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Glycolisis in Cancer – Targetting Pkm2 (Pyruvate Kinase M2)

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ABSTRACT

Glycolysis is a defining characteristic of malignancy, frequently remaining upregulated even when oxygen levels are sufficient. Pyruvate kinase M2 (PKM2) acts as a fundamental enzymatic regulator within this "Warburg effect". This article examines the distinct regulatory mechanisms of PKM2 and its role in the advancement of cancer. Targeting PKM2 represents a potential therapeutic avenue to disrupt the metabolic pathways of cancer cells and impede the growth of tumors. We further review current progress in PKM2-focused strategies, including the use of small molecule activators and inhibitors.

INTRODUCTION

Malignant cells demonstrate a specialized metabolic phenotype defined by high glucose consumption and the generation of lactate, regardless of oxygen availability. This metabolic shift, known as the Warburg effect, is a primary hallmark of cancer. Pyruvate kinase M2 (PKM2) is a critical enzyme in this transition. PKM2 is an isoform of pyruvate kinase found mostly in embryonic and neoplastic tissues. Its complex regulation and diverse functions facilitate cancer progression, positioning it as an ideal target for clinical intervention.

Glycolysis converts glucose into pyruvate to produce ATP and NADH. In cancer, this pathway is upregulated to support the high energy and biosynthetic needs of rapid cell division. This metabolic reprogramming is influenced by environmental conditions as well as genetic and epigenetic alterations. PKM2 catalyzes the final step of glycolysis, converting phosphoenolpyruvate (PEP) to pyruvate. It is overexpressed across various cancers, where it encourages cell survival, proliferation, and spread.

KEY CONCEPTS AND MECHANISMS

The Warburg Effect Cancer cells often prioritize glycolysis over oxidative phosphorylation (OXPHOS) for energy. This shift provides:

- Accelerated production of ATP.
- Substrates for the biosynthesis of macromolecules, including lipids, amino acids, and nucleotides.
- Maintenance of redox balance through the production of NADPH.

PKM2 Isoforms PKM2 is one of four pyruvate kinase variants (PKM1, PKM2, PKR, and PKL). Its characteristics include:

- Primary expression in cancer and embryonic cells.
- Lower enzymatic activity compared to PKM1 due to its dimeric configuration.
- Allosteric sensitivity to metabolites such as fructose-1,6-bisphosphate.

The Role of PKM2 in Malignancy

PKM2 supports tumor progression through several pathways:

- Driving glycolysis and the accumulation of biomass.
- Acting as a co-activator for gene transcription, specifically affecting β-catenin and HIF-1α.
- Influencing cell signaling via NF-κB and STAT3.
- Promoting metastasis and angiogenesis while inhibiting programmed cell death (apoptosis).

THERAPEUTIC INTERVENTIONS

Targeting PKM2 has become a primary focus for cancer therapy:

- **Inhibitors:** Small molecules like TEA-1 and shikonin reduce cancer cell proliferation by inhibiting PKM2.
- **Activators**: Compounds such as D-allose, DTT, and MEF-2 can activate PKM2 to promote oxidative phosphorylation, thereby reducing tumor growth and inducing apoptosis.
- **Degradation:** Proteasome inhibitors like bortezomib can target PKM2 for degradation to achieve anti-cancer effects.
- **Combination Therapy:** Efficacy is often improved when PKM2 targeting is paired with immunotherapy or standard chemotherapy.

SYSTEMIC IMPACT: CANCER CACHEXIA

Cancer cachexia is a complex syndrome marked by severe weight loss and metabolic dysfunction.

- **Etiology:** Driven by tumor-secreted factors, pro-inflammatory cytokines, and host-derived hormonal changes.
- **Symptoms:** Characterized by muscle wasting, fatigue, anorexia, and nausea.
- **Management:** Requires a multimodal approach including nutritional support, exercise, and pharmacological aids like Anamorelin (a ghrelin receptor agonist) or Megestrol acetate.

CONCLUSION

PKM2 is a pivotal regulator of the metabolic shifts necessary for tumor growth. While targeting this enzyme is promising, challenges regarding potency and specificity remain. Early intervention and a comprehensive management strategy—addressing both the metabolic drivers like PKM2 and systemic issues like cachexia—are essential for improving patient prognosis.

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