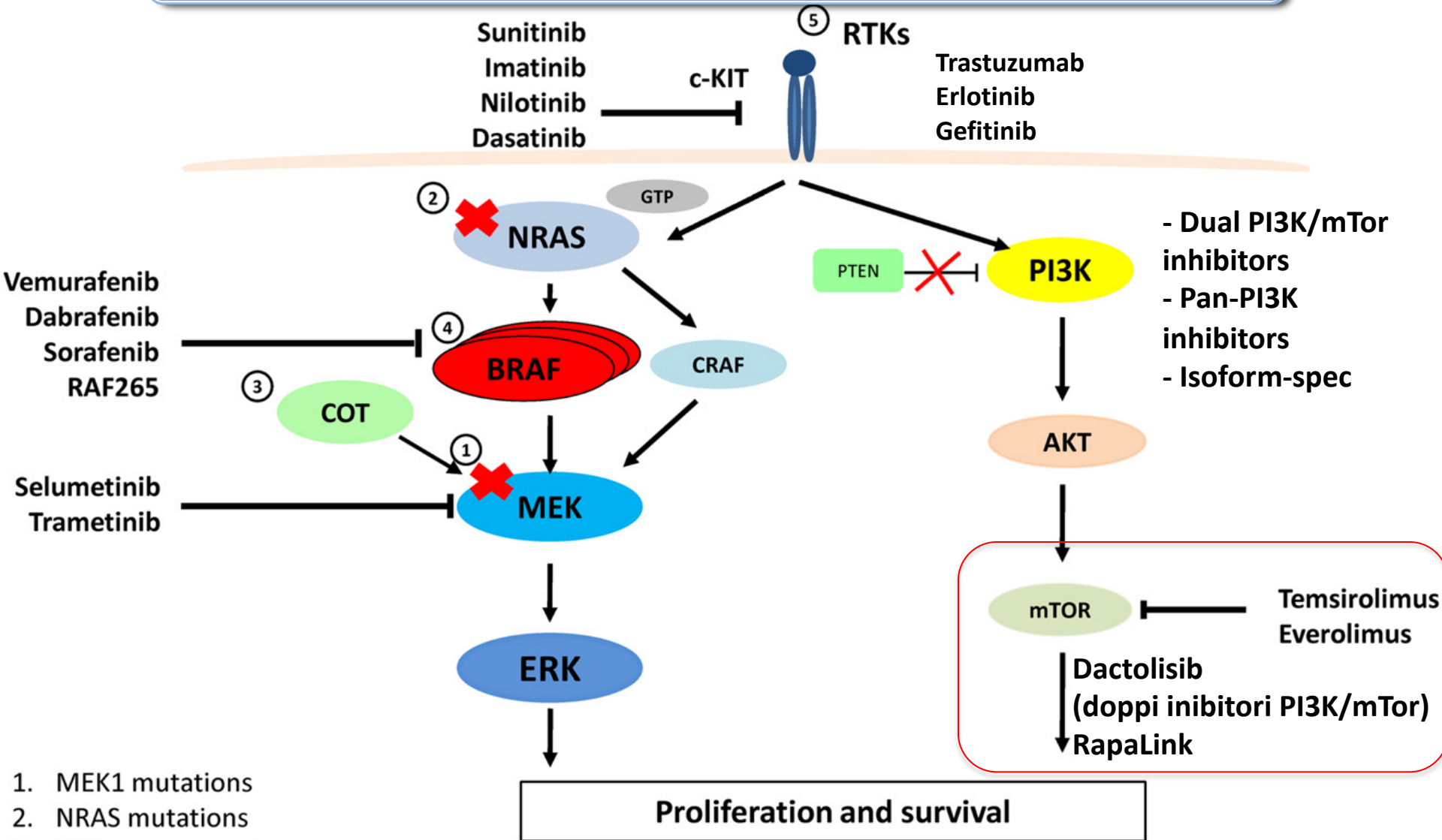


mTOR pathway is hyperactivated in tumors

- La via di segnalazione di mTOR è **iper attivata** nell'80% dei tumori.
- L'iper attivazione di mTORC1 è dovuta a **mutazioni** del gene o dei regolatori (PI3K, Akt, PTEN, TSC).

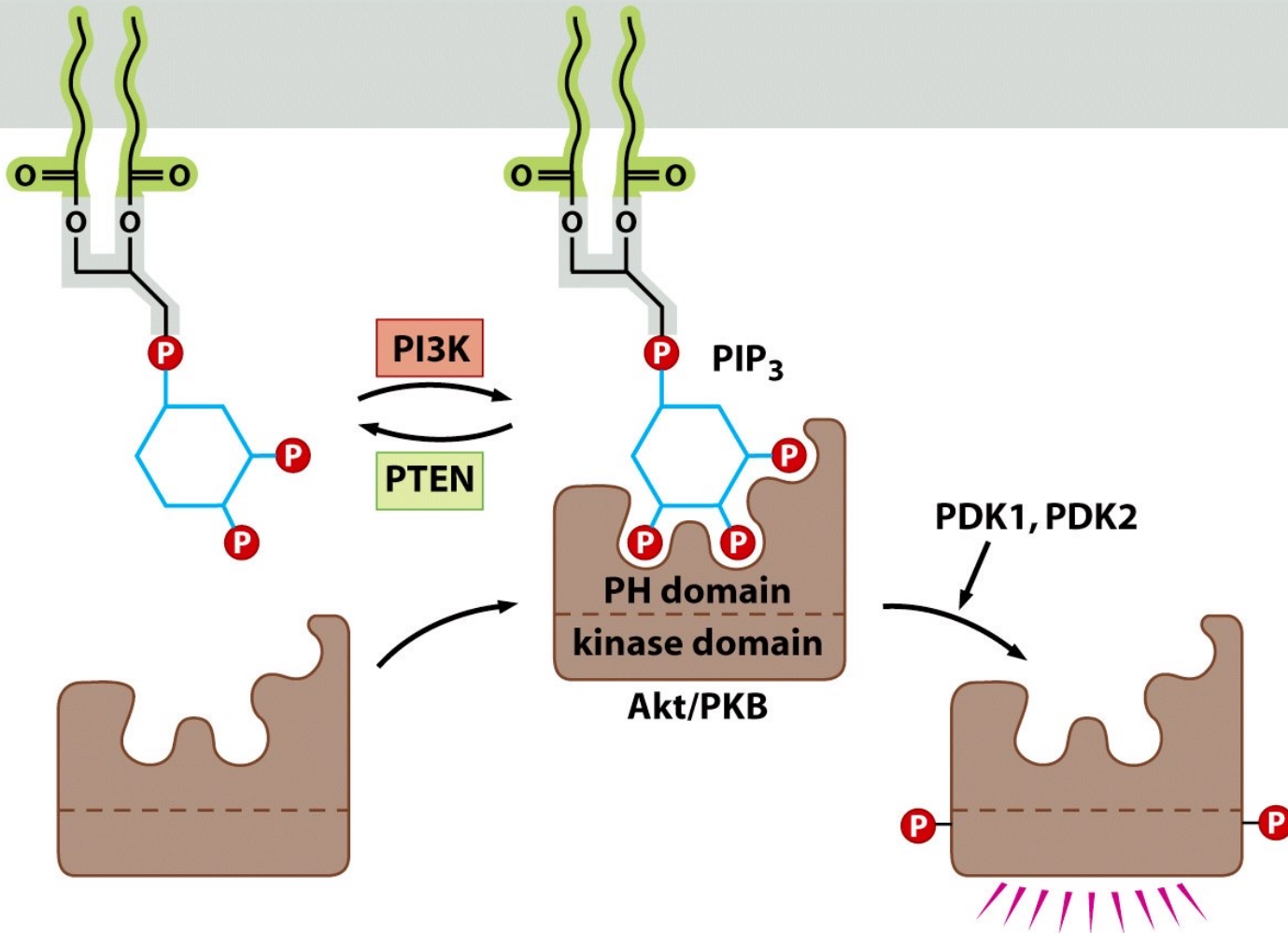


Targeted therapies against mTOR



1. MEK1 mutations
2. NRAS mutations
3. COT overexpression
4. BRAF amplification/ splicing
5. RTKs overexpression/activation (PDGFR β , IGR1F)

PTEN (Phosphatase and Tensin homolog) agisce come antagonista di PI3K



L'attività di PTEN è persa nel 30-40% di tutti i tumori

Cancer type	Type of alteration
Glioblastoma (25–50%)	<i>PTEN</i> mutation
Ovarian carcinoma	<i>PTEN</i> mutation; <i>AKT2</i> amplification; <i>PI3K</i> amplification; <i>PI3K p85α</i> mutation
Breast carcinoma	increased Akt1 activity; <i>AKT2</i> amplification; <i>PTEN</i> mutation
Endometrial carcinoma (35%)	<i>PTEN</i> mutation; <i>PTEN</i> methylation ^a
Hepatocellular carcinoma	<i>PTEN</i> mutation
Melanoma	<i>PTEN</i> mutation; <i>PTEN</i> methylation ^a
Lung carcinoma	<i>PTEN</i> mutation
Renal cell carcinoma	<i>PTEN</i> mutation
Thyroid carcinoma	<i>PTEN</i> mutation; Akt/PKB overexpression
Lymphoid	<i>PTEN</i> mutation
Prostate carcinoma (40–50%)	<i>PTEN</i> mutation
Colon carcinoma (>30%)	Akt/PKB overexpression; <i>PI3K</i> mutation

^aMethylation refers to repression of transcription of a gene through methylation of cytidines in its promoter; see Section 7.8.

Adapted from I. Vivanco and C.L. Sawyers, The phosphatidylinositol 3-kinase-AKT pathway in human cancer, *Nat. Rev. Cancer* 2:489–501, 2002.

