III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

PTEN: MECANISMOS ONCOGÉNICOS RELACIONADOS CON UN GEN SUPRESOR DE TUMORES

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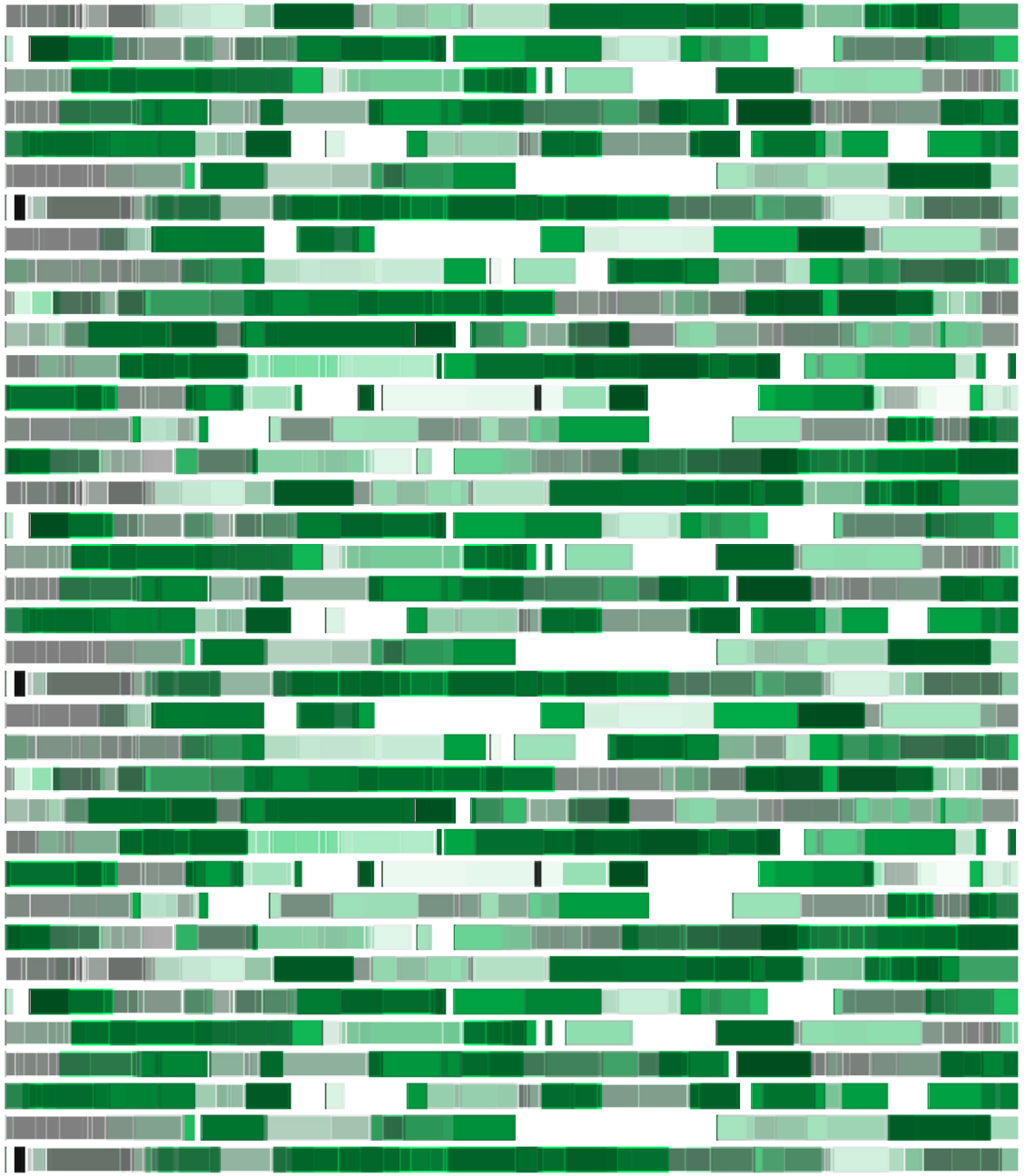


Organizador por:

HENDERE HEALTHCARE

CONTENTS

CONTENTS

PAM Pathway: The "Engine" of Cell Growth

A balance between activation & inhibition

✓The PAM pathway is one of the main growth regulatory pathways:

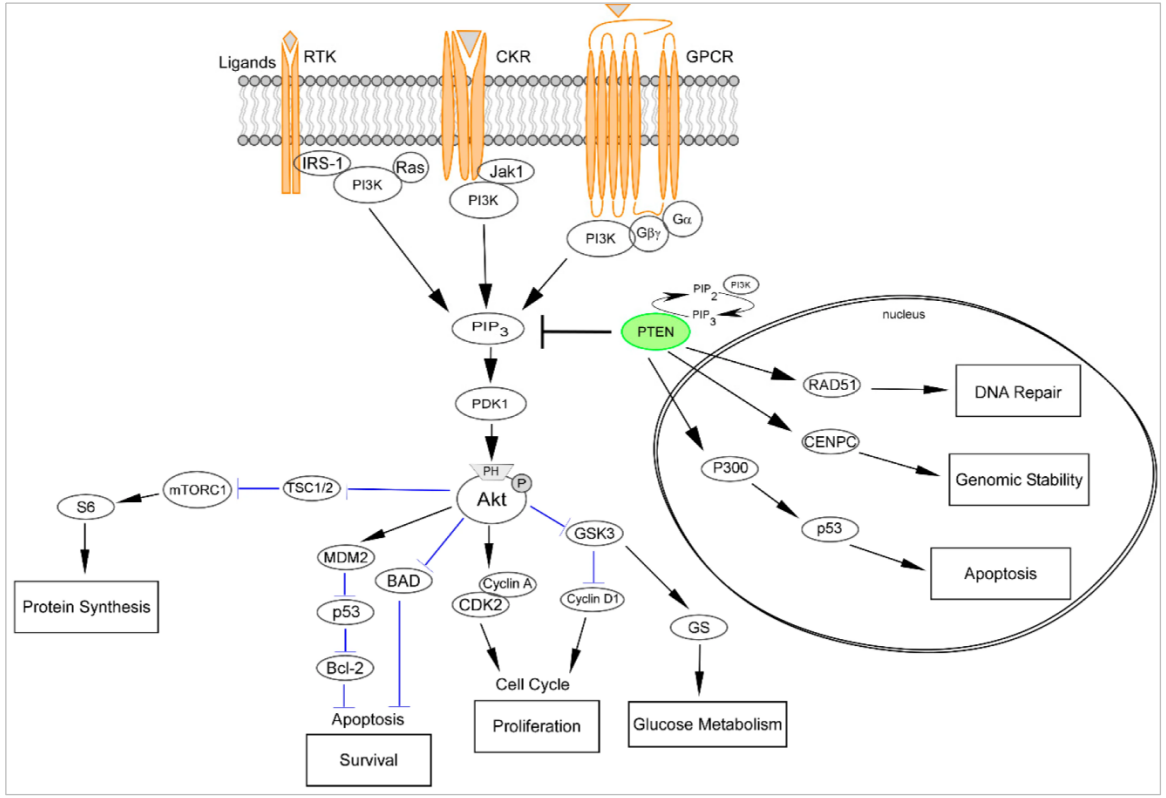
- Promotes: Proliferation & Survival GO!
- Inhibits: Apoptosis STOP

✓Three major nodes:

- *PI3K*
- *AKT*
- *MTOR*

✓One negative regulator:

