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Mini Review* | *Open Access

Targeting CDK4/6 and MEK Synergistically Induces Autophagy and Inhibits SQSTM1/p62-Mediated EMT via the AMPK/mTOR Pathway in Gastric Cancer

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Key words: Gastric cancer; KRAS mutation; CDK4/6 and MEK inhibition; Autophagy; AMPK/mTOR signaling; SQSTM1/p62; Epithelial-mesenchymal transition (EMT)

Abstract

KRAS mutations are prevalent in gastric cancer (GC) and often correlate with therapeutic resistance and unfavorable prognosis. Combined inhibition of MEK and CDK4/6 has shown synergistic antitumor activity in KRAS-mutant GC models, both in vitro and in vivo. Mechanistically, this dual blockade induces autophagy through activation of the AMPK/mTOR pathway, contributing to suppressed tumor proliferation. Notably, combining this strategy with autophagy inhibitors further enhances antitumor effects, suggesting that targeting metabolic adaptability may be therapeutically advantageous.

Concurrently, SQSTM1/p62—an autophagy receptor protein—was found to be overexpressed in GC tissues and positively associated with poor patient prognosis. Functional studies revealed that p62 promotes tumor cell proliferation, migration, and epithelial-mesenchymal transition (EMT) by modulating E-cadherin, N-cadherin, and vimentin expression levels. These findings highlight a dual role of autophagy in GC progression, where autophagy induction suppresses tumor growth via metabolic stress, yet elevated p62 expression drives EMT and malignancy.

This review discusses how targeting CDK4/6 and MEK not only disrupts proliferation but also modulates autophagy to inhibit p62-driven EMT. This integrative approach, acting through the AMPK/mTOR pathway, may offer an effective strategy against KRAS-mutant and p62-overexpressing gastric cancers.

1. Introduction

Gastric cancer (GC) remains one of the most lethal malignancies globally, with KRAS mutations frequently implicated in aggressive subtypes and therapeutic resistance [1]. Traditional therapies often fall short due to metabolic plasticity and adaptive survival pathways in tumor cells. Recent studies have demonstrated that dual inhibition of CDK4/6 and MEK pathways results in synergistic suppression of tumor growth, primarily via the induction of autophagy

Table 1: Summary of Key Molecular Players in Gastric Cancer Progression.

Molecule	Function	Role in Gastric Cancer
KRAS	Oncogene	Promotes proliferation and resistance
CDK4/6	Cell cycle kinase	Target for growth inhibition
MEK	MAPK pathway component	Targeted to suppress proliferation
AMPK	Energy sensor	Induces autophagy upon activation
mTOR	Growth regulator	Inhibited during autophagy activation
SQSTM1/p62	Autophagy adaptor	Promotes EMT and poor prognosis

[2]. In parallel, elevated expression of the autophagy cargo receptor SQSTM1/p62 is linked with epithelial-mesenchymal transition (EMT) and poor prognosis in GC [3]. Understanding the molecular interplay among these pathways may unlock new therapeutic strategies.

2. Mechanistic Insights: The AMPK/mTOR Axis and Autophagy

The AMPK/mTOR pathway is a critical regulator of cellular energy homeostasis and autophagy. MEK and CDK4/6 inhibition has been shown to activate AMPK while suppressing mTOR, triggering autophagy [2]. This response can be cytostatic or cytotoxic depending on context. In KRAS-mutant GC, autophagy induction appears to be a beneficial therapeutic event that limits tumor progression. However, inhibiting autophagy alongside CDK4/6-MEK therapy can further enhance anticancer efficacy [2]. This dual effect suggests a complex regulatory network where autophagy must be precisely modulated(Table 1).

3. SQSTM1/p62: A Driver of EMT and Tumor Progression

SQSTM1/p62 plays a multifaceted role in oncogenesis. Beyond its role in autophagy, p62 is implicated in the activation of EMT-related signaling pathways [3]. Overexpression of p62 correlates with upregulation of mesenchymal markers such as N-cadherin and vimentin and downregulation of epithelial markers like E-cadherin. This transition enhances cell migration and invasion, fostering metastasis [3,4]. The modulation of p62 via autophagy or targeted inhibition may, therefore, be a promising adjunct to CDK4/6-MEK-based therapies.

4. Clinical Implications and Future Directions

Given the overlapping roles of autophagy and EMT in GC, a dual-targeting approach involving CDK4/6, MEK, and possibly p62 represents a multifaceted strategy to combat tumor growth and metastasis. Ongoing and future clinical trials should assess the safety and efficacy of these combinations. Furthermore, molecular profiling of p62 and autophagy markers may serve as useful biomarkers for patient stratification.

5. References

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