Eventi che promuovono la proliferazione cellulare nei tumori

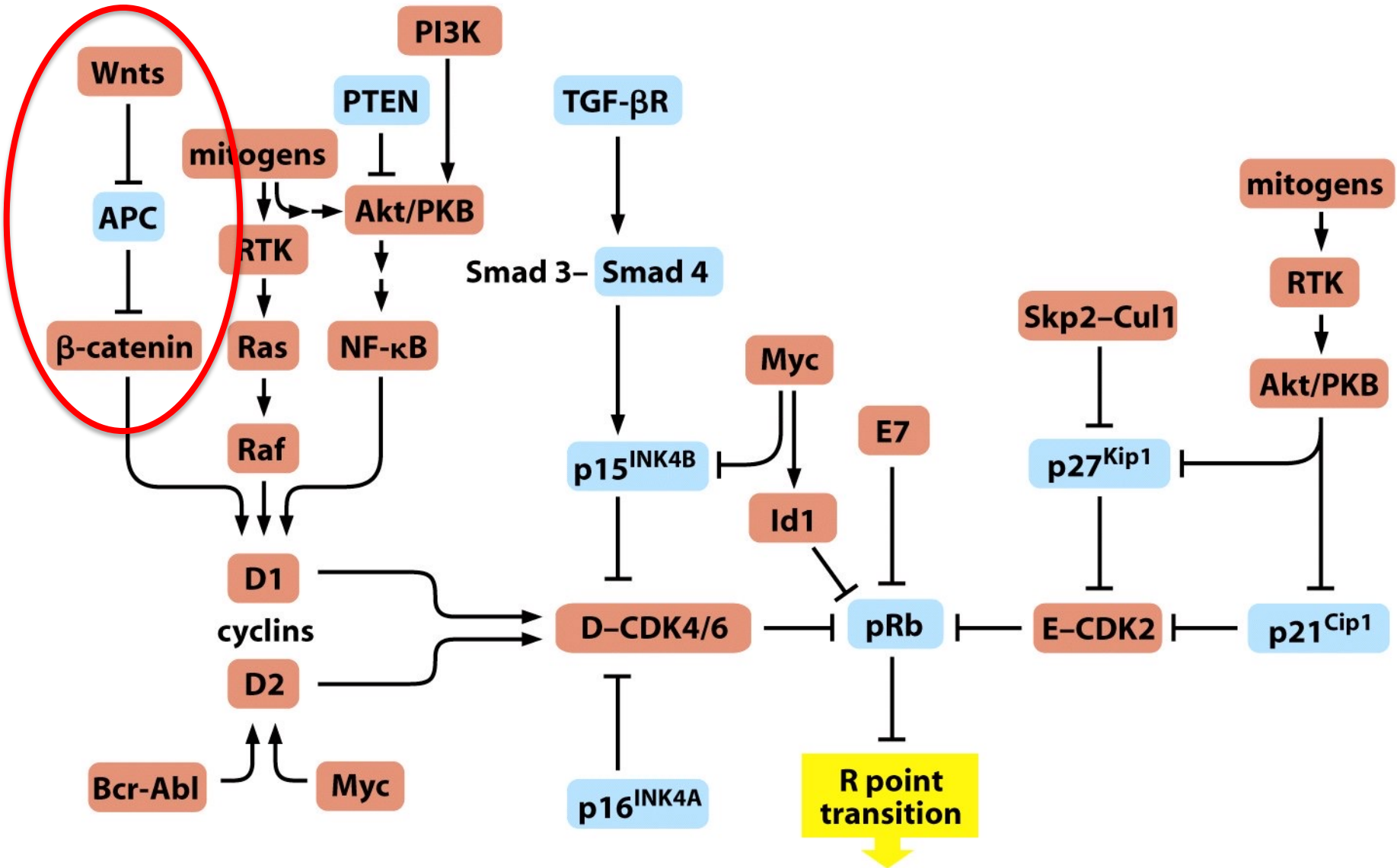
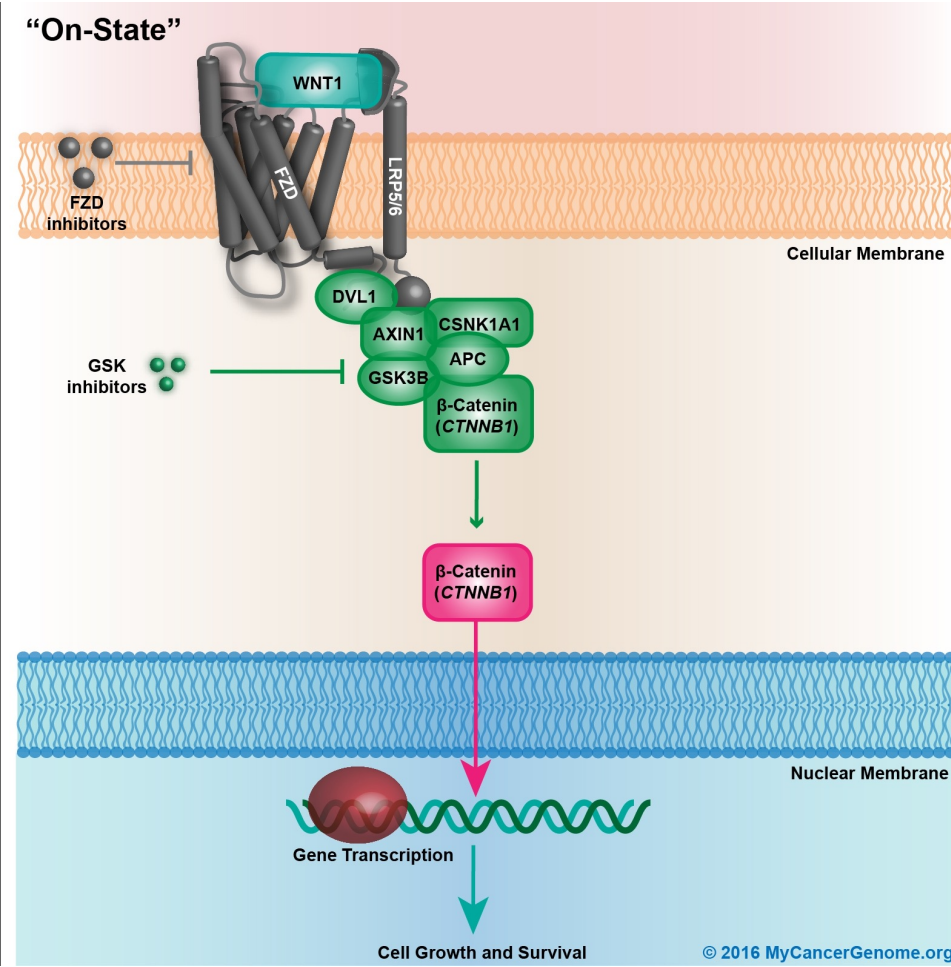
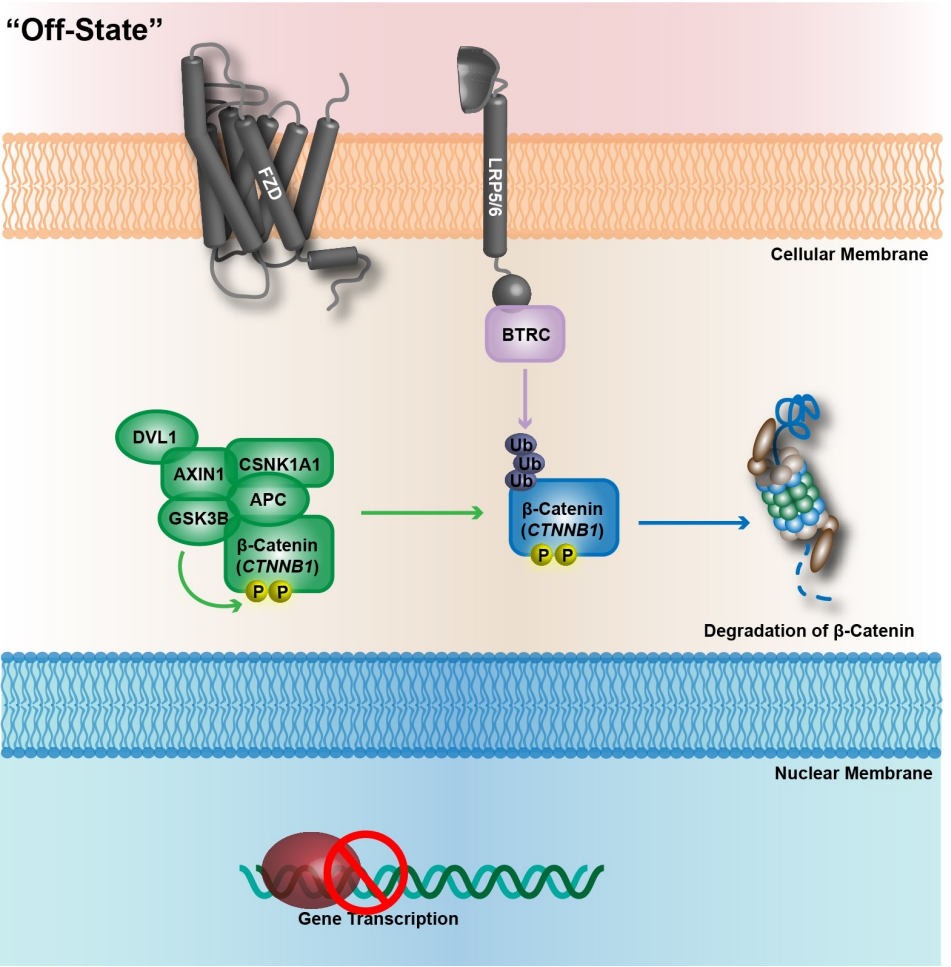
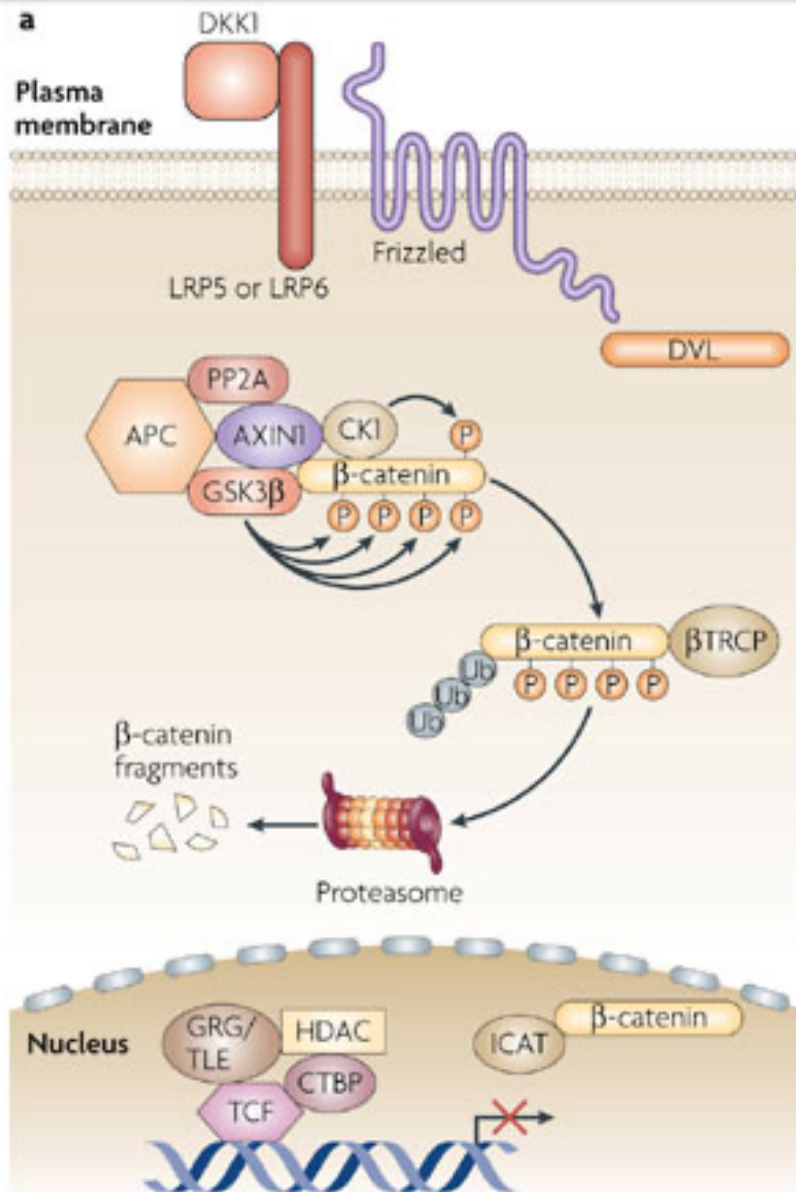