- *PTEN*



Fusco N *et al*, Genes (Basel) 2020

PAM Pathway: The "Engine" of Cell Growth

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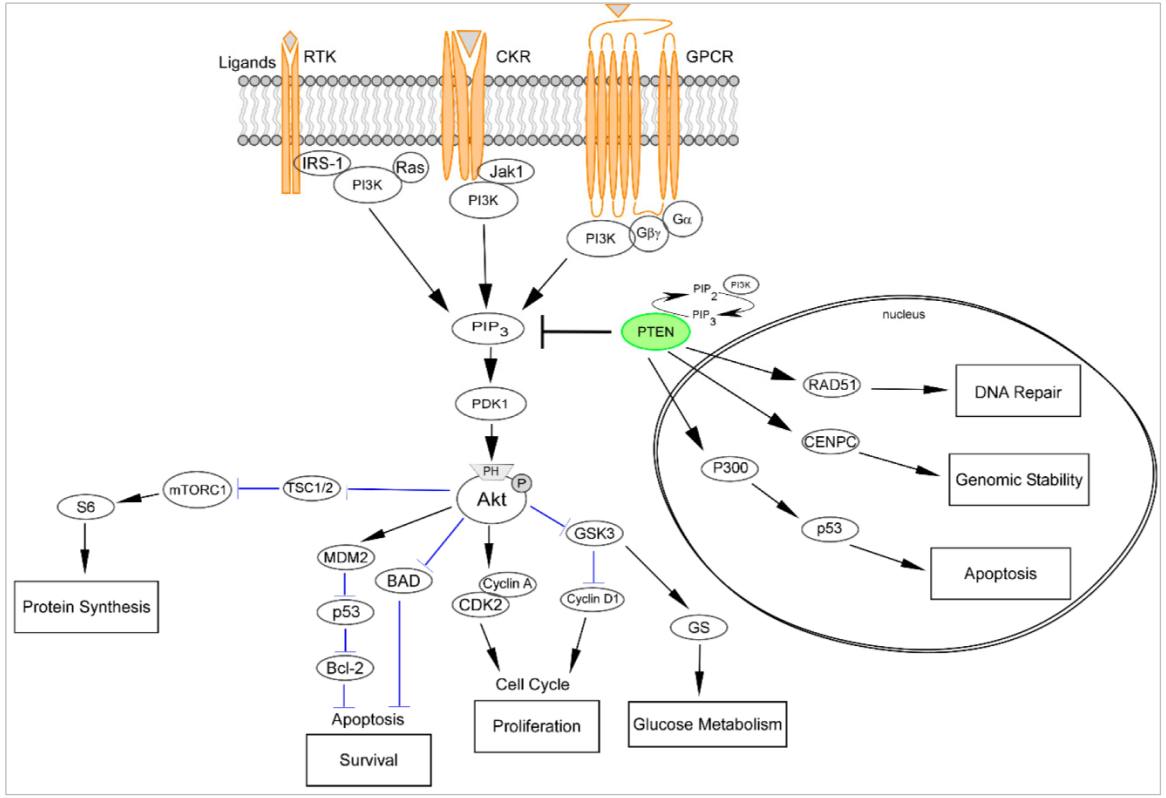
3. *MTOR*

✓One negative regulator:

4. *PTEN*



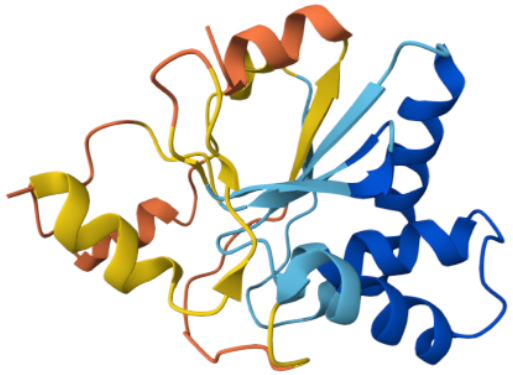
Fusco N *et al*, Genes (Basel) 2020

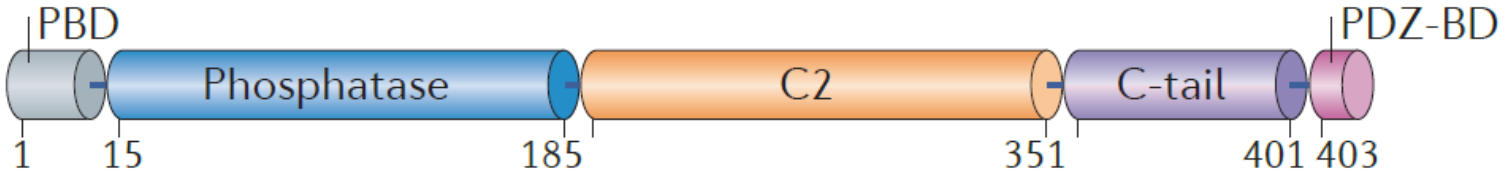
CONTENTS

PTEN: The "Guardian" of the Genome

Structural overview

- ✓ *PTEN* is a tumor suppressor gene located on chr10 (10q23.3)
- ✓ The gene has a length of 200 kb and comprises 9 exons
- ✓ The polypeptide consists of 403 aa with 5 functional domains
- ✓ PTEN protein can be localized in the cytoplasm or nucleus



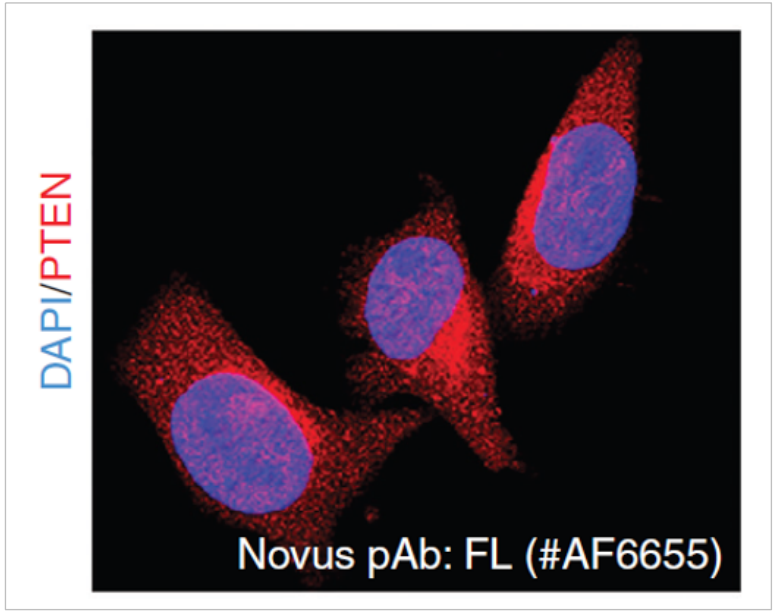


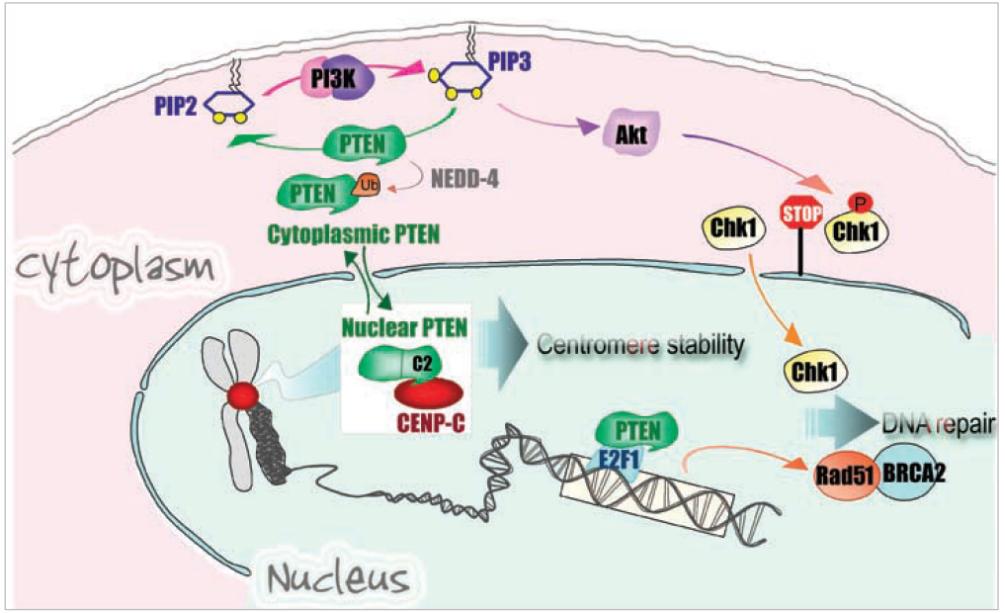
Song MS *et al*, Nat Rev Mol Cell Biol 2012; https://alphafold.ebi.ac.uk/entry/AF-P60484-3-F1

