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Physiological Role of Proteins as Receptors in Cell Signaling and Signal Transduction Pathways

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ABSTRACT

Receptors play an important key role in cell signaling as they are able to detect chemical signals or physical stimuli. Receptors are generally proteins located on the cell surface or within the interior of the cell such as the cytoplasm, organelles, and nucleus. Cell surface receptors usually bind with extracellular signals or ligands, which causes a conformational change in the receptor that leads it to initiate enzymic activity. Cells have proteins called receptors that bind to signaling molecules and initiate a physiological response. Different receptors are specific for different molecules. Dopamine receptors bind dopamine, insulin receptors bind insulin, and nerve growth factor receptors bind nerve growth factor. In fact, there are hundreds of receptor types found in cells, and varying cell types have different populations of receptors. Receptors can also respond directly to light or pressure, which makes cells sensitive to events in the atmosphere. Activation of receptors can trigger the synthesis of small molecules called second messengers, which initiate and coordinate intracellular signaling pathways. For example, cyclic AMP (cAMP) is a common second messenger involved in signal transduction cascades. In fact, it was the first-second messenger ever discovered. The cAMP is synthesized from ATP by the enzyme adenylyl cyclase, which resides in the cell membrane. The activation of adenylyl cyclase can result in the manufacture of hundreds or even thousands of cAMP molecules. These cAMP molecules activate the enzyme protein kinase A (PKA), which then phosphorylates multiple protein substrates by attaching phosphate groups to them. Each step in the cascade further amplifies the initial signal, and the phosphorylation reactions mediate both short and long-term responses in the cell. Examples of second messengers include diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3), which are both produced by the enzyme phospholipase and a membrane protein.

I.INTRODUCTION

The cell signaling or cell communication is the ability of a cell to receive, process, and transmit signals with its environment. Cell signaling is a fundamental property of all cellular life in prokaryotes and eukaryotes. Signals that originate from outside a cell (extracellular signals) can be physical agents like mechanical pressure, voltage, temperature, light, or chemical signals (e.g., small molecules, peptides, or gas). Cell signaling can occur over short or long distances, and as a result can be classified as autocrine, juxtacrine, intracrine, paracrine, or endocrine. Signaling molecules can be synthesized from various biosynthetic pathways and released through passive or active transports, or from cell damage [1-2].

Signal transduction begins with the transformation of a signal into a chemical one, which can directly activate an ion channel or initiate a second messenger system cascade that propagates the signal through the cell. The downstream effects of these signaling pathways may include additional enzymatic activities such as proteolytic cleavage, phosphorylation, methylation and ubiquitinylation.

Each cell is programmed to respond to specific extracellular signal molecules[5], and is the basis of development, tissue repair, immunity and homeostasis. Errors in signaling interactions may cause diseases such as cancer, autoimmunity and diabetes.

Receptors play a key role in cell signaling as they are able to detect chemical signals or physical stimuli. Receptors are generally proteins located on the cell surface or within the interior of the cell such as the cytoplasm, organelles, and nucleus. Cell surface receptors usually bind with extracellular signals or ligands, which causes a conformational change in the receptor that leads it to initiate enzymic activity, or to open or close ion channel activity[3].

II.RECEPTORS ROLE IN CELL SIGNALING

Cells have proteins called receptors that bind to signaling molecules and initiate a physiological response. Different receptors are specific for different molecules. Dopamine receptors bind dopamine, insulin receptors bind insulin, and nerve growth factor receptors bind nerve growth factor, and so on. In fact, there are hundreds of receptor types found in cells, and varying cell types have different populations of receptors. Receptors can also respond directly to light or pressure, which makes cells sensitive to events in the atmosphere.

Receptors are generally transmembrane proteins, which bind to signaling molecules outside the cell and subsequently transmit the signal through a sequence of molecular switches to internal signaling pathways. Membrane receptors fall into three major classes: G-protein-coupled receptors, ion channel receptors, and enzyme-linked receptors. These receptor classes refer to the mechanism by which the receptors transform external signals into internal ones via protein action, ion channel opening, or enzyme activation, respectively, because membrane receptors interact with both extracellular signals and molecules within the cell. They permit signaling molecules to affect cell function without actually entering the cell. This is important because most signaling molecules are either too big or too charged to cross a cell's plasma membrane.