Figure 8.35 *The Biology of Cancer* (© Garland Science 2007)

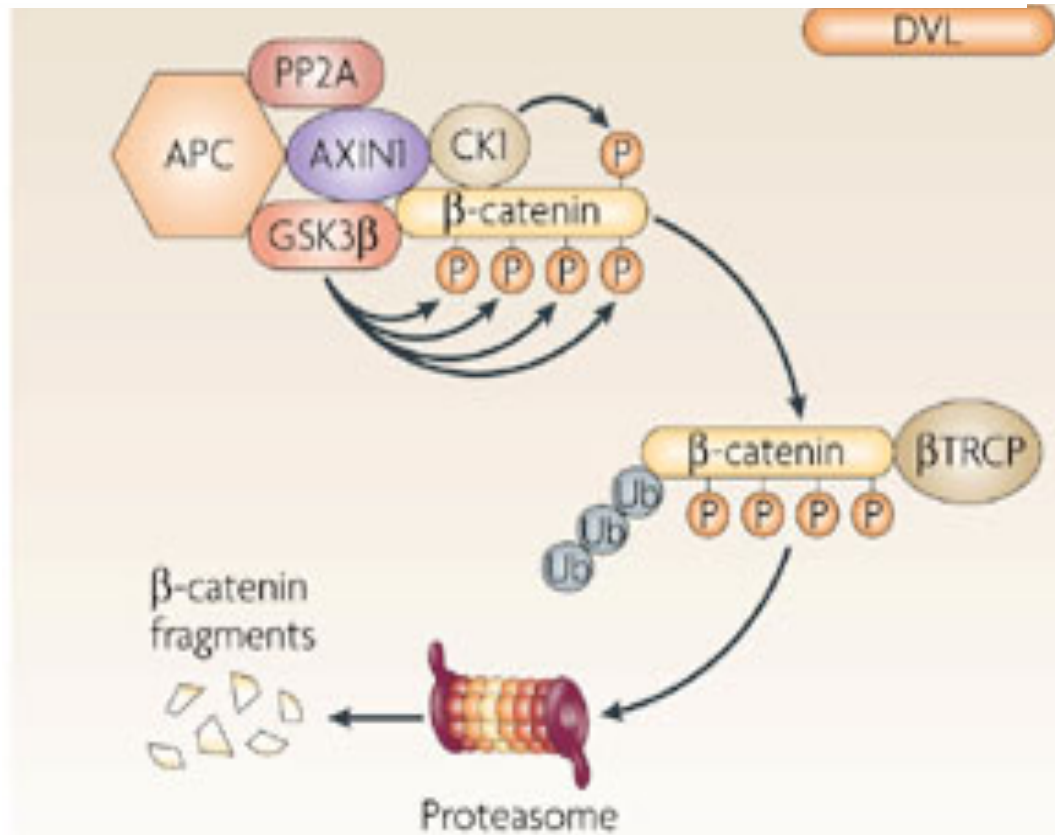
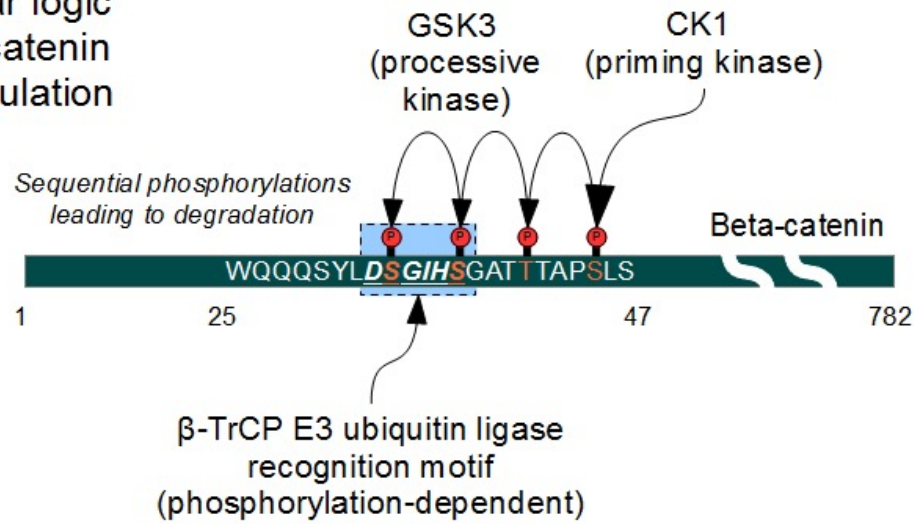
La pathway di Wnt promuove proliferazione cellulare e staminalità



La fosforilazione di beta-catenina ne induce la degradazione via ubiquitina-proteasoma



Molecular logic of beta-catenin level regulation



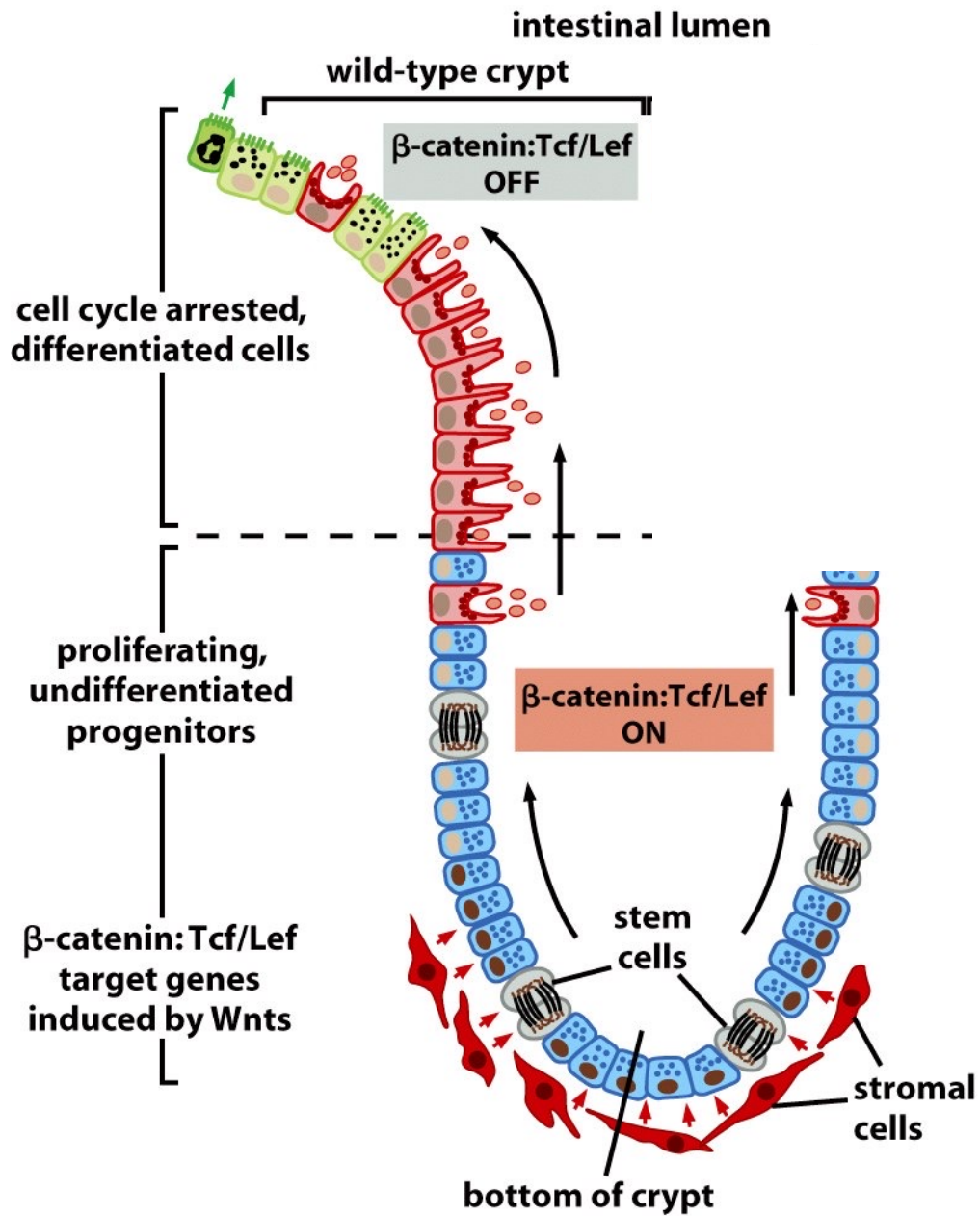


Figure 7.24a *The Biology of Cancer* (© Garland Science 2007)