PTEN: The "Guardian" of the Genome

Biological functions depend on protein localization

- ✓ Cytoplasm: Negative regulatory function of the PAM pathway
- ✓ Nucleus: Chromosome stability by interacting with centromeres





Yin Y & Shen WH, Oncogene 2008; Fan X *et al*, Cold Spring Harb Perspect Med 2020

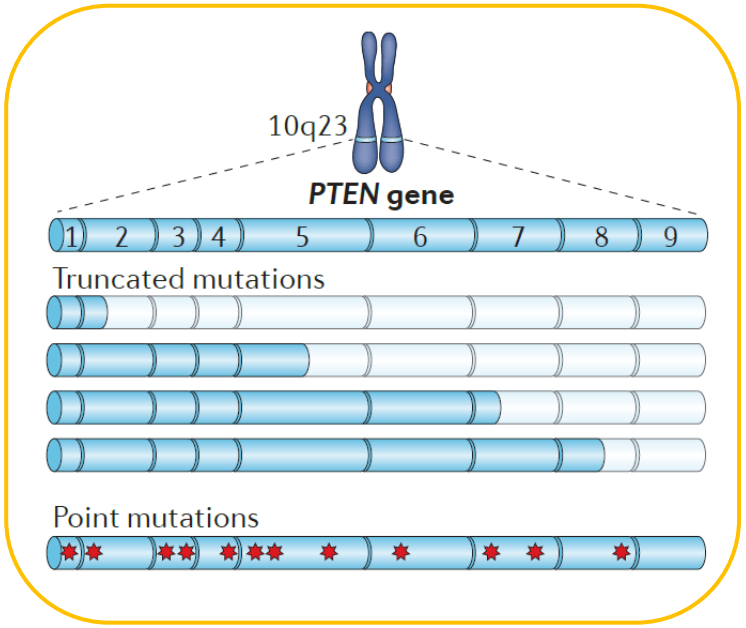
CONTENTS

Oncogenic Mechanisms

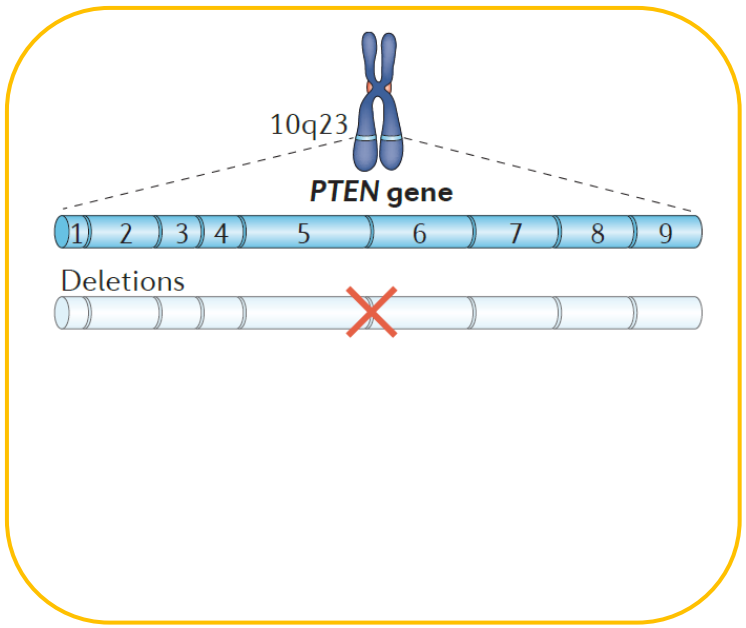
How does *PTEN* fail? On-target

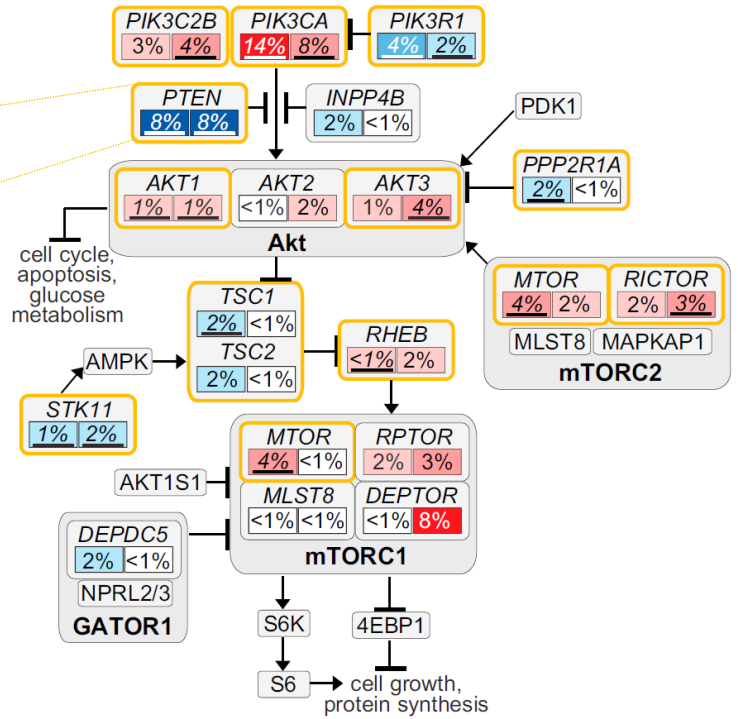
PTEN	
8%	8%

1 Mutations



2 Loss





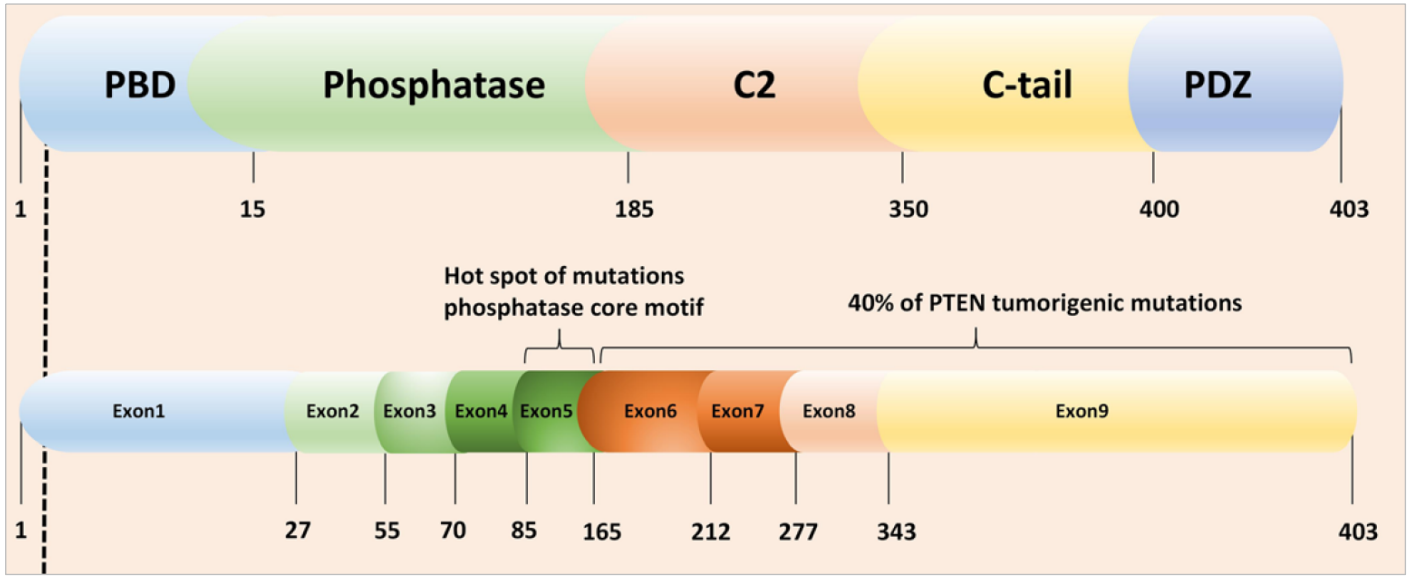
Song MS *et al*, Nat Rev Mol Cell Biol 2012; Zhang Y *et al*, Cancer Cell 2017