1. **Cell response to signals:**

- Once a receptor protein receives a signal, it undergoes a conformational change, which in turn launches a series of biochemical reactions within the cell. These intracellular signaling pathways, also called signal transduction cascades, typically amplify the message, producing multiple intracellular signals for every one receptor that is bound.

- Activation of receptors can trigger the synthesis of small molecules called second messengers, which initiate and coordinate intracellular signaling pathways. For example, cyclic AMP (cAMP) is a common second messenger involved in signal transduction cascades. (In fact, it was the first second messenger ever discovered.)

- The cAMP is synthesized from ATP by the enzyme adenylyl cyclase, which resides in the cell membrane. The activation of adenylyl cyclase can result in the manufacture of hundreds or even thousands of cAMP molecules. These cAMP molecules activate the enzyme protein kinase A (PKA), which then phosphorylates multiple protein substrates by attaching phosphate groups to them. Each step in the cascade further amplifies the initial signal, and the phosphorylation reactions mediate both short and long-term responses in the cell.

- Other examples of second messengers include diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3), which are both produced by the enzyme phospholipase, also a membrane protein. IP3 causes the release of Ca^{2+} yet another second messenger from intracellular stores. Together, DAG and Ca^{2+} activate another enzyme called protein kinase C (PKC).[4-5]

2. Process of Signals Affect Cell Function:

Protein kinases such as PKA (protein kinase A) and PKC (protein kinase C) catalyze the transfer of phosphate groups from ATP molecules to protein molecules. Within proteins, the amino acids serine, threonine, and tyrosine are especially common sites for phosphorylation. These phosphorylation reactions control the activity of many enzymes involved in intracellular signaling pathways. Specifically, the addition of phosphate groups causes a conformational change in the enzymes, which can either activate or inhibit the enzyme activity. When appropriate, protein phosphatases remove the phosphate groups from the enzymes, thereby reversing the effect on enzymatic activity.

Phosphorylation allows for intricate control of protein function. Phosphate groups can be added to multiple sites in a single protein, and a single protein may in turn be the substrate for multiple kinases and phosphatases. At any one time, a cell is receiving and responding to numerous signals, and multiple signal transduction pathways are operating in its cytoplasm. Many points of intersection exist among these pathways. For instance, a single second messenger or protein kinase might play a role in more than one pathway. Through this network of signaling pathways, the cell is constantly integrating all the information it receives from its external environment.

III.SIGNAL TRANSDUCTION PATHWAYS

1.MAPK (MITOGEN ACTIVATED PROTEIN KINASE)/ERK(EXTRA CELLULAR SIGNAL REGULATED KINASE)PATHWAY

The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, such as mitogen-activated protein kinases (MAPKs), originally called extracellular signal-regulated kinases (ERKs), which communicate by adding phosphate groups to a neighboring protein (phosphorylating it), thereby acting as an "on" or "off" switch.

When one of the proteins in the pathway is mutated, it can become stuck in the "on" or "off" position, a necessary step in the development of many cancers. In fact, components of the

MAPK/ERK pathway were first discovered in cancer cells, and drugs that reverse the "on" or "off" switch are being investigated as cancer treatments[6-7].

a. Ras activation

Receptor-linked tyrosine kinases, such as the epidermal growth factor receptor (EGFR), are activated by extracellular ligands, such as the 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 that binds to the phosphotyrosine residues of the activated receptor. GRB2 binds to the guanine nucleotide exchange factor SOS 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). The Ras protein can then bind GTP and become active. Apart from EGFR, other cell surface receptors that can activate this pathway via GRB2 include Trk A/B, Fibroblast growth factor receptor (FGFR) and PDGFR.

b.Regulation of translation and transcription

Three of the many proteins that are phosphorylated by MAPK are shown in the figure to the right. One effect of MAPK activation is to alter the translation of mRNA to proteins. MAPK phosphorylates the 40S ribosomal protein S6 kinase (RSK). This activates RSK, which, in turn, phosphorylates ribosomal protein S6.[5] Mitogen-activated protein kinases that phosphorylate ribosomal protein S6 were the first to be isolated.

