CDKN1A

CDKN1A, also known as cyclin-dependent kinase inhibitor 1A or p21, is a protein involved in cell cycle regulation and inhibition of cell proliferation. It plays a crucial role in maintaining the stability of the cell cycle and preventing uncontrolled cell division. Here are some key features and functions of CDKN1A:

Inhibition of Cell Cycle Progression: CDKN1A functions as a cell cycle inhibitor, primarily by inhibiting the activity of cyclin-dependent kinases (CDKs). CDKs are enzymes that regulate the progression of the cell cycle. CDKN1A inhibits the action of CDKs, leading to cell cycle arrest.

Tumor Suppressor: CDKN1A is classified as a tumor suppressor gene because it helps prevent the uncontrolled growth and division of cells. When functioning correctly, CDKN1A helps maintain genomic stability and prevents the formation of tumors.

Response to DNA Damage: CDKN1A can be activated in response to DNA damage caused by various factors, such as radiation, chemicals, or cellular stress. When DNA damage is detected, CDKN1A is upregulated, leading to cell cycle arrest. This pause in the cell cycle allows the cell to repair DNA damage before continuing to divide, reducing the risk of mutations.

Transcriptional Regulation: The expression of CDKN1A is tightly regulated at the transcriptional level. It can be induced by various transcription factors, including p53. Activation of p53, often in response to DNA damage, leads to the upregulation of CDKN1A, contributing to cell cycle arrest.

Senescence: CDKN1A is also involved in cellular senescence, which is a state of irreversible growth arrest that cells enter into in response to stress or damage. Senescent cells can no longer divide and are associated with aging and age-related diseases.

Anti-Apoptotic Role: In addition to its role in cell cycle regulation, CDKN1A can have an anti-apoptotic (anti-cell death) effect under certain conditions. It can inhibit apoptosis by preventing the activation of pro-apoptotic factors.

Clinical Significance: Mutations or dysregulation of CDKN1A can have implications for cancer development and other diseases. Loss of CDKN1A function may lead to uncontrolled cell division and an increased risk of cancer.

Therapeutic Target: Understanding the role of CDKN1A in cell cycle regulation and cancer has led to investigations into its potential as a therapeutic target. Researchers are exploring ways to manipulate CDKN1A to induce cell cycle arrest in cancer cells as a treatment strategy.

In summary, CDKN1A is a critical protein involved in regulating the cell cycle, responding to DNA damage, and preventing uncontrolled cell proliferation. Its role as a tumor suppressor and its involvement in DNA repair processes make it an important focus of research in the fields of cancer biology and cell biology.

CDKN1A in glioblastoma

Its role in glioblastoma is complex and multifaceted:

Tumor Suppressor Function: CDKN1A is considered a tumor suppressor because it inhibits cell cycle progression by blocking the activity of cyclin-dependent kinases (CDKs). In glioblastoma, the loss or reduced expression of CDKN1A can lead to uncontrolled cell division, contributing to tumor growth and progression.

p53 Pathway Regulation: CDKN1A is a downstream target of the tumor suppressor protein p53. In response to DNA damage or cellular stress, p53 activates CDKN1A expression, leading to cell cycle arrest and DNA repair. Glioblastoma often exhibits mutations or dysregulation of p53, which can affect the induction of CDKN1A and promote uncontrolled cell proliferation.

Chemotherapy Resistance: Glioblastoma is notoriously resistant to chemotherapy, and CDKN1A has been implicated in this resistance. Some studies have suggested that overexpression of CDKN1A may contribute to resistance to certain chemotherapeutic agents used in glioblastoma treatment.

Radiation Sensitivity: Radiation therapy is a standard treatment for glioblastoma. CDKN1A has been studied in the context of radiation sensitivity, and its expression levels can affect the response of glioblastoma cells to radiation therapy. Higher CDKN1A expression may be associated with increased sensitivity to radiation-induced cell death.

Prognostic Marker: CDKN1A expression levels have been investigated as potential prognostic markers in glioblastoma. Some studies have suggested that low CDKN1A expression may be associated with poorer patient outcomes, including shorter overall survival.