Oncogenic Mechanisms

1

How does *PTEN* fail? On-target -> Mutations

- ✓ *PTEN* is the second most mutated gene in human cancer (after *TP53*)
- ✓ The exon 5 is the most frequent mutation site (phosphatase domain)
- ✓ The exons 6, 7 & 8 also present a significant amount of mutations

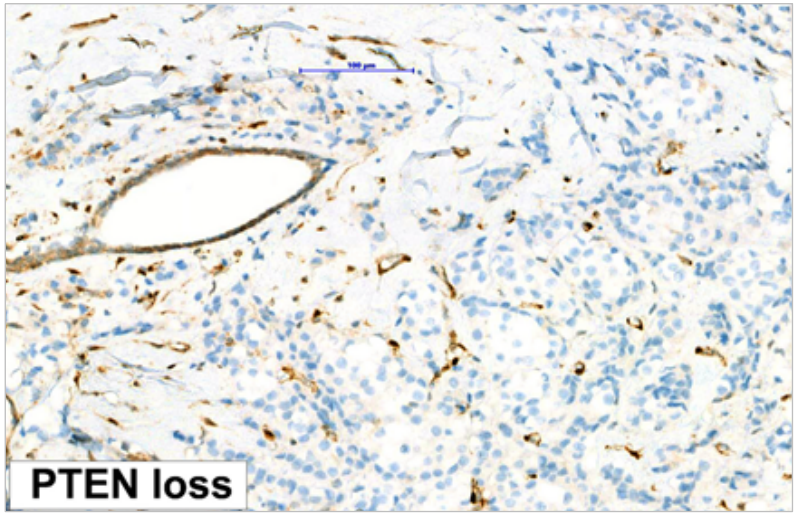


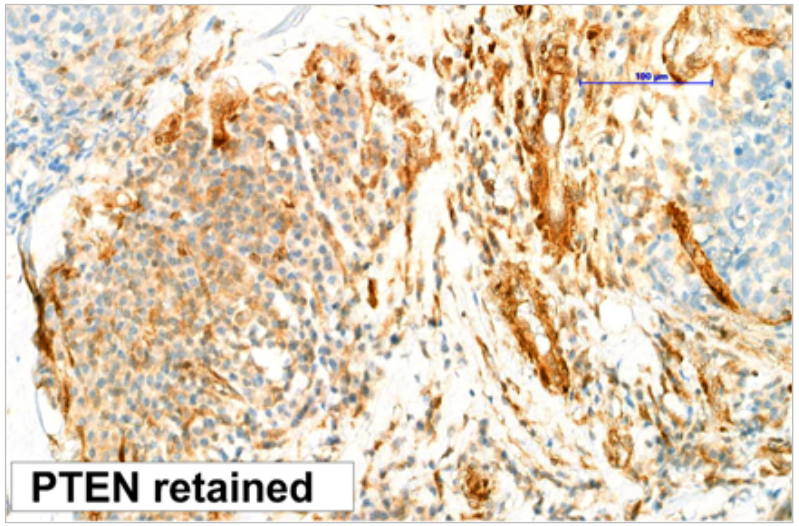
Liu J *et al*, J Cell Physiol 2023

Oncogenic Mechanisms

How does *PTEN* fail? On-target -> Loss

- ✓ The deletion are the most frequently event:
  - Hemizygous loss: affecting one *PTEN* copy
  - Homozygous loss: affecting both *PTEN* copies
- ✓ *PTEN* gene loss impacts in PTEN protein expression