MAPK regulates the activities of several transcription factors. MAPK can phosphorylate C-myc. MAPK phosphorylates and activates MNK, which, in turn, phosphorylates CREB. MAPK also regulates the transcription of the C-Fos gene. By altering the levels and activities of transcription factors, MAPK leads to altered transcription of genes that are important for the cell cycle. The 22q11, 1q42, and 19p13 genes, by affecting the ERK pathway, are associated with schizophrenia, schizoaffective disorder, bipolar disorder, and migraines.

c.Regulation of cell cycle entry and proliferation

Role of mitogen signaling in cell cycle progression:

The ERK pathway plays an important role of integrating external signals from the presence of mitogens such as epidermal growth factor (EGF) into signaling events promoting cell growth and proliferation in many mammalian cell types. In a simplified model, the presence of mitogens and growth factors trigger the activation of canonical receptor tyrosine kinases such as EGFR leading to their dimerization and subsequent activation of the small GTPase Ras. This can lead to a series of phosphorylation events downstream in the MAPK cascade (Raf-MEK-ERK) ultimately resulting in the phosphorylation and activation of ERK[7-8].

The phosphorylation of ERK results in an activation of its kinase activity and leads to phosphorylation of its many downstream targets involved in regulation of cell proliferation. In most cells, some form of sustained ERK activity is required for cells to activate genes that induce cell cycle entry and suppress negative regulators of the cell cycle. Two such important targets include Cyclin D complexes with Cdk4 and Cdk6 (Cdk4/6) which are both phosphorylated by ERK. The transition from G1 to S phase is coordinated by the activity of Cyclin D-Cdk4/6, which increases during late G1 phase as cells prepare to enter S-phase in response to mitogens.

Cdk4/6 activation contributes to hyper-phosphorylation and the subsequent destabilization of retinoblastoma protein (Rb). Hypo-phosphorylated Rb, is normally bound to transcription factor E2F in early G1 and inhibits its transcriptional activity, preventing expression of S-phase entry genes including Cyclin E, Cyclin A2 and Emi1. ERK1/2 activation downstream of mitogen induced Ras signaling is necessary and sufficient to remove this cell cycle block and allow cells to progress to S-phase in most mammalian cells[9].

2. Ras SIGNALING PATHWAY

Ras, short for rat sarcoma, belongs to the monomer GTP binding protein with weak GTPase activity. Normally, Ras distributes on the cytoplasmic side of the plasma membrane and is inactive through the binding with GDP. In the Ras signaling pathway, activated Ras further stimulates the phosphorylation of its substrate proteins, mediating many signaling pathways involved in various significant cellular processes. The Ras signaling pathway is involved in many important cellular processes such as cell proliferation and survival, differentiation, apoptosis, cytoskeletal movement, protein transport and secretion.

Generally, Ras combines with GDP and is in an inactive state. When Ras protein is released from Ras/GDP and binds to GTP, Ras is activated. Guanylate exchange factors (GEFs) (e.g. Sos, means the mammalian orthologues of Sos, SOS1 and SOS2, function downstream of many growth factor and adhesion receptors) are stimuli for the activation of Ras. GAP (GTPase activating proteins) catalyzing the hydrolysis of GTP to GDP in Ras/GTP, deactivating Ras.GEFs promote the release of GDP from Ras/GDP. Sos cannot bind directly to the receptor due to the lack of the SH2 domain (SH2 domains represent the major class of protein domains in metazoans that interact with proteins phosphorylated on the amino acid residue tyrosine).

The adaptor protein Grb2 binds to the phosphotyrosine residue of the receptor via SH2 and then binds to Sos through SH3. Sos subsequently contacts Ras on the membrane to activate Ras. Or Ras is activated through the activation of RPTK by growth factors such as EGF, PDGF, and FGF. Active Ras binds and activates Raf. Activated Raf phosphorylates and activates MEK1/2. MEK 1/2 phosphorylates ERK1/2 to activate it. Activation of ERK1/2 into the nucleus activates the expression of many downstream genes such as Elk-1, elf-4E to promote cell proliferation and differentiation. In addition; activated Ras can directly bind and activate PI3K. Activation of PI3K converts PIP2 into PIP3. The second messenger PIP3 further stimulates PDK, which subsequently activates Akt, starting the PI3K-AKt signaling pathway that regulates cell proliferation.

Ral GDS (Ral guanine nucleotide dissociation stimulator is a protein that is encoded by the RALGDS gene in humans) stimulates GDP to dissociate from the Ras-related RalA and RalB GTPases, which allows GTP binding and activation of the GTPases. RalBP can inhibit RacGTP and Cdc42 enzymes, and then regulate actin cytoskeleton remodeling and activate transcription factor NF-κβ through Rac/Cdc42. The process promotes the production of anti-apoptotic proteins to inhibit apoptosis[10-11].

