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Protein Kinase Inhibitors in the Treatment of Lung Cancer

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Introduction

1) Lung cancer remains the leading cause of cancer-related mortality worldwide

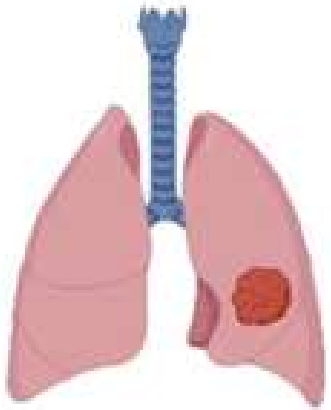
2) non–small cell lung cancer (NSCLC) accounting for approximately 85 % of all cases .

,3) chemotherapy which offered limited survival benefits and significant toxicity.

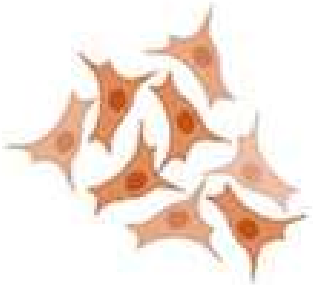
4) discovery of oncogenic driver mutations (PK)

Lung Cancer (LC)

SUB-TYPE



ORIGIN



- Small-cell Lung Cancer **SCLC** (~15%)
  - Neuroendocrine cell
- Non-small cell Lung Cancer **NSCLC** (~85%)
  - Lung Adenocarcinoma **LUAD**
    - Alveolar type II Epithelial Cell
  - Lung Squamous-cell Carcinoma **LUSC**
    - Basal Epithelial Cell
  - Large-cell Carcinoma **LCC**
    - Various Epithelial Cells

we will focus on four key concepts:

1)What are protein kinases?

2)Why are protein kinases critically important in lung cancer?

3)What exactly are protein kinase inhibitors and how do they work?

4)What is the clinical evidence and recent updates on PKIs in the treatment of NSCLC?