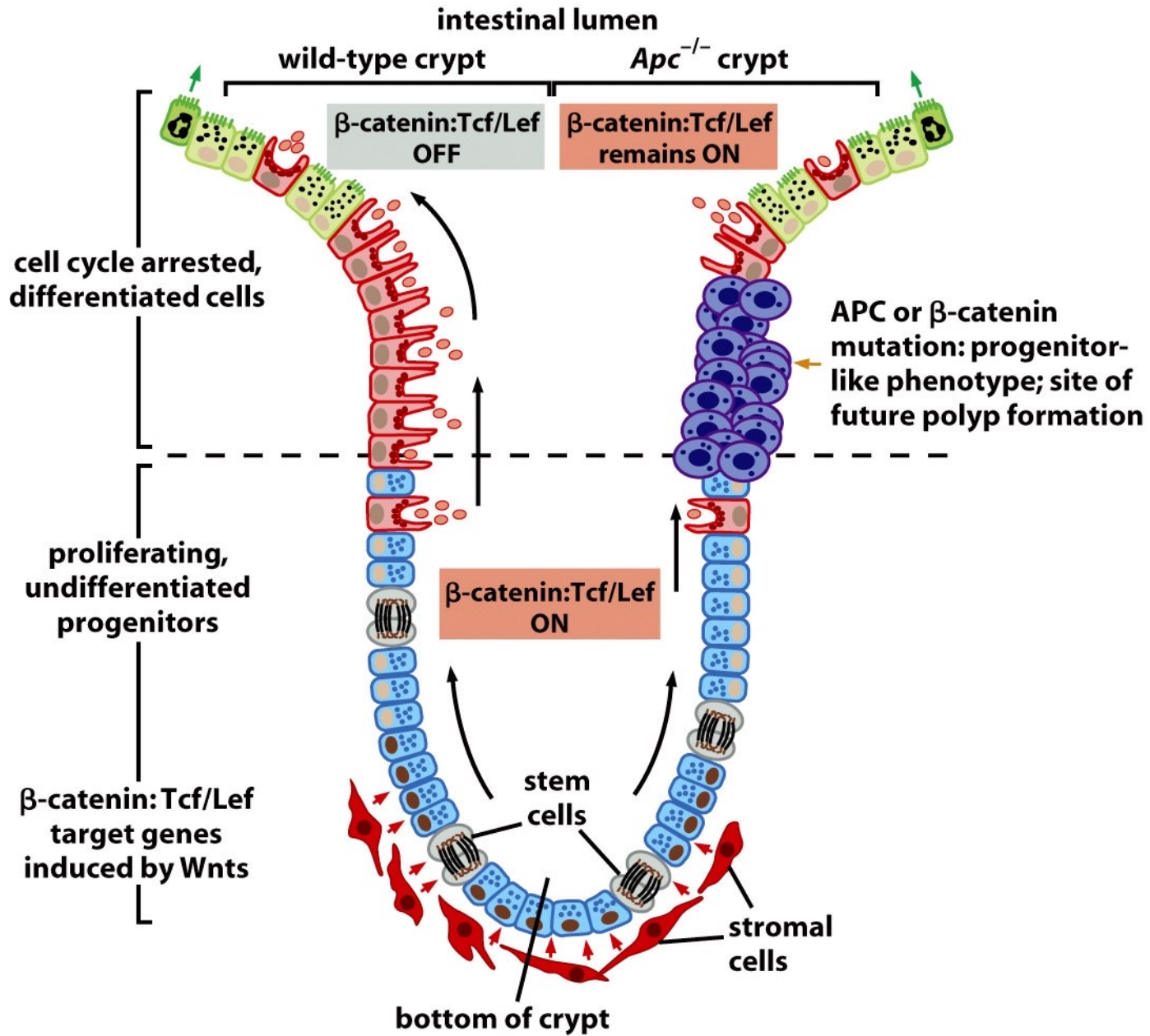
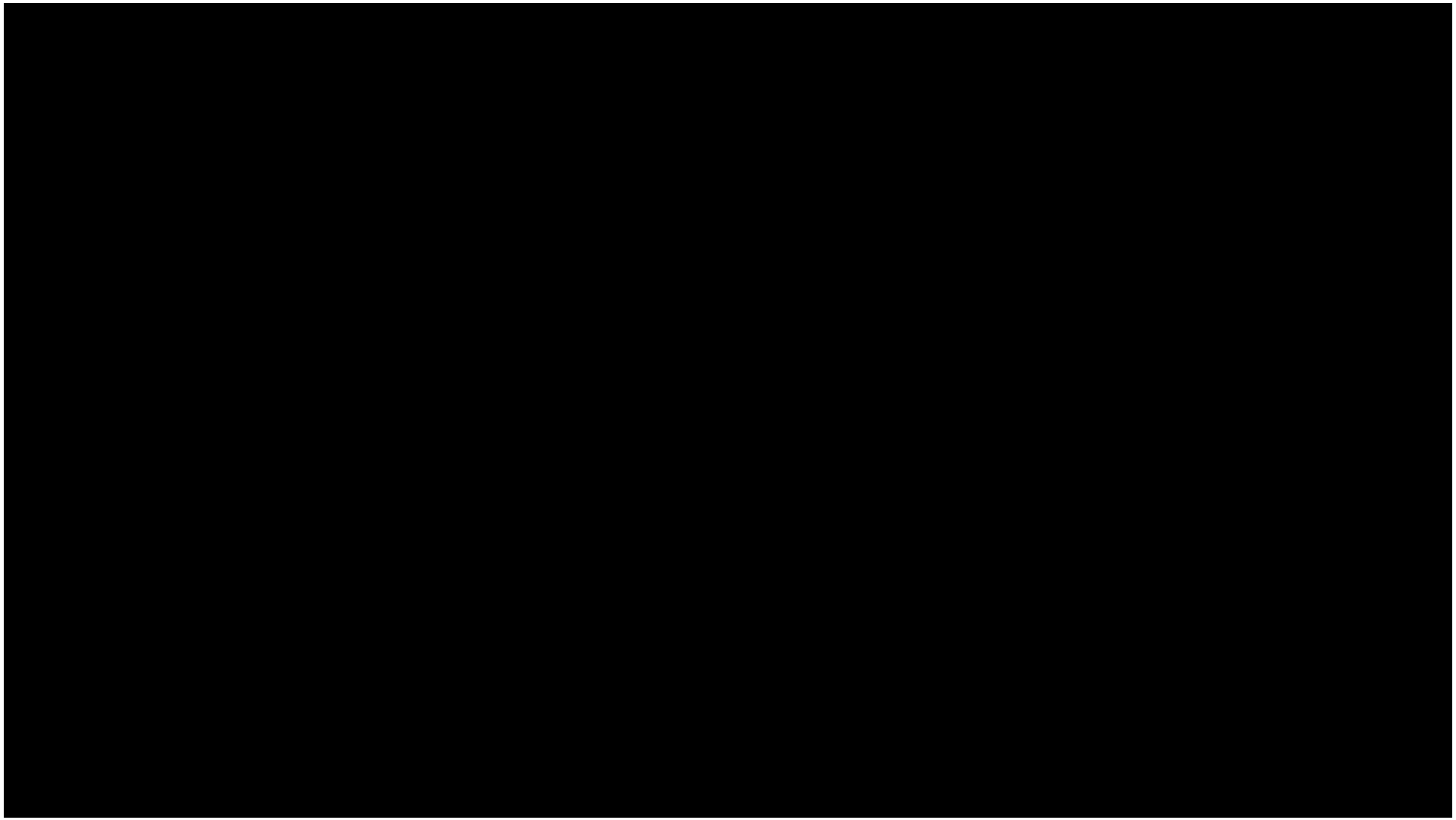


Figure 7.24a *The Biology of Cancer* (© Garland Science 2007)

APC deletion and adenoma formation

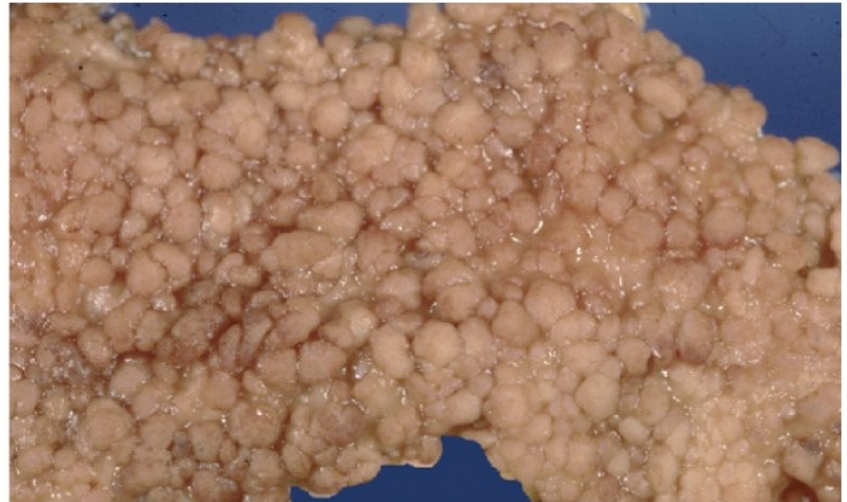


**Mutazioni del gene APC nella sindrome FAP
(poliposi adenomatosa familiare)
e nei tumori sporadici del colon, pancreas, stomaco e prostata**