Diseases and Ras Signaling Pathway

The most common Ras gene mutation in tumors is the substitution of the 12th and 13th glycine or the 61st glutamine by other amino acid residues. AP (GTPase accelerating proteins) is unable to hydrolyze GTP in mutant RAS. Without the help of GAP, the hydrolysis of GTP will be completely dependent on the GTPase of RAS itself, so the hydrolysis will last longer. This means that Ras/GTP cannot become Ras/GDP and is in a GTP-bound state for a long time, which causes excessive activation of the Ras-Raf-MEK-ERK pathway, resulting in excessive cell proliferation and tumorigenesis.

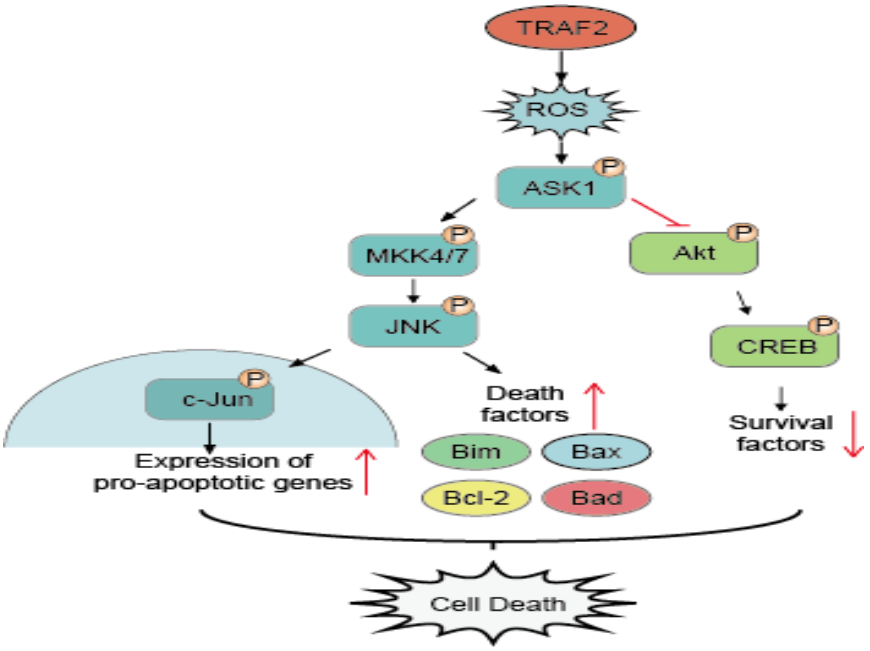
3. JNK SIGNALING PATHWAY

The c-Jun N-terminal kinase (JNK) pathway is one of the majors signaling cassettes of the mitogen-activated protein kinase (MAPK) signaling pathway. It functions in the control of a number of cellular processes, including proliferation, embryonic development and apoptosis. The pathway takes its name from the c-Jun N-terminal kinases 1–3 (JNK1–JNK3), which are the MAPKs that interact with the final effectors. The JNK pathway is activated by a number of mechanisms typical to understand. This complexity is evident by the fact that there are 13 MAPK kinase kinases (MAPKKKs) responsible for signaling the information into the JNK pathway. The JNK pathway can also be activated through G protein-coupled receptors (GPCRs) using G proteins such as G12/13.

JNK pathway contributes to the control of a large number of cellular processes:

- Phosphorylation of the transcription factor p53

- The JNK pathway has been implicated in the mitogen activated protein kinase (MAPK) signaling in cardiac hypertrophy.



(Fig:1) Downstream signaling of JNK pathway.

JNK can promote apoptosis by two distinct mechanisms. In the first mechanism targeted at the nuclear events, activated JNK translocate to the nucleus and transactivates c-Jun and other target

