CDC42

CDC42 is a small GTPase protein that belongs to the Rho family of GTPases. It is involved in regulating a wide range of cellular processes, such as cell polarity, cytoskeletal organization, cell cycle progression, and cell migration.

CDC42 is activated by GTP binding and inactivated by GTP hydrolysis, and its activity is regulated by guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors (GDIs).

CDC42 plays a critical role in the establishment and maintenance of cell polarity by regulating the organization of the actin cytoskeleton and the localization of signaling molecules to specific regions of the cell. It also plays a role in the regulation of cell migration by controlling the formation of filopodia and lamellipodia, which are involved in cell protrusion and adhesion to the extracellular matrix.

Dysregulation of CDC42 function has been implicated in several human diseases, including cancer, neuronal disorders, and cardiovascular disease. For example, aberrant CDC42 activity has been linked to the development and progression of breast cancer, while mutations in genes that regulate CDC42 signaling have been associated with neurodevelopmental disorders such as X-linked intellectual disability.

Due to its critical role in cellular physiology and disease, CDC42 is an important subject of research in the fields of cell biology, biochemistry, and pharmacology.

Diffuse invasion is an important factor leading to treatment resistance and a poor prognosis in gliomas. Zhang et al. found that expression of the tripartite motif containing 56 (TRIM56), a RING-finger domain containing E3 ubiquitin ligase, was markedly higher in glioma than in normal brain tissue, and was significantly correlated with malignant phenotypes and a poor prognosis. In vitro and in vivo experimental studies revealed that TRIM56 promoted the migration and invasion of glioma cells. Mechanistically, TRIM56 was transcriptionally regulated by SP1 and promoted the K48-K63-linked poly-ubiquitination transition of IQGAP1 at Lys-1230 by interacting with it, which in turn promoted CDC42 activation. This mechanism was confirmed to mediate glioma migration and invasion.

The study provides insights into the mechanisms through which TRIM56 promotes glioma motility, i.e., by regulating IQGAP1 ubiquitination to promote CDC42 activation, which might be clinically targeted for the treatment of glioma [1].

Zhang et al crucially identified that KIF4A drives glioma growth by Rac1/Cdc42 transcriptional repressors to induce cytoskeletal remodeling in glioma cells. Knockdown of KIF4A decreased RohA, Rac1, Cdc42, Pak1 and Pak2 expression level. The study provided a prospect that KIF4A functions as an oncogene in glioma [2].

How pericytes contribute to brain tumor infiltration is not known. In a study Caspani et al. investigated

the underlying mechanism by which the most lethal brain cancer, Glioblastoma Multiforme (GBM) interacts with pre-existing blood vessels (co-option) to promote tumor initiation and tumor progression.

Using mouse xenografts and laminin-coated silicone substrates, they showed that GBM malignancy proceeds via specific and previously unknown interactions of tumor cells with brain pericytes. Two-photon and confocal live imaging revealed that GBM cells employ novel, Cdc42-dependent and actin-based cytoplasmic extensions, that we call flectopodia, to modify the normal contractile activity of pericytes. This results in the co-option of modified pre-existing blood vessels that support the expansion of the tumor margin. Furthermore, this data provide evidence for GBM cell/pericyte fusion-hybrids, some of which are located on abnormally constricted vessels ahead of the tumor and linked to tumor-promoting hypoxia. Remarkably, inhibiting Cdc42 function impairs vessel co-option and converts pericytes to a phagocytic/macrophage-like phenotype, thus favoring an innate immune response against the tumor.

The work, therefore, identifies for the first time a key GBM contact-dependent interaction that switches pericyte function from tumor suppressor to tumor promoter, indicating that GBM may harbor the seeds of its own destruction. These data support the development of therapeutic strategies directed against co-option (preventing incorporation and modification of pre-existing blood vessels), possibly in combination with anti-angiogenesis (blocking new vessel formation), which could lead to improved vascular targeting not only in Glioblastoma but also for other cancers [3].

1)
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