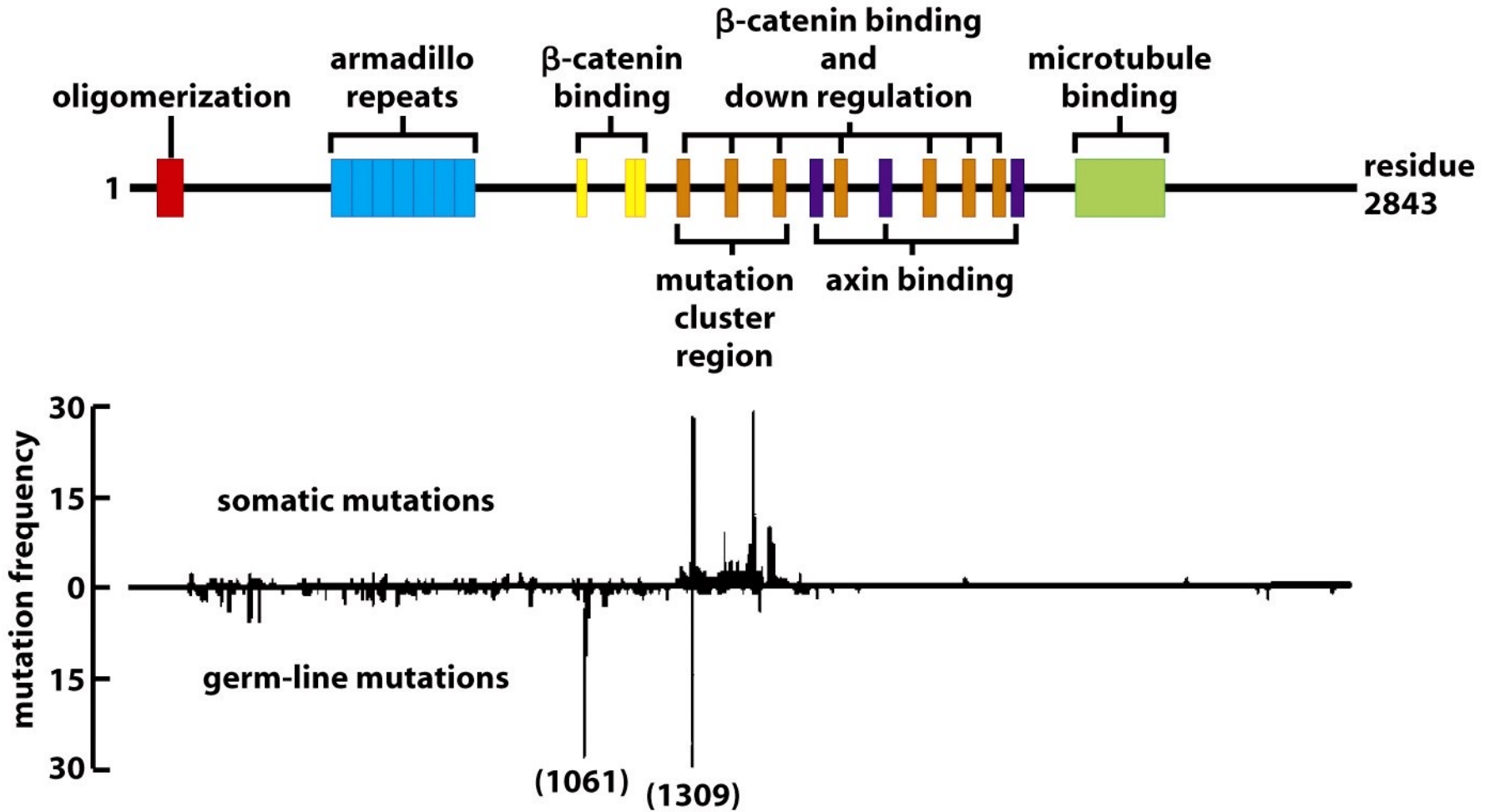
normale



FAP

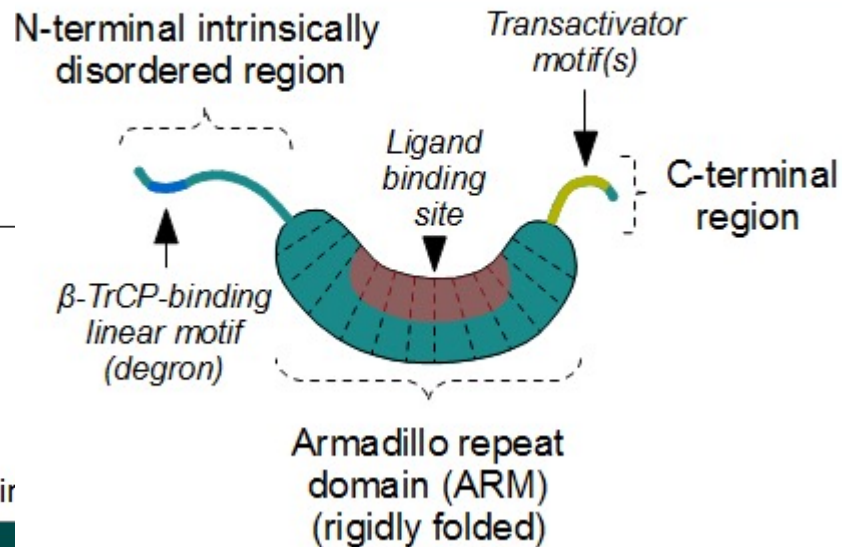
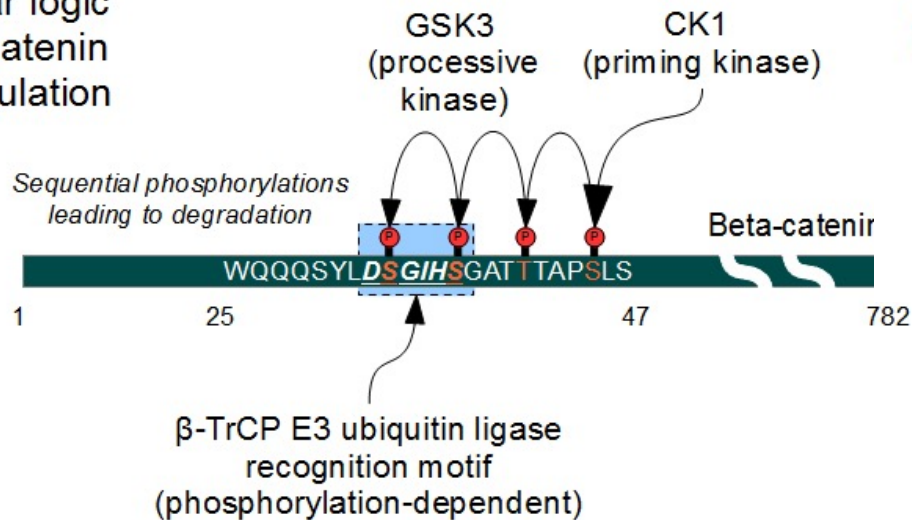