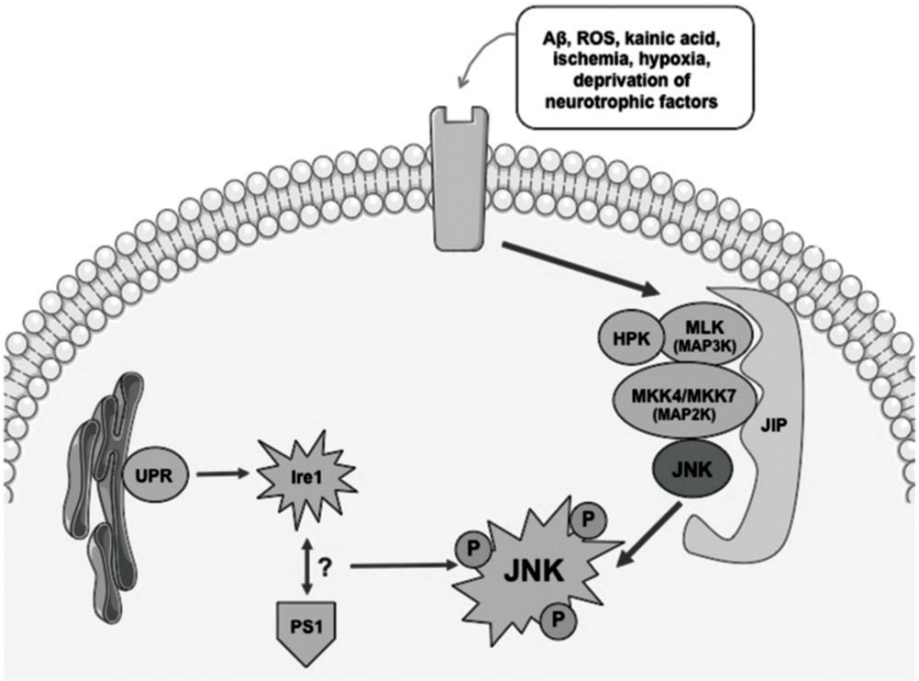
transcription factors (TF). JNK can promote apoptosis by increasing the expression of pro-apoptotic genes through the transactivation of c-Jun/AP1-dependent or p53/73 protein-dependent mechanisms. In pathways directed at mitochondrial apoptotic proteins, activated JNK translocate to mitochondria[13].

There, JNK can phosphorylate the BH3 only family of Bcl2 proteins to antagonize the anti apoptotic activity of Bcl2 or Bcl-XL. In addition, JNK can stimulate the release of cytochrome c (Cyt C) from the mitochondrial inner membrane through a Bid-Bax-dependent mechanism, promoting the formation of apoptosomes consisting of cytochrome c, caspase-9 and Apaf-1. This complex initiates the activation of caspase-9-dependent caspase cascade.

In another mechanism, JNK can promote the release of Smac/Diablo (Smac) that can inhibit the TRAF2/IAP1 inhibitory complex, thereby relieving the inhibition on caspase-8 to initiate caspase activation. In addition, by phosphorylating BAD and its sequestering partner 14-3-3, JNK can promote BAD-mediated neutralization of the Bcl2 family of anti-apoptotic proteins. Finally, JNK can phosphorylate Bcl2 for suppressing its anti-apoptotic activity.

JNK/SAPKs are clearly involved in ischemia-induced cell death and reperfusion injury in several different tissues and the control of insulin sensitivity in metabolic regulation. There are many other suggestions in the literature that link JNK/SAPK signaling to additional human diseases such as type I diabetes, osteosarcoma, ataxia and immune system dysfunction. JNKs probably play a role in chronic inflammation, airway hyper responsiveness and protease-directed tissue remodeling. It is likely that selective JNK1, JNK2 and JNK3 inhibitors will be needed for specificity and lack of toxicity. It may also be useful to develop specific MKKK inhibitors to selectively block JNK activation in response to different upstream inputs.

Activation of the JNK pathway relies on the coordinated interaction of the scaffold proteins belonging to the JNK activation complex. These proteins are able to mediate the biochemical signal amplification and also to ensure substrate-specificity as well as a coordinated cascade signaling. The interaction between scaffold proteins leads to the activation of JNK by bi phosphorylating different substrates enables the activation of different functions.



(Fig:2) Mechanisms involved in activation of the JNK pathway.

Different stress conditions might activate JNK signaling via scaffold proteins. UPR (unfolded protein response) and an interaction between IRE1 (inositol requiring 1; ERN1, endoplasmic reticulum-to-nucleus signaling 1) and PS1 have also been described as potential activators of JNK. ROS, radical oxygen species; Aβ, β amyloid; JIP, JNK interacting protein; UPR, unfolded protein response; Ire, endoplasmic reticulum to nucleus signaling 1.

Different stimuli that have been described as able to trigger the signaling response to JNK include nerve growth factor (NGF) deprivation, trophic support withdrawal, DNA damage, oxidative stress, amyloidal (Aβ) exposure, low potassium, excitotoxic stress, UV irradiation, tumor necrosis factor (TNF).