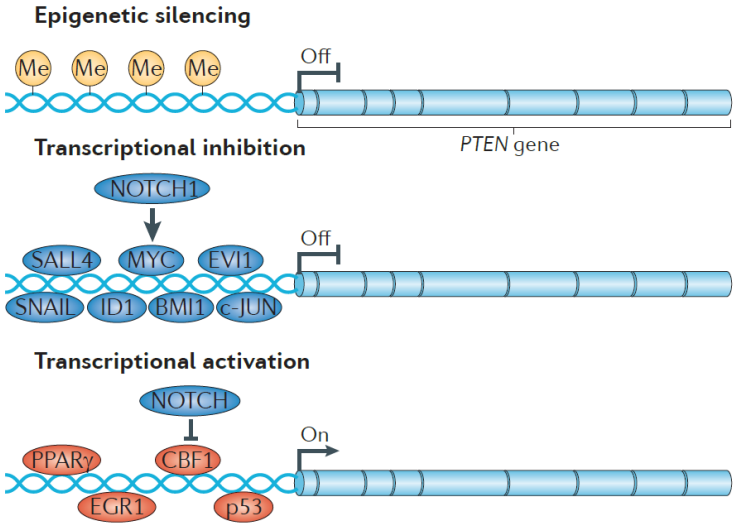


Fusco N *et al*, Virchows Arch 2025

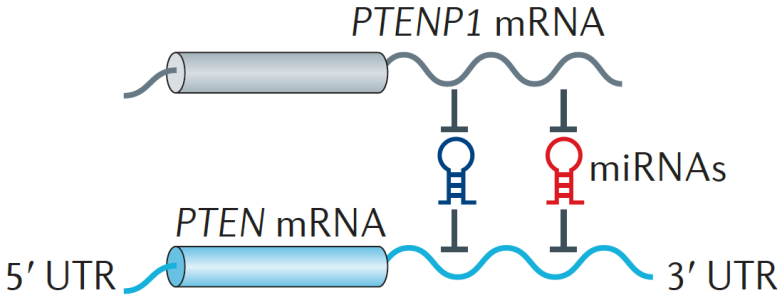
Oncogenic Mechanisms

How does *PTEN* fail? Off-target

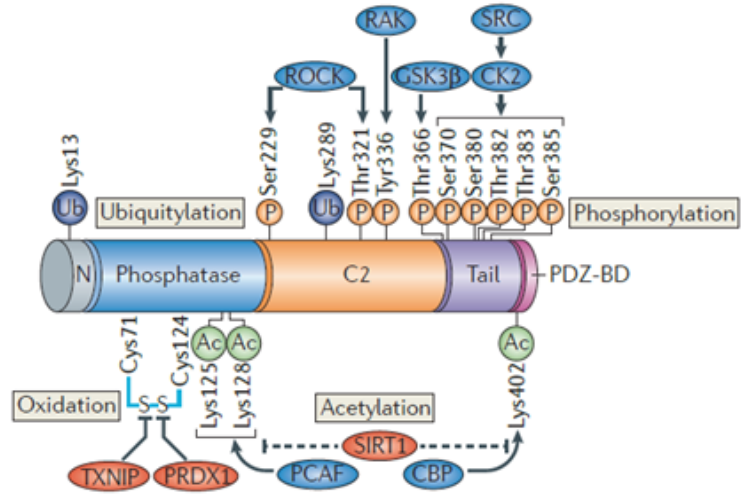
1 Transcriptional level



2 Post-transcriptional level



3 Post-translational level



Song MS *et al*, Nat Rev Mol Cell Biol 2012; Zhang Y *et al*, Cancer Cell 2017

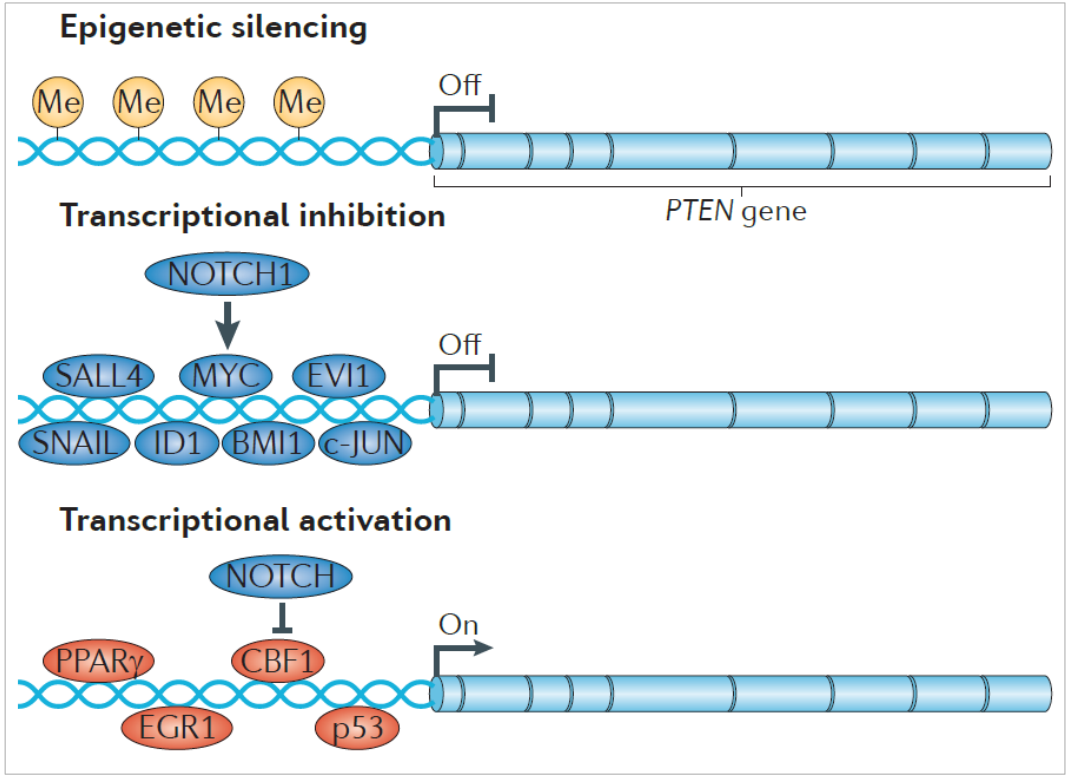
Oncogenic Mechanisms

1

How does *PTEN* fail? Off-target -> Transcriptional level

- ✓ An epigenetic silencing through aberrant methylation of the *PTEN* promoter STOP

- ✓ Active *NOTCH1* has reported to:
  - Inhibit *PTEN* through *MYC* STOP
  - Activate *PTEN* through *CBF1* GO!

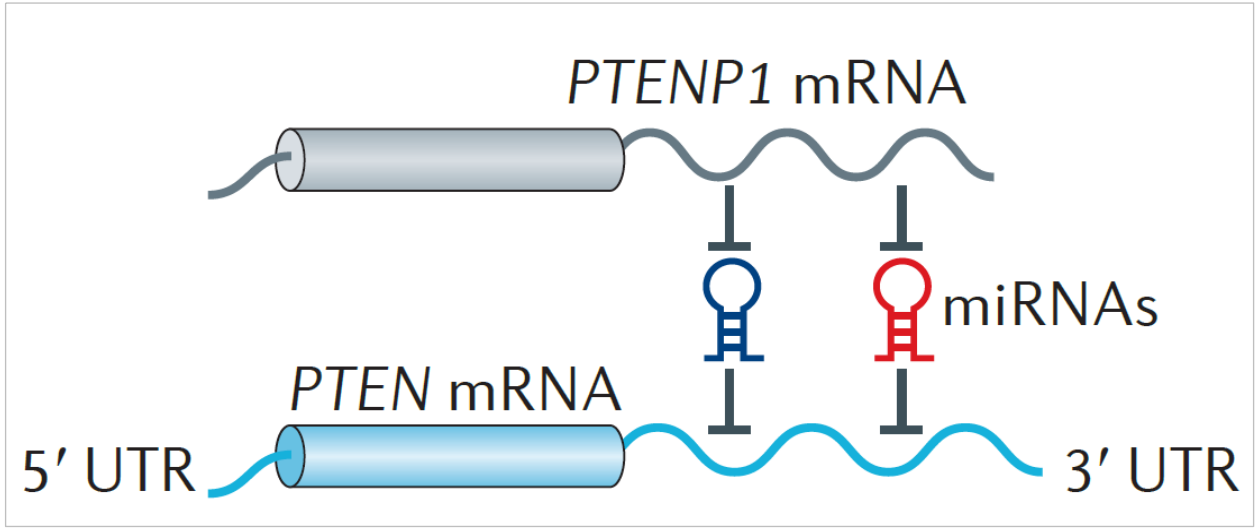


Song MS *et al*, Nat Rev Mol Cell Biol 2012

Oncogenic Mechanisms

How does *PTEN* fail? Off-target -> Post-transcriptional level

- ✓ If miRNAs are overexpressed they downregulate *PTEN* by binding to the 3´UTR of the mRNA STOP
- ✓ *PTENP1* is a pseudogen that acts as a decoy sequestering miRNAs GO!

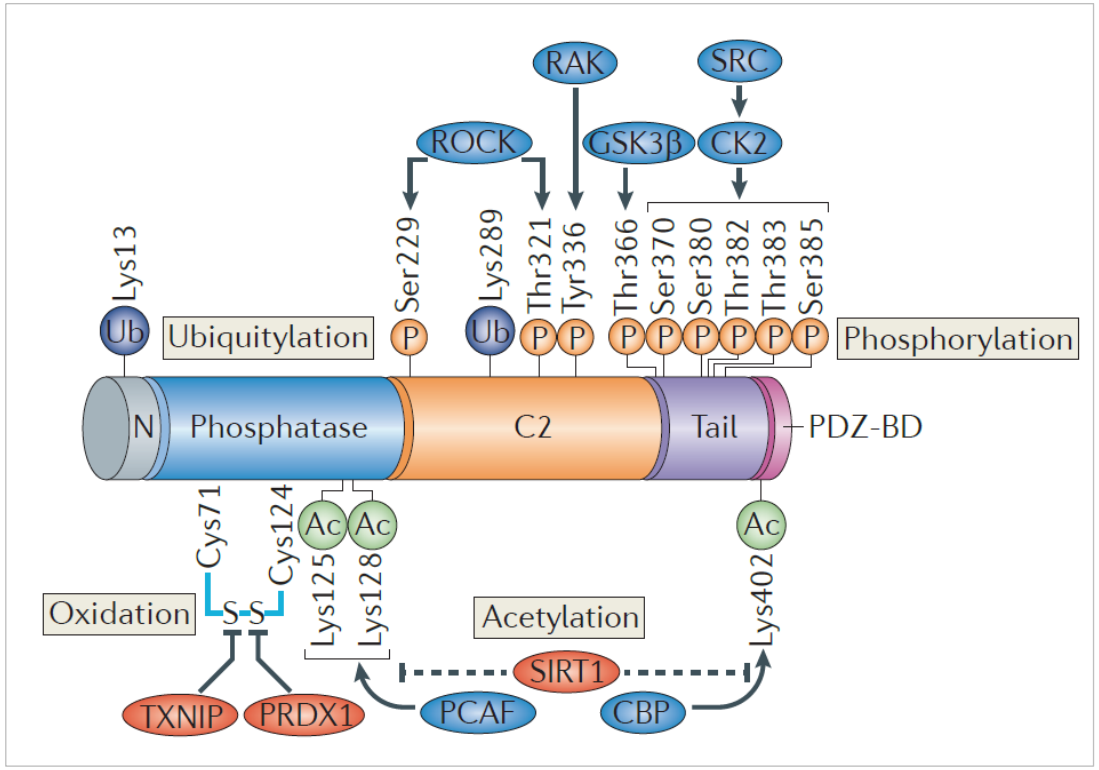


Song MS *et al*, Nat Rev Mol Cell Biol 2012

Oncogenic Mechanisms

How does *PTEN* fail? Off-target -> Post-translational level

- ✓ Ubiquitylation controls PTEN protein degradation & nuclear-cytoplasmic shuttling STOP GO!
- ✓ Phosphorylation stabilizes PTEN protein but inhibits its membrane localization STOP
- ✓ Acetylation inhibits PTEN protein catalytic activity STOP
- ✓ Oxidation inactivates PTEN protein STOP