Struttura e mutazioni tumorigeniche del gene APC

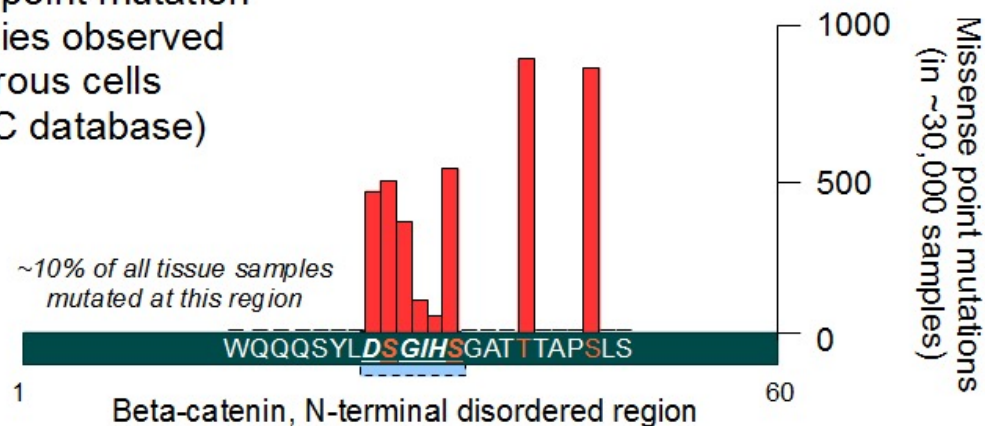


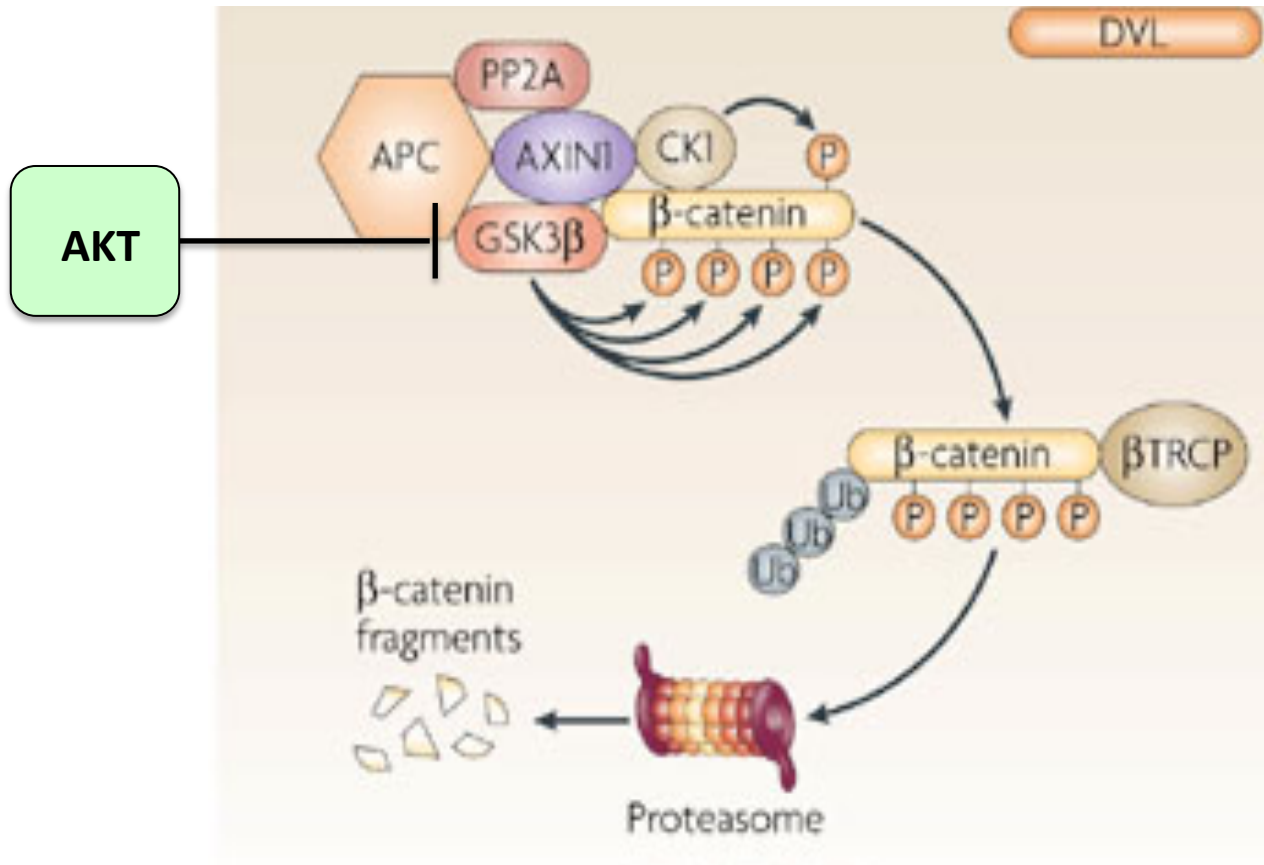
Struttura e mutazioni di β -catenina

Molecular logic of beta-catenin level regulation

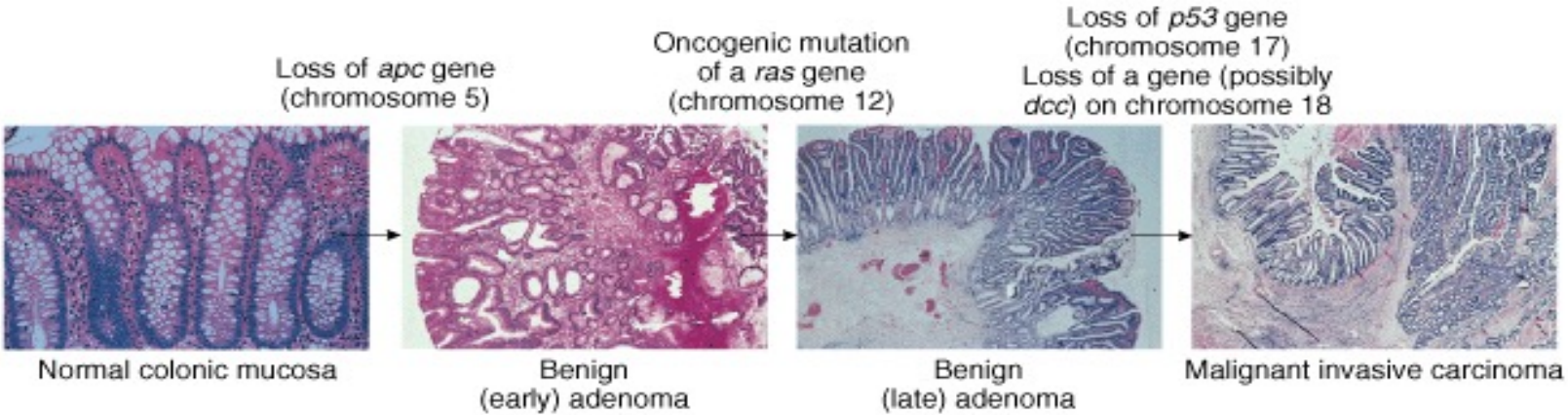
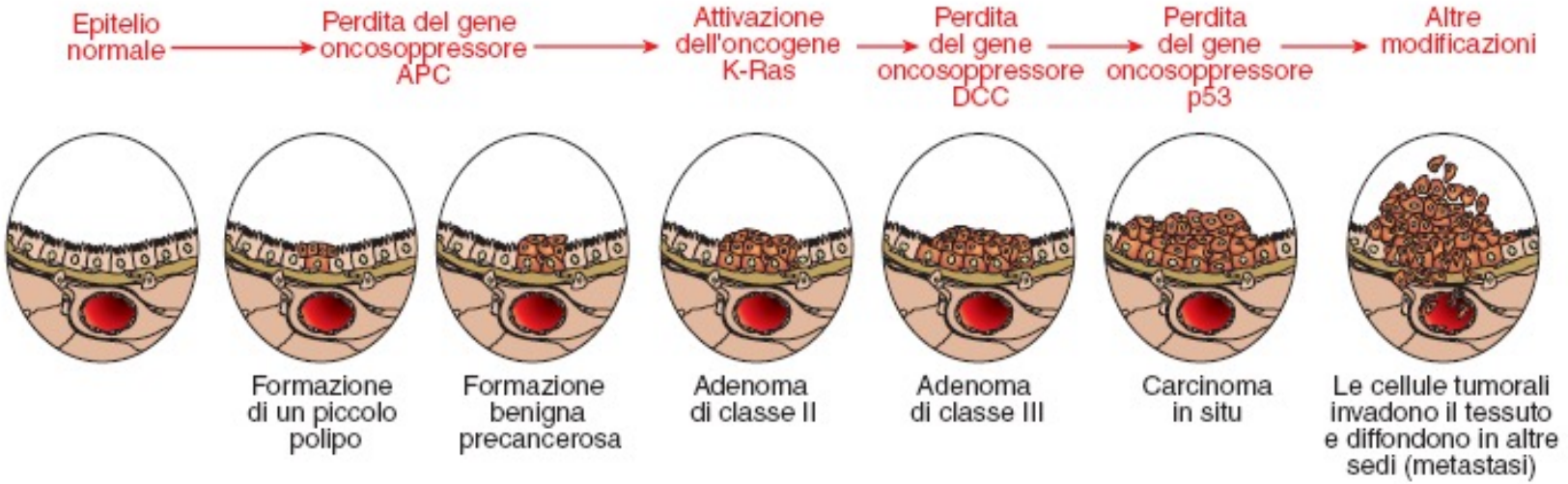


Somatic point mutation frequencies observed in cancerous cells (COSMIC database)





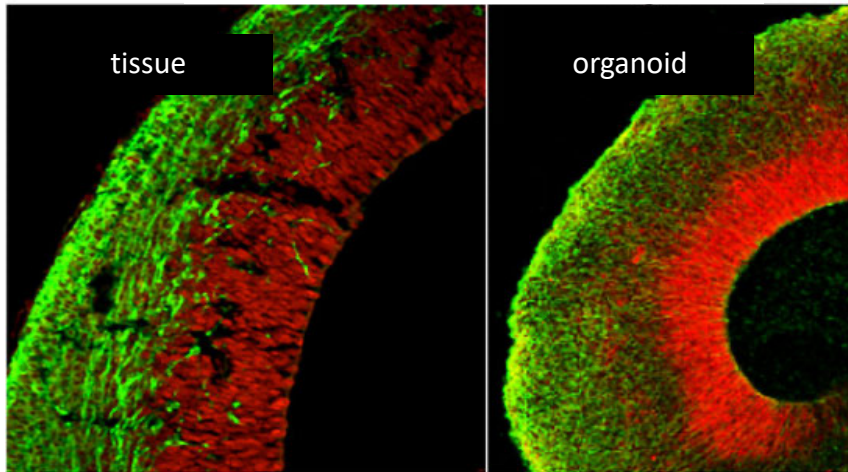
Evoluzione del cancro al colon



COLTURE ORGANOTIPICHE o ORGANOIDI

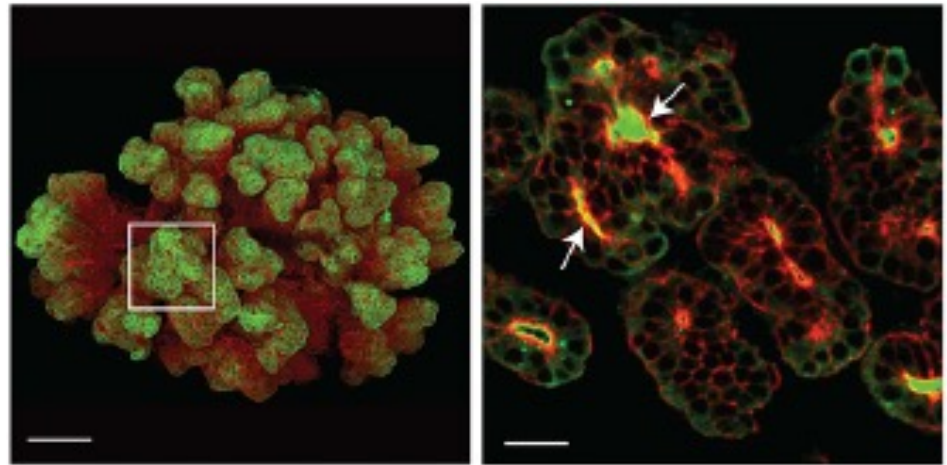
Colture 3D derivate da proliferazione e differenziamento in vitro di cellule staminali che ricapitolano l'organizzazione e le funzioni del tessuto/organo corrispondente