Many are the scaffold proteins that have been described as the signaling proteins that converge in the activation of JNK: JIP1a (JNK interacting protein 1a) and JIP1b (also named IB1), JIP2 and JIP3 (also named JSAP1) JNK-interacting leucine zipper protein (JLP) and plenty of SH3. JIPs belong to second-order-activating proteins that are dependent on previous interaction with MAPK activating kinases (MAPKKs) and MAPKK activating kinases. This type of coordination is called the "signalosome" that leads to the activation of JNK is complex and requires interaction of first messengers at different cellular levels for further activation of the scaffold-protein-complex and finally activating JNK. Endoplasmic reticulum's (ER) stress phenomena that induce the unfolded protein response (UPR) signaling are also involved in the control of activation of JNK pathway

(Figure 1). As a result of anomalous protein burden, an interaction between Ire1 and Presenilin 1 (PS1) has been proposed to enable the activation of JNK thus leading to proapoptotic signaling activation. Direct modulation of JNK-activation by the cdk5/p35 complex has also been described, although the underlying mechanisms that lead to this molecular phenomenon are still unclear.

The main cellular substrate activated by JNK mediated phosphorylation is c-Jun (Figure 2), which in turn is able to interact with JunB, JunD, c-Fos, and ATF constituting the AP-1 transcription factor and regulating maturation of the cellular stress response or modulating the signals that lead finally to activation of caspases. Moreover, JNK is able to phosphorylate and activate directly apoptosis-related proteins such as BIM (homologous to BAX) and BMF, both proapoptotic proteins resulting in activation of caspases. JNK also phosphorylates DP5-HRK, Bcl-2, and Bcl-xL, which are anti-apoptotic proteins inhibited by phosphorylation by JNK[14-15] (Fig 3).

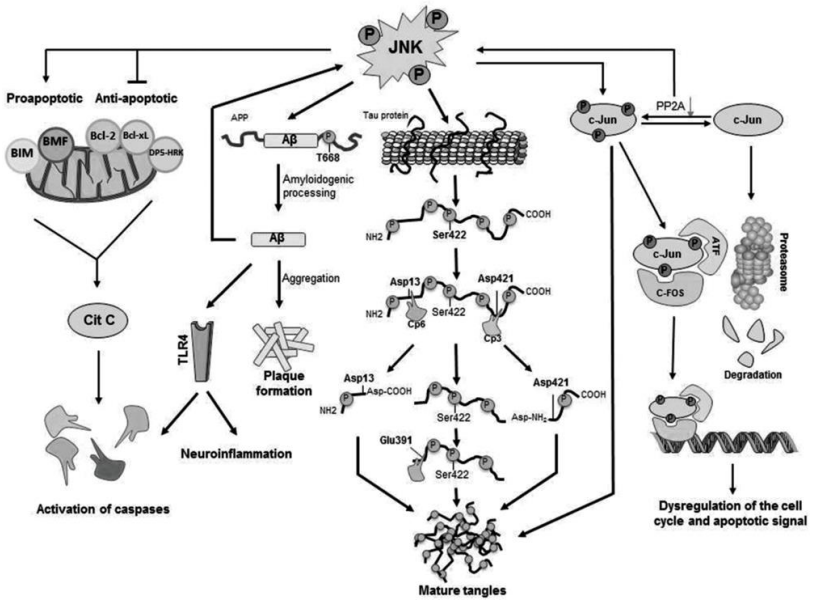


Figure 3

4. Pi3 SIGNALING PATHWAY

The PI3K-PKB/Akt pathway is highly conserved, and its activation is tightly controlled via a multistep process (Fig. 1) Activated receptors directly stimulate class 1A PI3Ks bound via their regulatory subunit or adapter molecules such as the insulin receptor substrate (IRS) proteins. This triggers activation of PI3K and conversion by its catalytic domain of phosphatidylinositol(3,4)-bisphosphate (PIP_2) lipids to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PKB/Akt binds to

PIP_3 at the plasma membrane, allowing PDK1 to access and phosphorylate T308 in the "activation loop," leading to partial PKB/Akt activation.