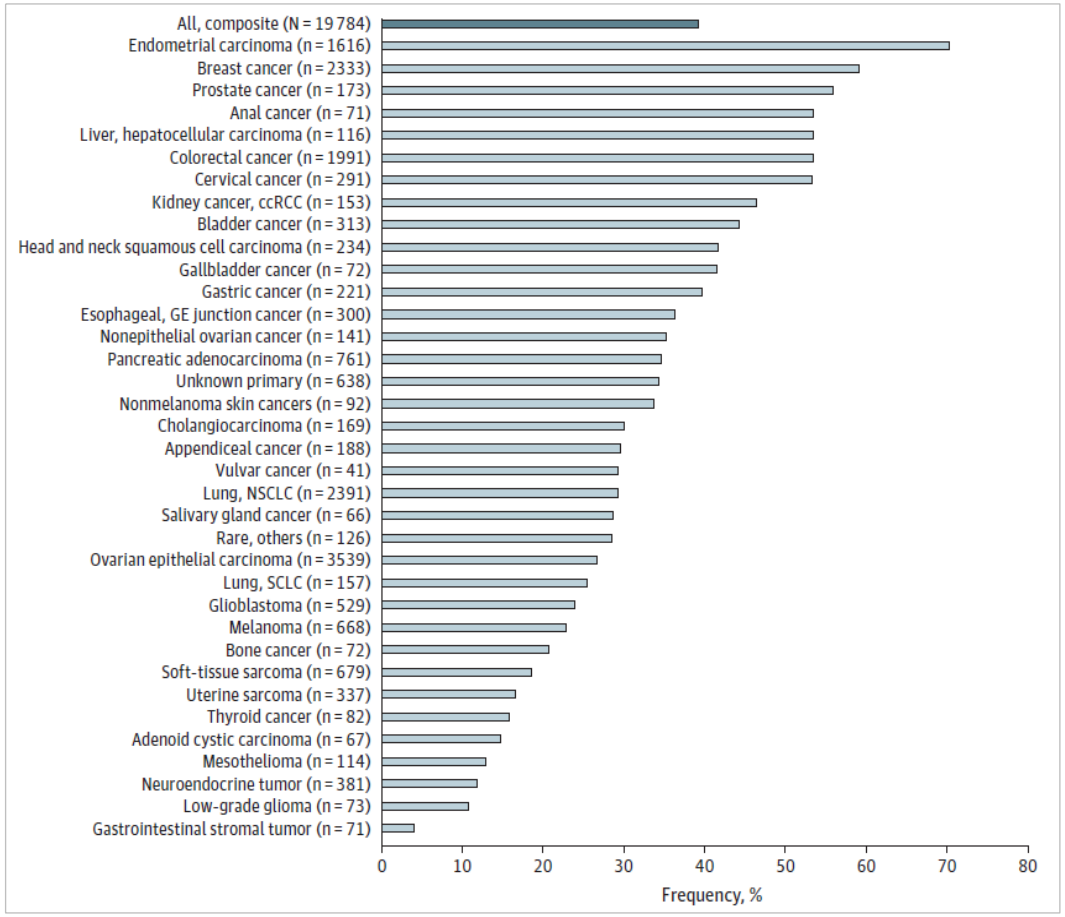


Song MS *et al*, Nat Rev Mol Cell Biol 2012

CONTENTS

Which Solid Tumors Present Alterations in *PTEN*?

Tumor-specific strategies for inactivation



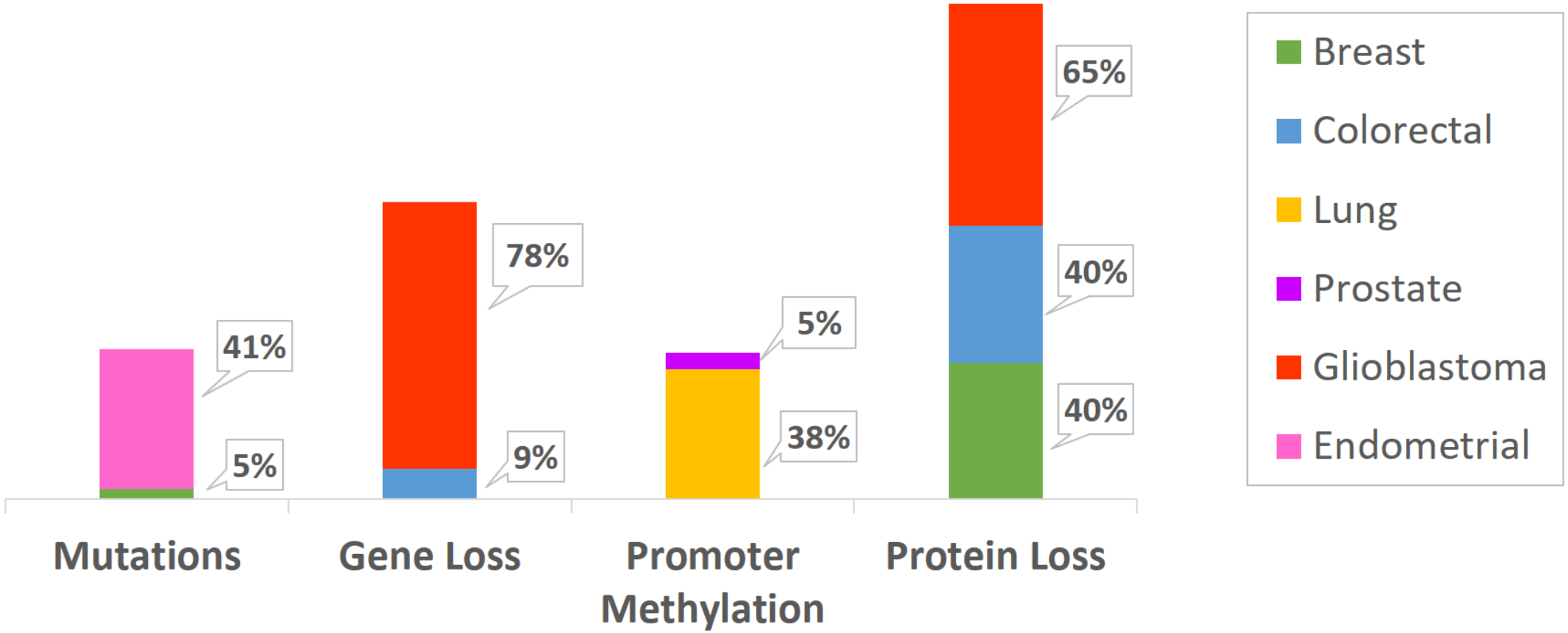
Analysis of **19.784** samples

Aberrations in the **PAM pathway** were identified in **38%** of the **patients**

Millis SZ *et al*, JAMA Oncol 2016

Which Solid Tumors Present Alterations in *PTEN*?