Brain

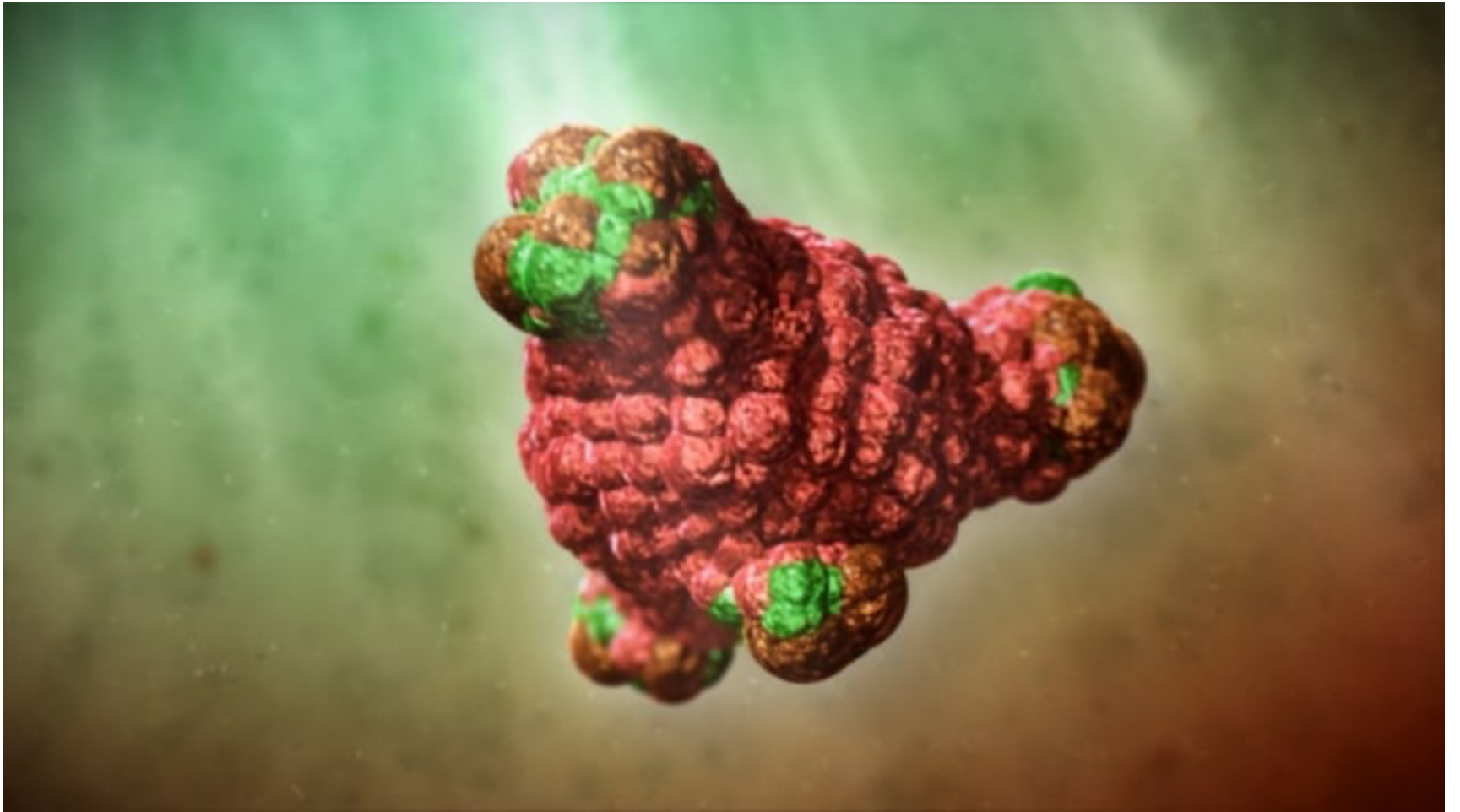


Repic & Lancaster , Plos Blogs 2013

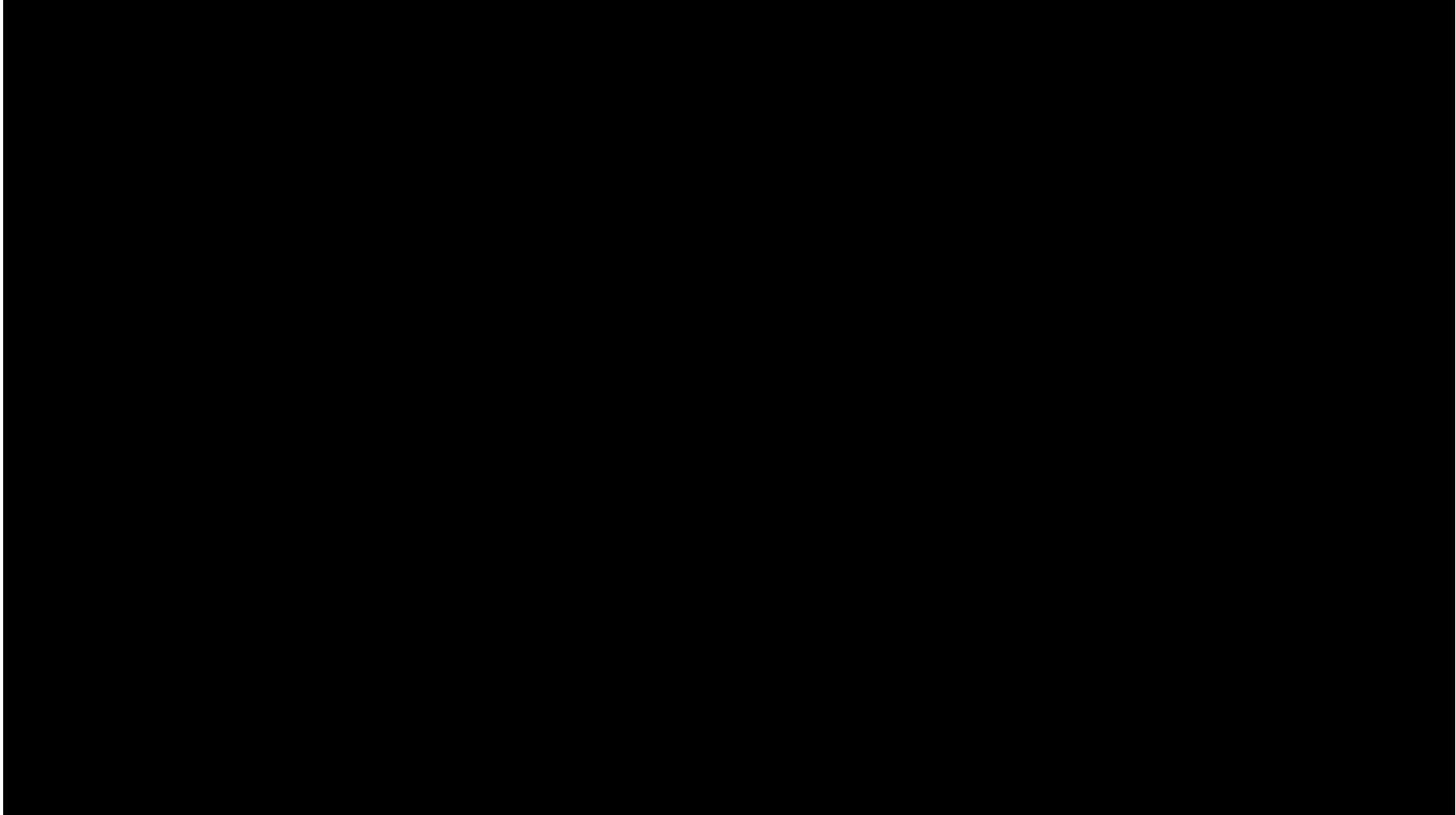
Mammary gland

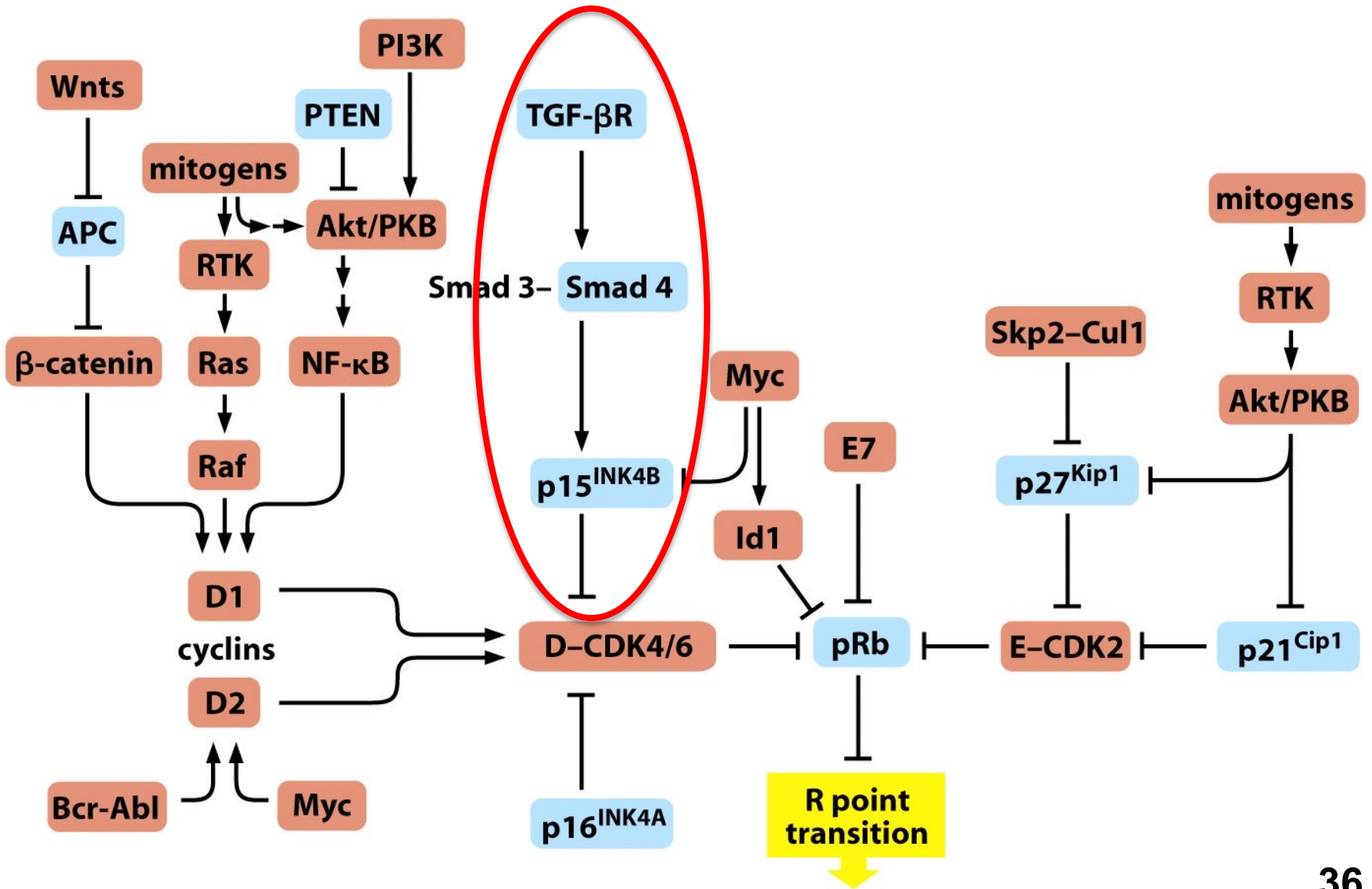


Jamieson et al., Development 2017



Modeling colon carcinogenesis with organoids



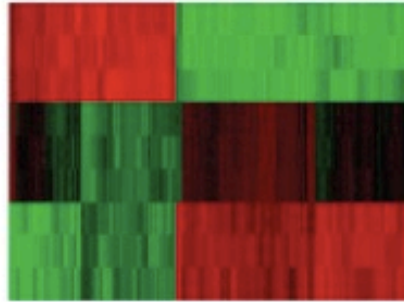


Applicazioni degli organoidi in biomedicina

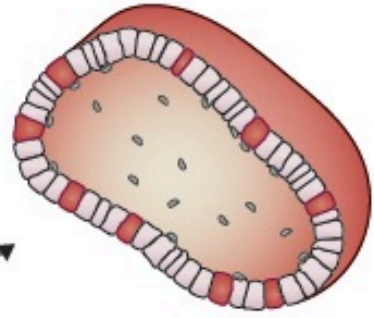
b Patient-derived tissue subunits



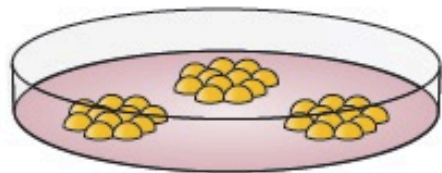
c Omics profiling



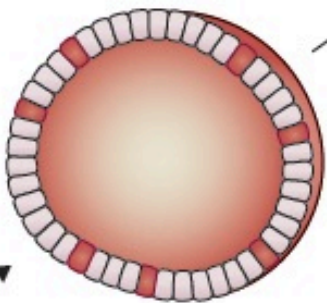
d Study host-microbe interaction



a



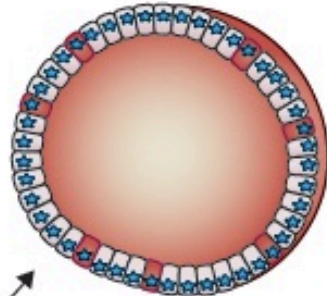
ESCs/iPSCs



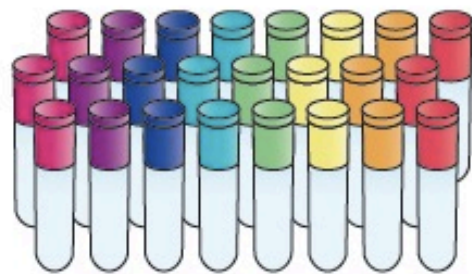
e Gene editing (e.g. CRISPR)