This PKB/Akt modification is sufficient to activate mTORC1 by directly phosphorylating and inactivating proline-rich Akt substrate of 40 kDa (PRAS40) and tuberous sclerosis protein 2 (TSC2)). mTORC1 substrates include the eukaryotic translation initiation factor 4E binding protein 1 (4EBP1), and ribosomal protein S6 kinase, 70 kDa, polypeptide 1 (S6K1), which, in turn, phosphorylates the ribosomal protein S6 (S6/RPS6), promoting protein synthesis and cellular proliferation[16-17].

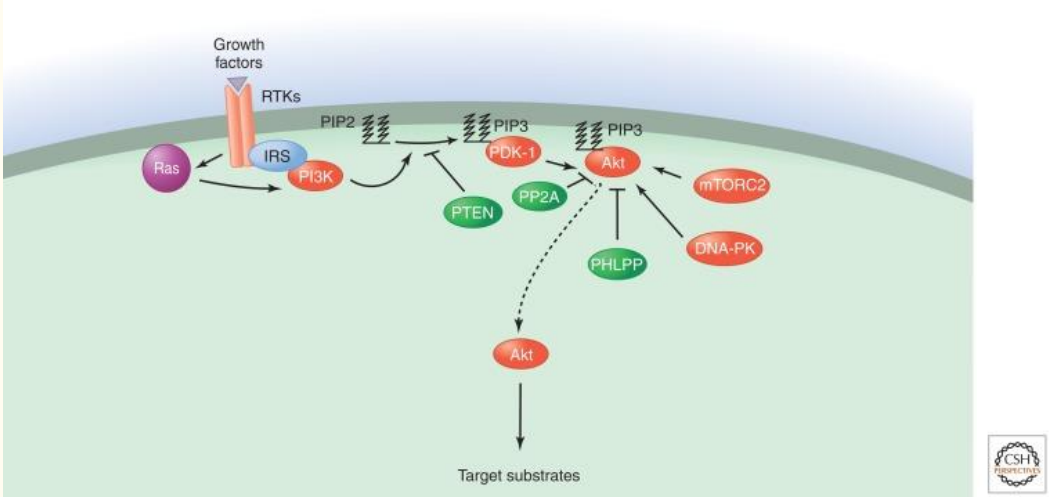


Figure 4.

PKB/Akt activation downstream of RTKs via the P13K pathway:

Phosphorylation of Akt at S473 in the carboxy-terminal hydrophobic motif, either by mTOR or by DNA-PK, stimulates full Akt activity. Full activation of Akt leads to additional substrate-specific phosphorylation events in both the cytoplasm and nucleus, including inhibitory phosphorylation of the pro-apoptotic FOXO proteins (Guertin et al. 2006). Fully active PKB/Akt mediates numerous cellular functions including angiogenesis, metabolism, growth, proliferation, survival, protein synthesis, transcription, and apoptosis (as shown in fig 5). Dephosphorylation of T308 by PP2A (Andjelković et al. 1996), and S473 by PHLPP1/2 and the conversion of PIP_3 to PIP_2 by PTEN (Stambolic et al. 1998) antagonize Akt signaling [18-20].