Tumor-specific strategies for inactivation



Khasarah G *et al*, Discov Oncol 2025

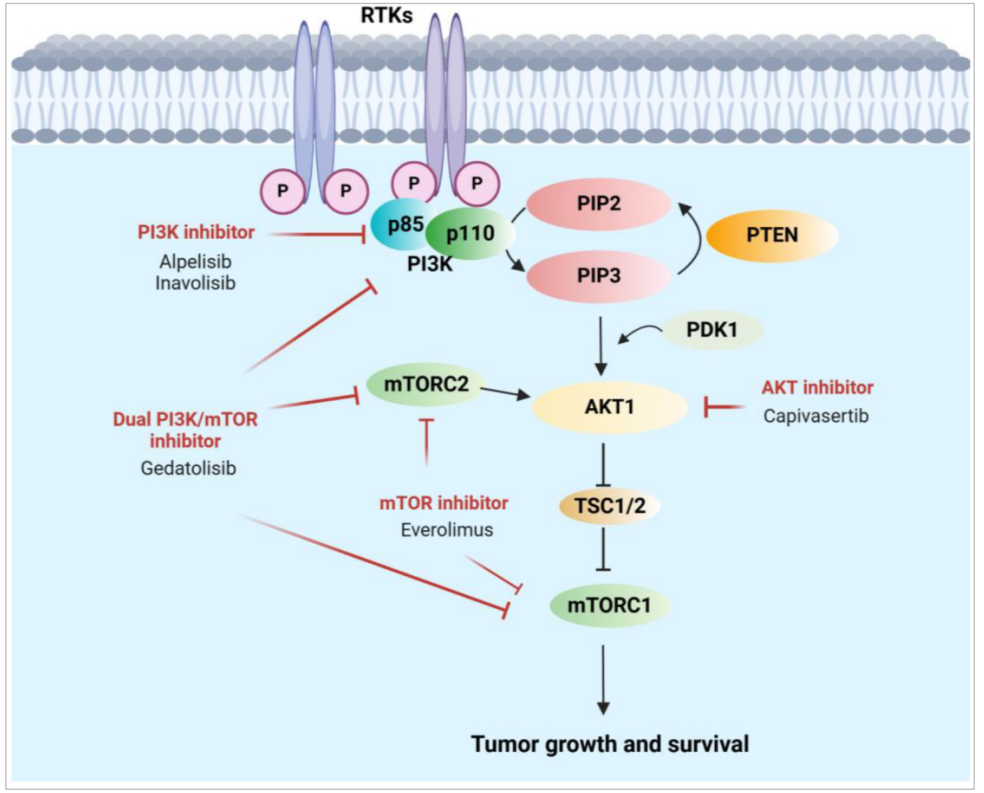
CONTENTS

PTEN Loss Clinical Implications

1) Targeted Therapy

- ✓ Dysregulation of the PAM pathway by activating mutations in *PIK3CA* & *AKT1* and/or inactivating *PTEN* are most frequently observed in breast tumors

- ✓ PAM pathway inhibitors (individual or dual approaches) are available in metastatic HR+/HER2- patients