Therapeutic Target: Because of its role in regulating cell proliferation and the cell cycle, CDKN1A has been explored as a potential therapeutic target in glioblastoma treatment. Researchers are investigating ways to manipulate CDKN1A expression or function to inhibit glioblastoma cell growth and enhance the effectiveness of other treatments.

It's important to note that the role of CDKN1A in glioblastoma is complex, and its impact on tumor development and treatment response may vary depending on the specific genetic and molecular characteristics of individual tumors. Research into the molecular mechanisms of glioblastoma and the role of CDKN1A continues to provide insights into potential therapeutic strategies for this challenging and aggressive cancer.

In a retrospective study, the objective was to identify polymorphic variants of CDKN1A, specifically c.93C > A (codon 31 Ser31Arg), and investigate its potential impact within the scope of bevacizumab therapy for glioblastoma. This study involved a cohort of 139 unrelated adult Chinese GBM patients in Taiwan. Genomic DNA extracted from tumor samples was utilized for genotyping using the polymerase chain reaction (PCR) restriction fragment length polymorphism method (PCR-RFLP analysis). Through unconditional logistic regression analysis, odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Our findings unveiled that among these GBM patients, the distribution of codon 31 polymorphisms was as follows: 23.02% were Serine homozygotes (Ser/Ser), 27.34% were Arginine homozygotes (Arg/Arg), and 49.64% were Serine/Arginine heterozygotes (Ser/Arg). While CDKN1A c.93C > A polymorphisms did not exhibit a direct association with overall survival in GBM patients, noteworthy survival benefits emerged among individuals with Arg/Arg and Arg/Ser genotypes who received combined concurrent chemoradiotherapy (CCRT) and bevacizumab treatment compared to those who underwent CCRT alone. Our findings indicate a significant involvement of the CDKN1A c.93C > A polymorphism in the development and onset of GBM, offering potential implications for the early prognostication of bevacizumab therapy outcomes [1)].

CUL4B has been shown to be upregulated and promotes progression and chemoresistance in several cancer types. However, its regulatory effect and mechanisms on TMZ resistance have not been elucidated. The aim of this study was to decipher the role and mechanism of CUL4B in TMZ resistance. Western blot and public datasets analysis showed that CUL4B was upregulated in glioma specimens. CUL4B elevation positively correlated with advanced pathological stage, tumor recurrence, malignant molecular subtype and poor survival in glioma patients receiving TMZ treatment. CUL4B expression was correlated with TMZ resistance in Glioblastoma cell lines. Knocking down CUL4B restored TMZ sensitivity, while upregulation of CUL4B promoted TMZ resistance in Glioblastoma cells. By employing senescence β-galactosidase staining, quantitative reverse transcription PCR and Chromatin immunoprecipitation experiments, we found that CUL4B coordinated histone deacetylase (HDAC) to co-occupy the CDKN1A promoter and epigenetically silenced CDKN1A transcription, leading to attenuation of TMZ-induced senescence and rendering the Glioblastoma cells TMZ resistance. Collectively, our findings identify a novel mechanism by which Glioblastoma cells develop resistance to TMZ and suggest that CUL4B inhibition may be beneficial for overcoming resistance [2].

1)
Cheng WY, Shen CC, Liang YJ, Chiao MT, Yang YC, Hsieh WY, Lin CH, Chen JP. Polymorphism at codon 31 of CDKN1A (p21) as a predictive factor for bevacizumab therapy in glioblastoma multiforme. BMC Cancer. 2023 Sep 20;23(1):886. doi: 10.1186/s12885-023-11400-5. PMID: 37730565.
2)
Ye X, Liu X, Gao M, Gong L, Tian F, Shen Y, Hu H, Sun G, Zou Y, Gong Y. CUL4B Promotes Temozolomide Resistance in Gliomas by Epigenetically Repressing CDNK1A Transcription. Front Oncol. 2021 Apr 2;11:638802. doi: 10.3389/fonc.2021.638802. PMID: 33869025; PMCID: PMC8050354.