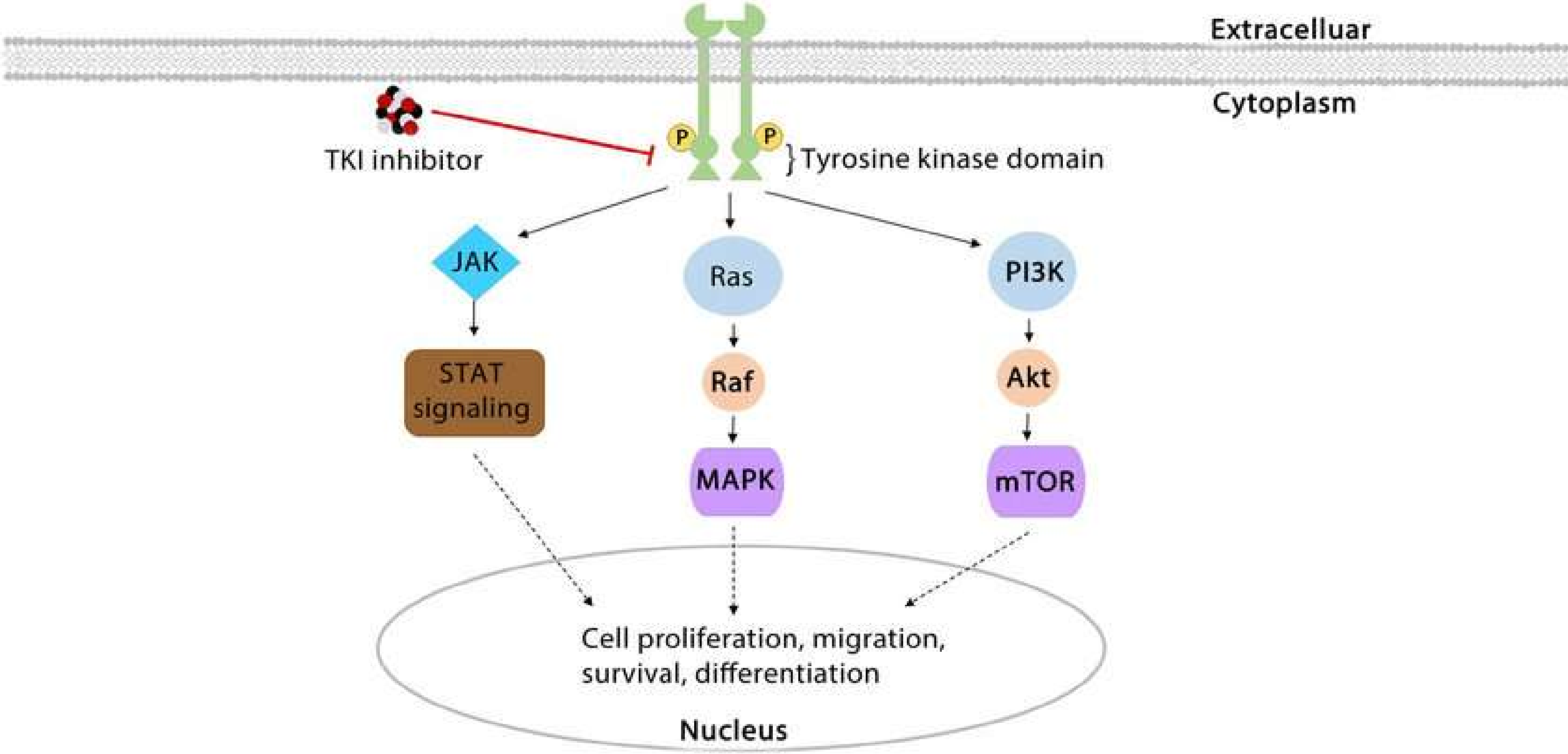
What Are Protein Kinases

- **Protein kinases** are enzymes that play a central role in regulating cellular activities.
- These enzymes add phosphate groups to proteins (**phosphorylation)**, which affects the protein's function, such as **cell growth, survival, and division**.

- In normal cells, this process is tightly regulated, but in cancer cells, mutations in certain kinases lead to continuous activation of these pathways, causing uncontrolled cell growth and survival.

Among all protein kinases implicated in NSCLC, **EGFR is the most clinically significant**. When mutated, **EGFR activates several major downstream pathways:**

- **RAS–RAF–MAPK pathway** → promotes **uncontrolled proliferation**
- **PI3K–AKT–mTOR pathway** → enhances **survival, anti-apoptosis**
- **JAK–STAT pathway** → contributes to **tumor progression and immune evasion**


Extracelluar
Cytoplasm
TKI inhibitor
P
P
} Tyrosine kinase domain
JAK
Ras
PI3K
STAT signaling
Raf
Akt
MAPK
mTOR
Cell proliferation, migration, survival, differentiation
Nucleus

