MAP Kinase Cascade

MAPK families play an important role in complex cellular programs like proliferation, differentiation, development, transformation, and apoptosis. Mitogen-activated protein kinases (MAPKs) are serine and threonine protein kinases that are highly conserved in eukaryotes, and are involved in signal transduction pathways that modulate physiological and pathophysiological cell responses. Uncontrolled growth is a necessary step for the development of all cancers. In many cancers (e.g. melanoma), a defect in the MAP/ERK pathway leads to that uncontrolled growth. Many compounds can inhibit steps in the MAP/ERK pathway, and therefore are potential drugs for treating cancer, e.g., Hodgkin disease.

The MAP Kinase Cascade depends upon the following factors:

1)**RECEPTORS**

MAP Kinase cascade is mainly based on the tyrosine kinase(these are enzyme linked receptor) receptor linked with kinase activity so that the receptor can phosphorylate other proteins inside the cell which can initiate a cascade of cell signalling.

If it is the Fibroblast Growth Factor Receptor, then it will be named as FGFR. .

If it is the Epidermal Growth Factor Receptor, then it will be named as EGFR.

2) SIGNALLING MOLECULE OR LIGAND

The signalling molecule or the ligand binds with the receptor to initiate the cascade of reactions. In MAPK pathway, the signalling molecules are the growth factors like –

Epidermal Growth Factor (EGF)

Platelet- Derived Growth Factor (PDGF)

Vesicular Endothelial Growth Factor (VEGF)

3) TRANSCRIPTION FACTORS

Myc (a family of regulator genes and proto-oncogenes that code for transcription factors), Elk (a transcription factor that regulates immediate early gene (IEG) expression via the serum response element (SRE) DNA consensus site), Ets (family of transcription factors, includes nuclear phosphoproteins that are involved in cell proliferation, differentiation and oncogenic transformation), gets activated and gets inside the nucleus to start the transcription of the desired gene. The proteins from the desired genes are involved in cyclin synthesis, cell growth, cell division, e.t.c. All these are involved in cell growth and cell living. Upregulated MAPK activity will result in transfer of normal cell to cancerous cell. If Ras protein is mutated, so that it always remains activated, may result in cancer.

4) THE CELLULAR ACTIVATOR

Ras activator

Receptor-linked tyrosine kinases such as the epidermal growth factor receptor (EGFR) are activated by extracellular ligands, such as epidermal growth

factor (EGF). Binding of EGF to the EGFR activates the tyrosine kinase activity of the cytoplasmic domain of the receptor. The EGFR becomes phosphorylated on tyrosine residues. Docking proteins such as GRB2 contain an SH2 domain(these are protein modules of approximately 100 amino acids, found in many proteins involved in tyrosine kinase signalling cascades. Their function is to bind tyrosine-phosphorylated sequences in specific protein targets) that binds to the phosphotyrosine residues of the activated receptor. GRB2 binds to the guanine nucleotide exchange factor SOS(In cell signalling, *Son of Sevenless* (*SOS*) refers to a set of genes encoding guanine nucleotide exchange factors that act on the Ras subfamily of small GTPases) by way of the two SH3 domains of GRB2. When the GRB2-SOS complex docks to phosphorylated EGFR, SOS becomes activated. Activated SOS then promotes the removal of GDP from a member of the Ras subfamily (most notably H-Ras or K-Ras). Ras can then bind GTP and become active.

Apart from EGFR, other cell surface receptors that can activate this pathway via GRB2 include Fibroblast growth factor receptor (FGFR) and PDGFR.

After Ras gets activated, it activates Raf, which is also known as MAP Kinase Kinase Kinase. Raf then activates MEK also known as MAP Kinase Kinase. MEK ultimately activates the final regulatory protein ERK (Extracellular Signal Regulated Kinase) also known as MAP Kinase. Activated ERK regulates growth factor-responsive targets in the cytosol and also translocates to the nucleus where it phosphorylates a number of transcription factors regulating gene expression.

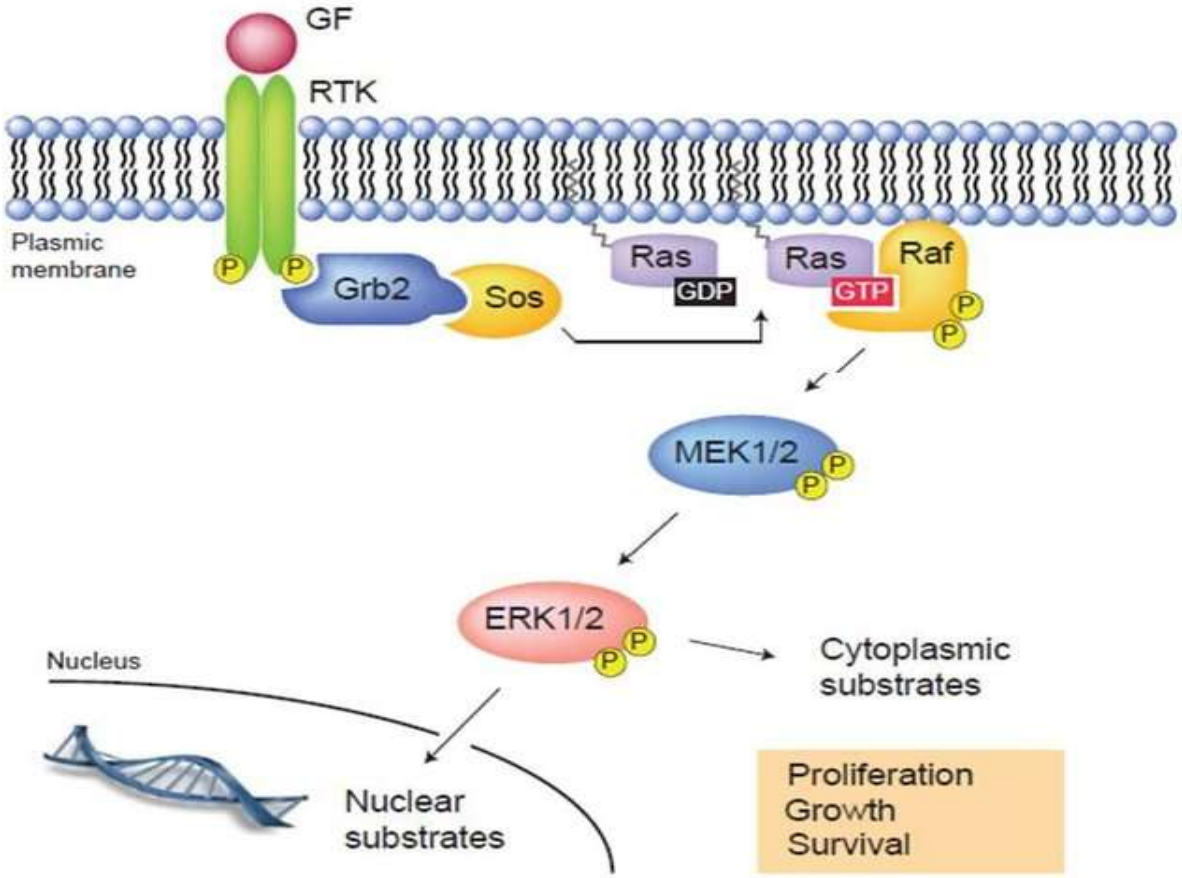

FIG: MAP Kinase Cascade