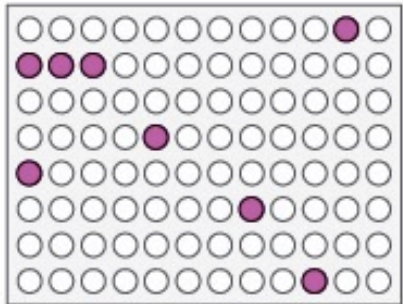
Targeted correction of mutations



g Biobank for academic studies

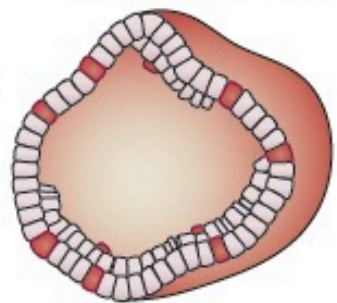


f High-throughput drug screening

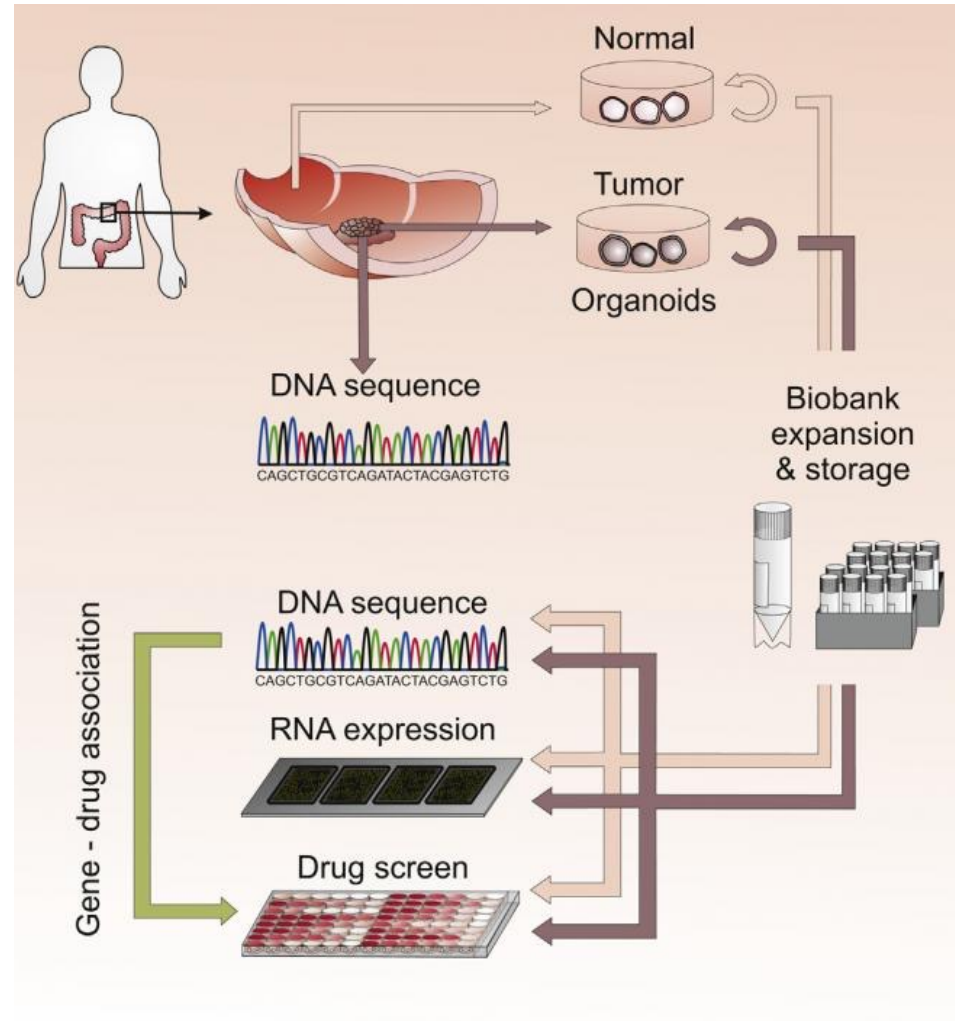
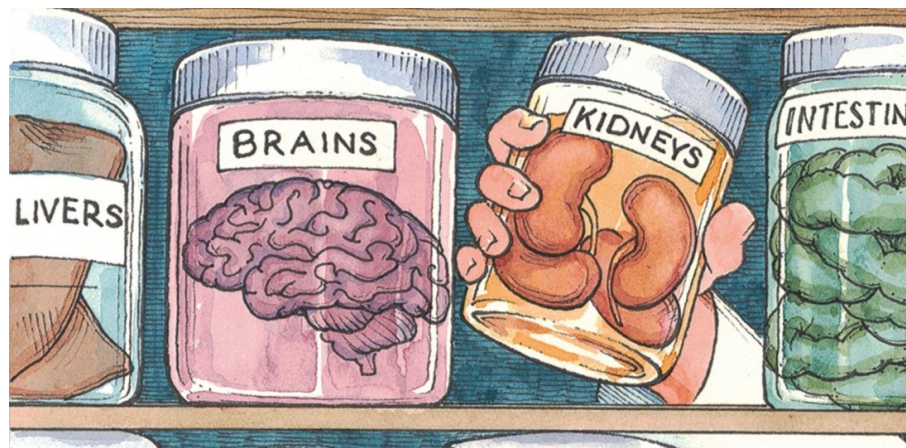


● Potential lead

Disease modelling

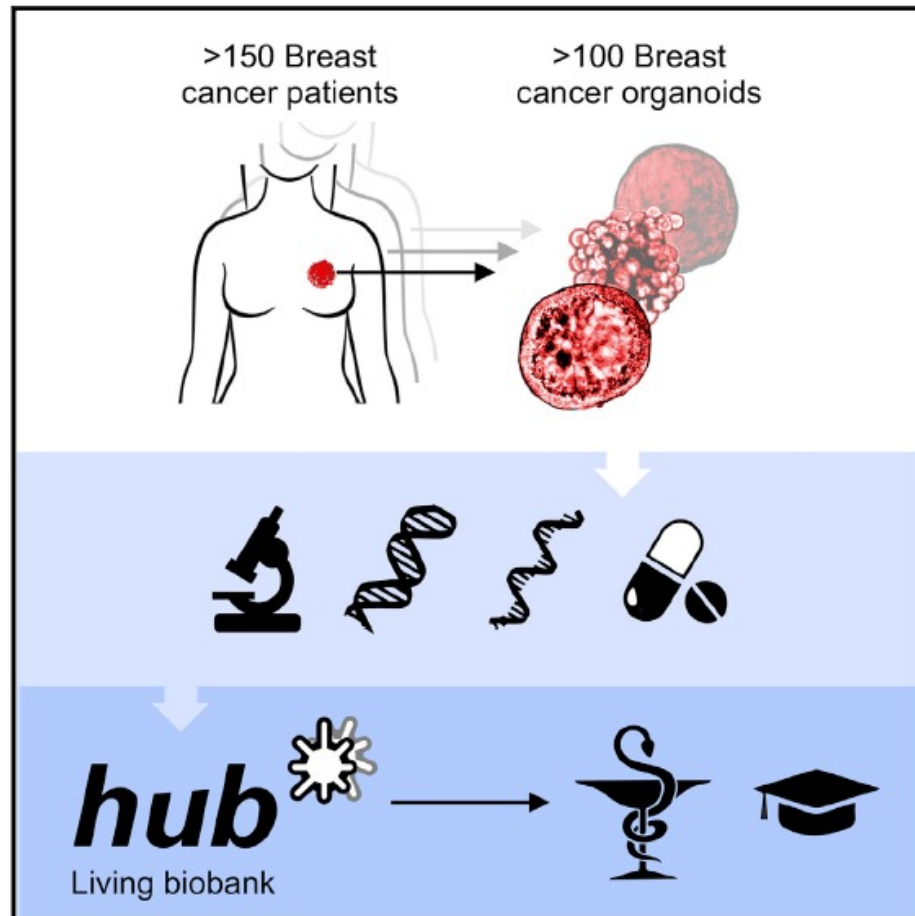


Applicazioni: biobanche di organoidi tumorali da pazienti



A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity

Graphical Abstract



Authors

Norman Sachs, Joep de Ligt,
Oded Kopper, ...,
Robert Gerhardus Jacob Vries,
Edwin Cuppen, Hans Clevers

Correspondence



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In Brief

The heterogeneity of breast cancer subtypes can be captured using organoid cultures that can facilitate drug screens that corroborate with patient responses.

Article

Breast Cancer Organoids Model Patient-Specific Response to Drug Treatment

Elena Campaner ^{1,2,†,‡}, Alessandro Zannini ^{1,2,†,‡}, Mariangela Santorsola ^{1,2,†} ,
Deborah Bonazza ^{3,4} , Cristina Bottin ^{3,4}, Valeria Cancila ⁵, Claudio Tripodo ^{5,6},
Marina Bortul ^{3,7}, Fabrizio Zanconati ^{3,4}, Stefan Schoeftner ^{1,2} and Giannino Del Sal ^{1,2,6,*,†}

Simple Summary: The possibility to generate in the laboratory faithful models of patients' tumors is of primary importance to capture cancer complexity and study therapy response in a personalized setting. Tumor organoids are 3D cell cultures, obtained from patients' tumor tissues, that recapitulate several characteristics of the original tumor, thus representing a clinically relevant patient avatar. This study reports the generation and the molecular characterization of patient-derived organoids from invasive breast carcinomas. Our results proved the usefulness of these cancer models for designing patient-specific therapeutic approaches to treat highly aggressive cancers, but also highlighted the need to further improve this methodology to overcome its current limitations.