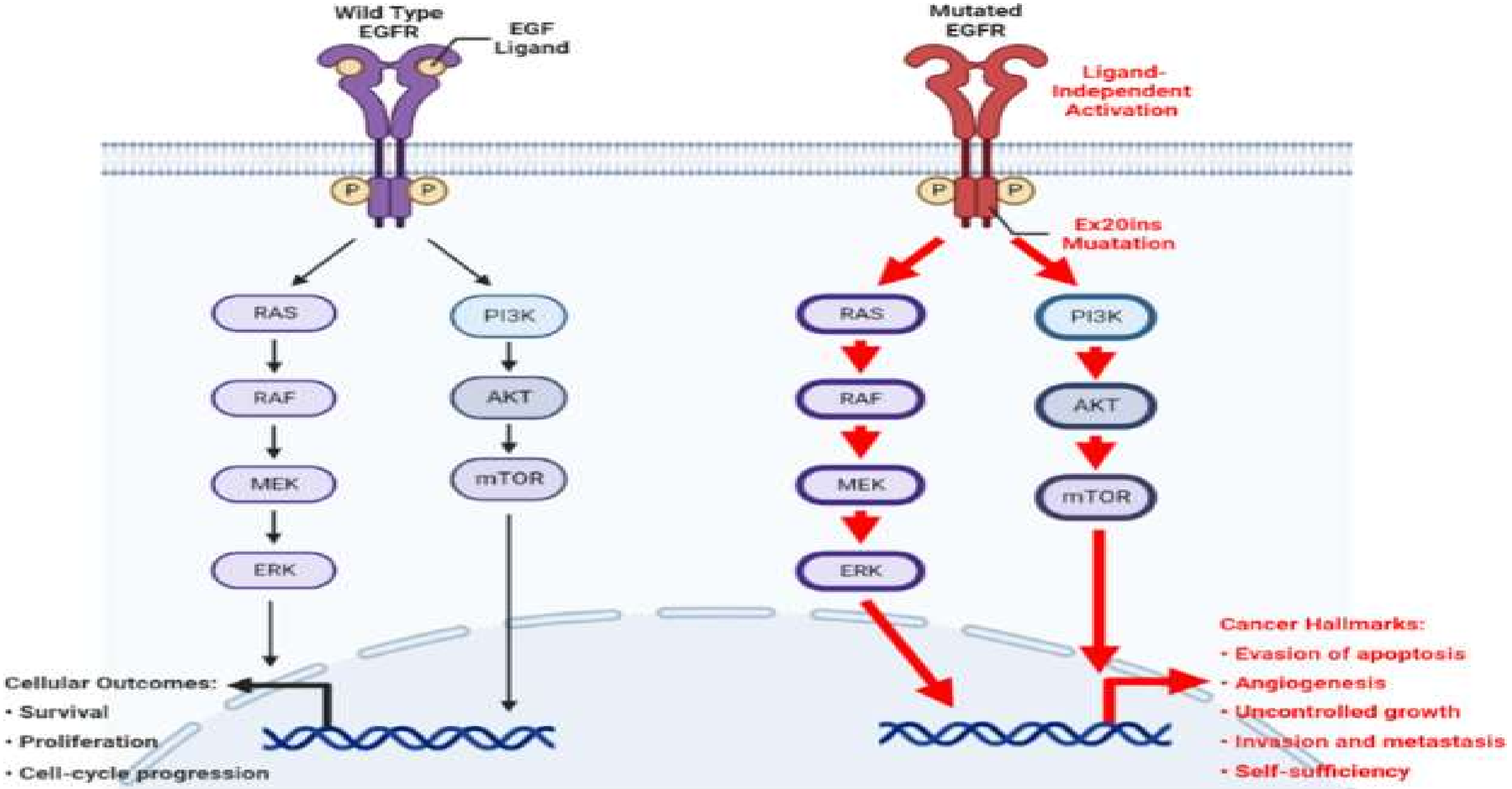
Why Are Protein Kinases Important in Lung Cancer

- In NSCLC, mutations or rearrangements in genes encoding protein kinases—such as EGFR, ALK, and ROS1—lead to continuous activation of downstream signaling pathways like PI3K/AKT and MAPK.

