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Perspective

Regulation of Translation and Transcription in Cell Signalling By Mitogen-Activated Protein Kinases

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DESCRIPTION

The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a protein chain in the cell that transmits a signal from a cell's surface receptor to the cell's DNA in the nucleus. The signal begins when a signalling molecule attaches to a cell surface receptor and ends when the nucleus' DNA expresses a protein and causes a cell change, such as cell division.

Many proteins, such as Mitogen-Activated Protein Kinases (MAPKs), formerly known as Extracellular Signal-Regulated Kinases (ERKs), communicate by phosphorylating (adding phosphate groups to) an adjacent protein, functioning as a voluntary state. When one of the pathway's proteins is altered, it can become stuck in the voluntary state, which is a critical step in the progression of many malignancies. In fact, cancer cells were the first to identify components of the MAPK/ERK pathway, and medications that reverse the "on" or "off" switch are being researched as cancer treatments. The binding of extracellular mitogen to a cell surface receptor initiates the MAPK/ERK pathway. This permits a Ras protein (a Small GTPase) to switch a GDP molecule for a GTP molecule, thereby turning the pathway on and off.

RAS can then stimulate MAP3K (eg: Raf), which in turn activates MAP2K, which in turn activates MAPK. Finally, MAPK can cause a transcription factor like Myc to become active. By altering the ERK pathway, the 22q11, 1q42, and 19p13 genes are linked to schizophrenia, schizoaffective disorder, bipolar disorder, and migraines.

Mitogen signaling's function in cell cycle progression

In many mammalian cell types, the ERK pathway plays a key role in integrating external signals from mitogens like Epidermal Growth Factor (EGF) into signaling events that promote cell growth and proliferation. In a simplified model, mitogens and growth factors activate canonical receptor tyrosine kinases like EGFR, resulting in their dimerization and subsequent activation of the small GTPase Ras. This results in a series of phosphorylation events downstream in the MAPK cascade (Raf-MEK-ERK), eventually phosphorylating and activating ERK.

When ERK is phosphorylated, its kinase activity is activated, and several of its downstream targets involved in cell proliferation regulation are phosphorylated. For most cells to activate genes that increase cell cycle entry and repress negative regulators of the cell cycle, continuous ERK activation is necessary. Cyclin D complexes with Cdk4 and Cdk6 (Cdk4/6) are two such key targets that are both phosphorylated by ERK. The activity of Cyclin D-Cdk4/6, which increases during late G1 phase as cells prepare to enter S-phase in response to mitogens, coordinates the transition from G1 to S phase.

Cdk4/6 activation causes retinoblastoma protein hyperphosphorylation and subsequent instability (Rb). In early G1, hypophosphorylated Rb binds to transcription factor E2F and suppresses its transcriptional activity, blocking the production of S-phase entry genes such as Cyclin E, Cyclin A2, and Emi1. In most mammalian cells, ERK1/2 activation downstream of mitogen-induced Ras signalling is both necessary and sufficient to break the cell cycle barrier and allow cells to advance to S-phase.

CONCLUSION

In eukaryotes ranging from yeast to humans, mitogen-activated protein kinase (MAPK) modules containing three sequentially active protein kinases are critical components of a variety of vital signal transduction pathways that regulate activities like cell proliferation, differentiation, and cell death.

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