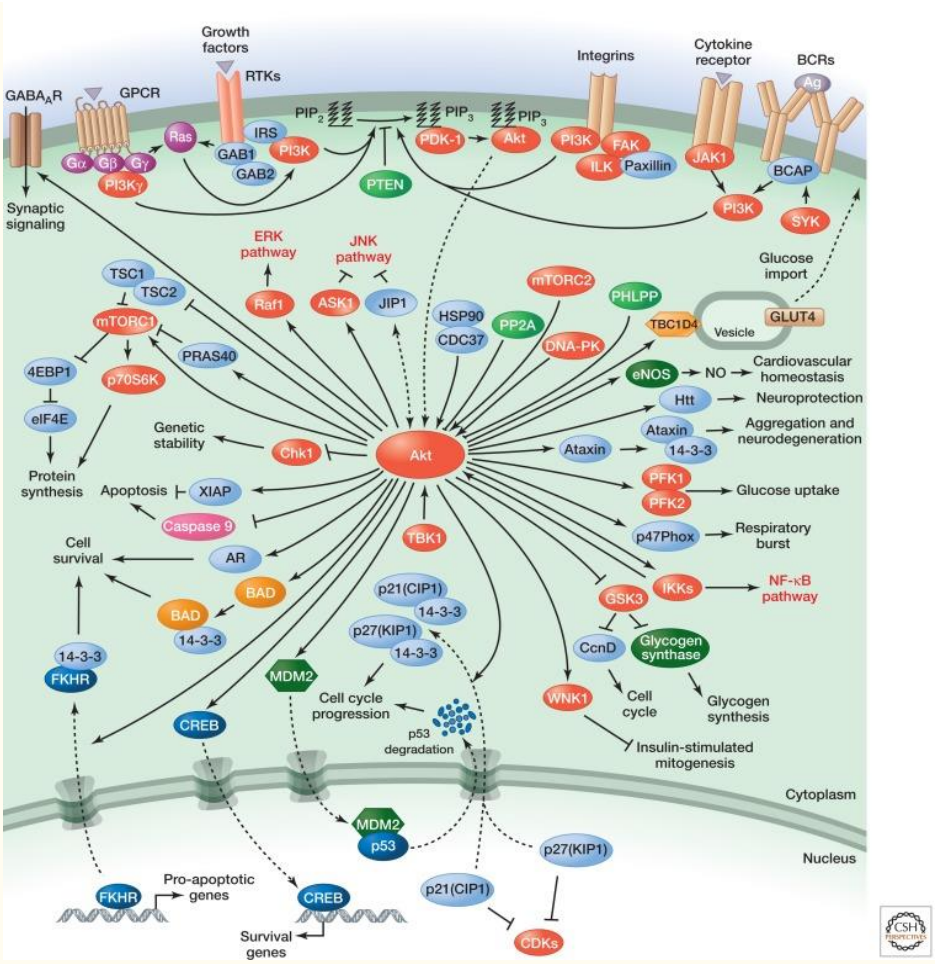


Fig 5

5. P38 Mitogen-Activated Protein Kinases (MAPK)

p38 mitogen-activated protein kinases are a class of mitogen-activated protein kinases (MAPKs) that are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation, apoptosis(Apoptosis is a form of programmed cell death that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes and death. These changes include blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, DNA fragmentation, and mRNA decay. The average adult human loses between 50 and 70 billion cells each day due to apoptosis. For an average human child between eight and fourteen years old, approximately twenty to thirty billion cells die per day and autophagy. Persistent activation of the p38 MAPK pathway in muscle satellite cells (muscle stem cells) due to ageing, impairs muscle regeneration.

p38 MAP Kinase (MAPK), also called RK or CSBP (Cytokinin Specific Binding Protein), is the mammalian orthologue of the yeast Hog1p MAP kinase, which participates in a signaling cascade controlling cellular responses to cytokines and stress. Four p38 MAP kinases, p38-α (MAPK14), -β (MAPK11), -γ (MAPK12 / ERK6), and -δ (MAPK13 / SAPK4), have been identified. Similar to the SAPK/JNK pathway, p38 MAP kinase is activated by a variety of cellular stresses including osmotic shock, inflammatory cytokines, lipopolysaccharides (LPS), ultraviolet light, and growth factors.

MKK3 and SEK activate p38 MAP kinase by phosphorylation at Thr-180 and Tyr-182. Activated p38 MAP kinase has been shown to phosphorylate and activate MAPKAP kinase 2 and to phosphorylate the transcription factors ATF2, Mac, MEF2, and p53. p38 also has been shown to phosphorylate post-transcriptional regulating factors like TTP, and in fruit flies it plays a role in regulating the circadian clock.

Clinical significance:

Oxidative stress is the most powerfully specific stress activating p38 MAPK. Abnormal activity (higher or lower than physiological) of p38 has been implicated in pathological stresses in several tissues, that include neuronal, bone, lung, cardiac and skeletal muscle, red blood cells, and fetal tissues. The protein product of proto-oncogene RAS can increase activity of p38, and thereby cause excessively high activity of transcription factor NF-κB. This transcription factor is normally regulated from intracellular pathways that integrate signals from the surrounding tissue and the immune system. In turn these signals coordinate between cell survival and cell death. Dysregulated NF-κB activity can activate genes that cause cancer cell survival, and can also activate genes that facilitate cancer cell metastasis to other tissues.

IV.CONCLUSION

Cells typically receive signals in chemical form via various signaling molecules. When a signaling molecule joins with an appropriate receptor on a cell surface, this binding triggers a chain of events that not only carries the signal to the cell interior, but amplifies it as well. Cells can also send signaling molecules to other cells. Some of these chemical signals such as neurotransmitters travel only a short distance, but others must go much farther to reach their targets.

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