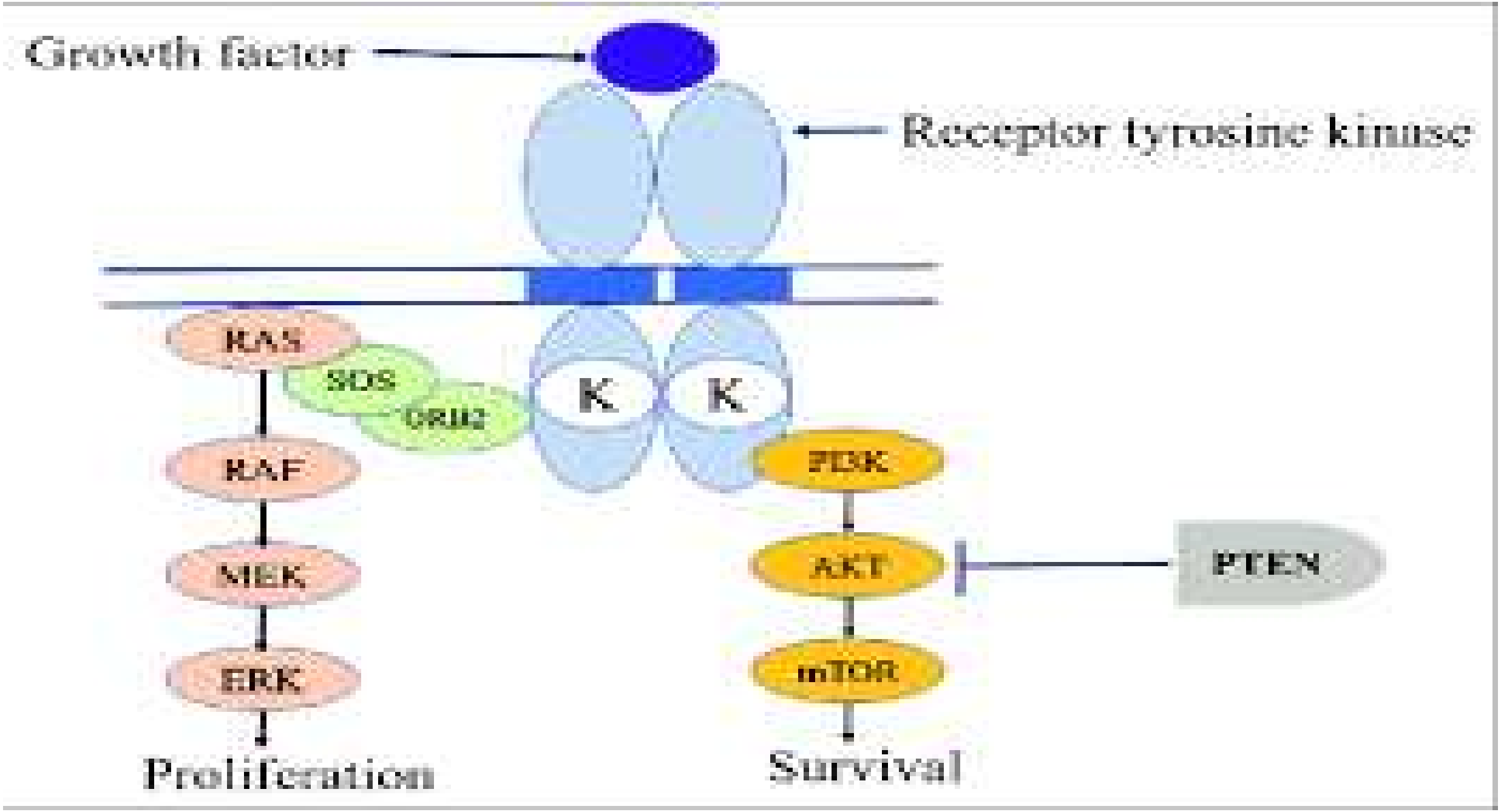
- Tumor cells become highly dependent on these signaling pathways, a concept known **as oncogenic addiction.**

Oncogenic addiction

*Cancer cells rely on a **single dominant oncogenic pathway** for survival and proliferation.*


Wild Type EGFR
EGF Ligand
Mutated EGFR
Ligand-Independent Activation
Ex20ins Muatation
P
P
RAS
RAF
MEK
ERK
PI3K
AKT
mTOR
Cellular Outcomes:
• Survival
• Proliferation
• Cell-cycle progression
Cancer Hallmarks:
- Evasion of apoptosis
- Angiogenesis
- Uncontrolled growth
- Invasion and metastasis
- Self-sufficiency

In NSCLC, mutations in **EGFR**, **ALK**, **ROS1**, and other genes lead to **overactive kinase signaling**, which drives the **cancerous behavior of these cells.** This is why targeting kinases has become a focal point of cancer treatment, particularly in **NSCLC**.


Growth factor
Receptor tyrosine kinase
RAS
SOS
GRB2
K
K
RAF
MEK
ERK
Proliferation
PI3K
AKT
PTEN
mTOR
Survival

Why Are Protein Kinases So Important in Lung Cancer

1) their role in **tumor progression**. For example, **EGFR mutations** are found in a significant number of NSCLC patients. These mutations make the tumor cells rely on the EGFR signaling pathway for **survival** and **growth.**

2)The continuous activation of such signaling pathways can be blocked by **protein kinase inhibitors**, offering a much more **targeted** treatment option than **traditional chemotherapy**.