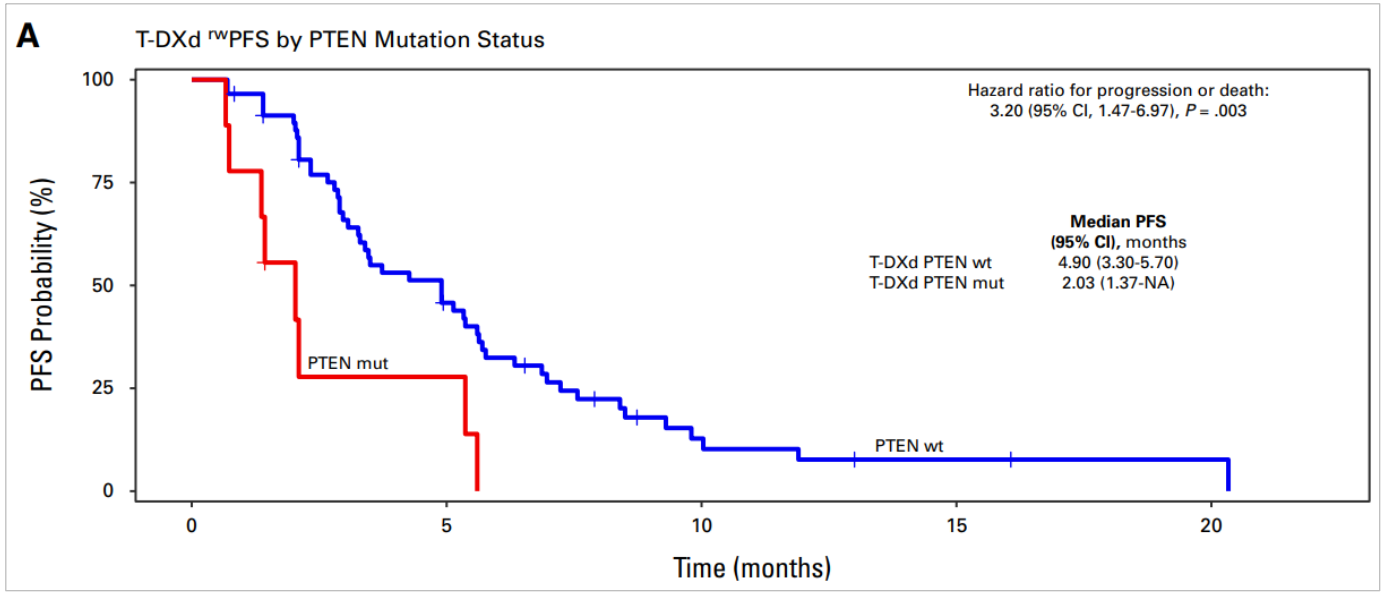


Liu L *et al,* Cancers (Basel) 2024

PTEN Loss Clinical Implications

2) Targeted Therapy Resistance

✓ *PTEN* loss is a key biomarker for anti-HER2 therapies in HER2+ breast cancer



Resistance to targeted therapy
Poor Prognosis
Reduced Survival

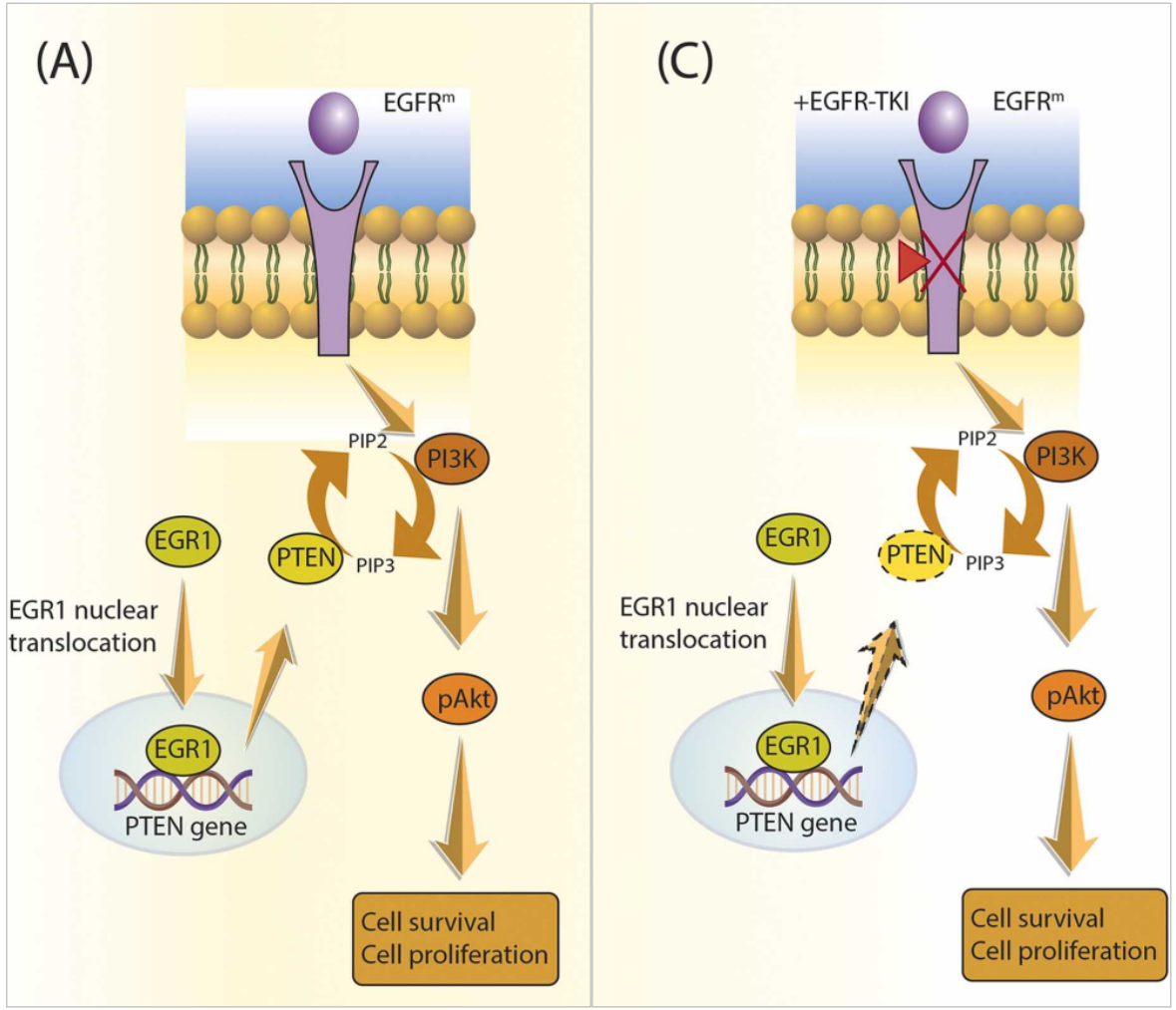
Mai M *et al*, JCO Precis Oncol 2025

PTEN Loss Clinical Implications

3) Targeted Therapy Resistance

✓ *PTEN* loss is a key biomarker in *EGFR+* NSCLC patients treated with TKIs

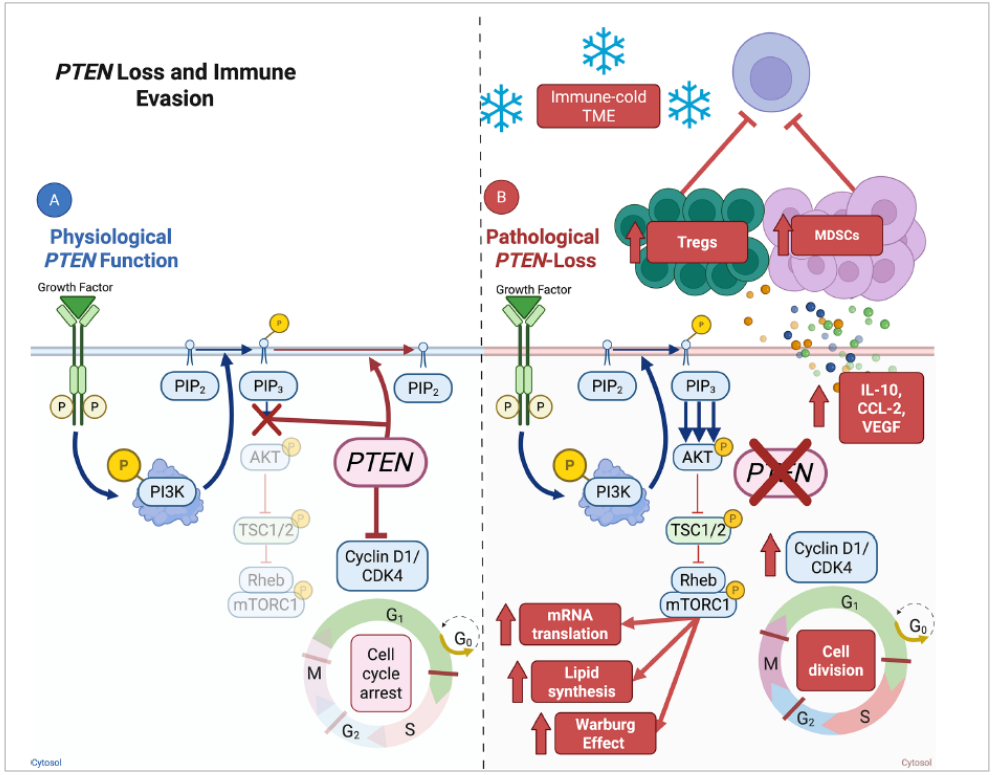
Resistance to targeted therapy
Poor Prognosis
Reduced Survival



Tufail M *et al*, Toxicol Rep 2025

PTEN Loss Clinical Implications

4) Immunotherapy Resistance



✓ *PTEN* loss leads to:

- Recruitment of immunosuppressive cells
- Reduced T-cell infiltration
- Induction of an *"immune-cold"* TME

Resistance to anti-PD1/PD-L1

Poor Prognosis

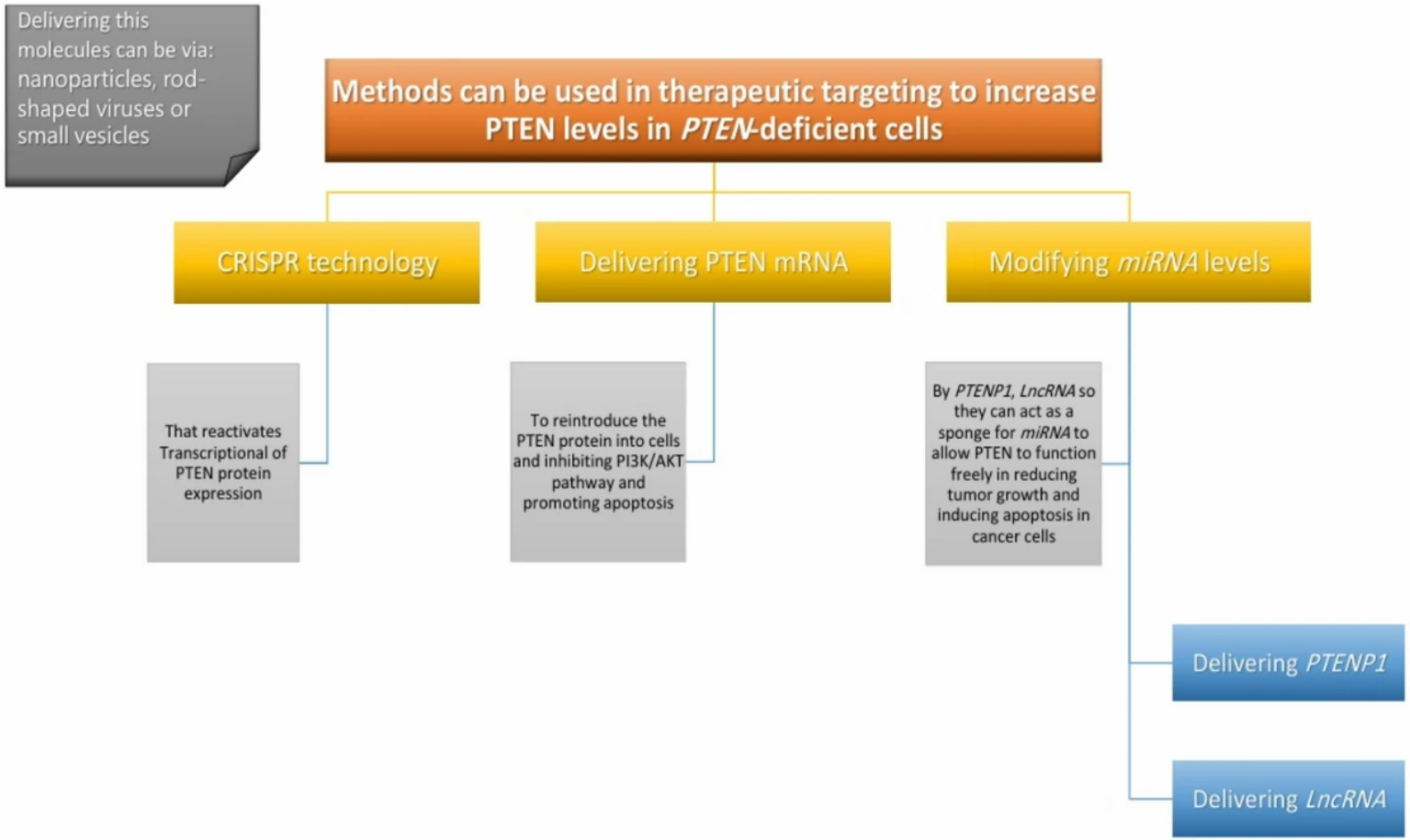
Reduced Survival

Paredes R *et al*, J Immunother Cancer 2025

CONTENTS

Future Therapeutic Approaches

PTEN Restoration in Solid Tumors



Khasarah G *et al*, Discov Oncol 2025

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025