3) By targeting these abnormal kinases, PKIs stop tumor growth,

improve **progression-free survival (PFS)**,

and have **fewer side effects** compared to chemotherapy.

What Are Protein Kinase Inhibitors

Protein kinase inhibitors (PKIs) are a class of drugs designed to block the action **of specific kinases involved in cancer cell growth**. These inhibitors bind to the ATP-binding site of the kinase, preventing it from being activated and stopping **the signal that drives the cancer's growth.**

There are different generations of PKIs used in NSCLC

- **First-generation** PKIs like **Gefitinib** and **Erlotinib** target EGFR mutations.
- **Second-generation** PKIs like **Afatinib** target multiple EGFR mutations and are more potent.
- **Third-generation** PKIs like **Osimertinib** are more effective at overcoming resistance mutations (like **T790M**) and have better efficacy against **brain metastases**.

- Major **Driver Mutations in NSCLC**

1. EGFR Mutations (30–40%)

- **Exon 19 deletion (~60%)**
- **L858R point mutation (~30%)**
- These mutations keep the EGFR receptor **permanently activated**, continuously triggering downstream oncogenic pathways such as MAPK, PI3K, and JAK–STAT.
- ➞ **Patients with these mutations show the highest sensitivity to EGFR-TKIs**, particularly **osimertinib and lazertinib**

2. ALK Rearrangements (5–7%)

- Younger age
- Non-smokers
- High incidence of CNS metastasis
- Effective therapies include:

. **Alectinib**

. **Brigatinib**

. **Lorlatinib**

3. ROS1 Rearrangements (1–2%)

Highly responsive to:

- **Crizotinib**

Entrectinib

Clinical Studies and Updates

- Recent clinical trials have established targeted therapy as first-line treatment
- Focus on efficacy, resistance, and CNS control
- Treatment decisions guided by NCCN and ESMO guidelines

- **Osimertinib: First-Line Standard of Care**
- Superior efficacy compared with earlier EGFR-TKIs
- Excellent CNS penetration
- Improved safety profile
- Recommended by NCCN and **ESMO** guidelines

why Osimertinib Is Preferred First-Line

- High activity in common **EGFR mutations** (Ex19del, L858R)
- Effective **against T790M** resistance mutation
- Lower rates of **severe rash** and **diarrhea**
- Suitable for **elderly** and **comorbid patients**

When Osimertinib Alone May Not Be Enough

- **Co-mutations: TP53, RB1, PIK3CA**
- **Bulky disease or high tumor burden**
- **Rapid early progression**
- **High risk of CNS metastases**

- **The Emerging First-Line Option: Amivantamab + Lazertinib**
- Dual targeted therapy approach
- Combines antibody and EGFR-TKI
- Designed to delay resistance

the MARIPOSA Trial

- Phase III, first-line EGFR-mutated NSCLC
- **Amivantamab** (EGFR–MET bispecific antibody)
- **Lazertinib** (next-generation EGFR-TKI)
- Compared with osimertinib

MARIPOSA Trial: Key Results

- **Superior PFS vs osimertinib alone**
- **Better suppression of MET-driven resistance**
- **Strong and durable CNS responses**
- **Benefit in TP53/RB1 co-mutated tumors**

Expanding Targeted Options in NSCLC

- **MET exon 14 skipping: Capmatinib**
- **RET fusions: Selpercatinib**
- **ROS1 rearrangements: Crizotinib, Entrectinib**

Lazertinib: Key Characteristics

- High **selectivity** for mutant EGFR
- Active against Ex19del, L858R, and T790M
- **Excellent CNS penetration**

- **Lazertinib:** Lower rates of skin rash
- **Reduced diarrhea**
- Less **mucositis** compared **with older TKIs**

Clinical Considerations for PKI–ICI Use

- EGFR/ALK-positive tumors → **PKIs first**
- ICIs considered after **TKI failure**
- Avoid concurrent use due **to toxicity**

To summarize,

protein kinases are central to the development and progression of **NSCLC**.

By understanding and targeting these pathways with **PKIs**, we have made great strides in treating this disease.

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