ORIGINAL RESEARCH PAPER

Oncology

KEY WORDS: cell signaling , Targeted therapies

# THE CELL SIGNALING AND ITS CRUCIAL ROLE IN ANTITUMOR TARGETED THERAPY

**Baig MQ** Associate Professor And Head Department Of Radiation Oncology, BRD Medical College Gorakhpur.

**Khan Mamun*** Assistant Professor Radiation Oncology Department Brd Medical College Gorakhpur. *Corresponding Author

**Wahikar Shilpa** Associate Professor Department Of Pathology BRD Medical College Gorakhpur

ABSTRACT

The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy in modern oncology treatment, the protein kinases are responsible for cellular transduction cell signaling and their hyper activity malfunction or over expression can be found in various types of malignancies .

Cells sense signals from extracellular and intracellular environment as well as directly from other cells and cells respond to these signals in a variety of ways like primarily modifying protein levels and its activities and location. Protein levels are controlled by rates of transcription, translation and proteolysis.

The signal transduction pathways regulate the differentiation, division and death in the mature and developing cells. Some pathways are common for all cells but some pathways are specific to specialized cells, for example synthesis and secretion of insulin by pancreas and migration and phagocytosis by neutrophils and likewise, abnormal behavior of altered cancer cells starts uncontrolled division & invasion & metastasis.

**Two common problem faced by a cell in signal transduction –**

A) How is the signal sensed?
B) How are the level of activities and levels of protein modified in response to signals?

Most signals are initiated by Ligands and are sensed by receptor to which they bind, binding of ligand to a receptor stimulates the activation of proteins necessary to continue the transmission of signal through the formation of multiprotein complexes and generation of small molecules that ares known as second messengers.

**SENSORY MACHINARY : LIGANDS AND RECEPTORS –**

**A) SIGNALS-** For signal transduction molecules that initiate signaling cascade include proteins, nucleotides, lipids, amino acids, gas and light.

Most extracellular signals which are protein like growth factors bind to receptors present on plasma membrane of cells but other molecules especially those that are steroid directly diffuse inside the cells and bind to receptor in the cytoplasm and finally reach to act at nucleus level.

Signaling molecules originate from variety of sources-some are stored in the cells and released to provide communication with other cells under specific conditions, other legends are stored outside the cells like in extracellular matrix become accessible in response to the tissue damage or remodeling of cells also respond to signals that arise from within, for example check point pathway is that ensure progression of cell cycle is a organized form of cell cycle which also sense DNA damage and do necessary repair before next mitosis happens.

**B) RECEPTORS-** Plasma membrane of cells serve to insulate the cells from the outside environment, but this barrier must be breached to transmit the signals of extracellular origin by crossing the plasma membrane either by activation of transmembrane receptorss or by using ligands that are membrane permeable.

Amplification of most signals is necessary for cellular response, receptor binds and responds to more than one ligand for example; epidermal growth factor receptor binds to transforming growth factor α (TGF), heparin binding factor (HB- EGF) β celluline extra the activation of receptor leads to stimulation of several downstream pathway that stimulate different targets.

Receptor also activate other receptor like activation of EGF receptor by G protein coupled receptors (GPCR) which occur is a result of protease cleavage and activation HB – EGF ( heparin binding – epidermal growth factor)

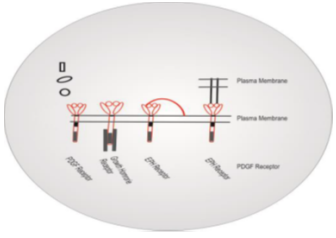


**FIG 1 – RECEPTOR KINASE ACTIVATION LEADS TUMOR PROGRESS**

**RECEPTOR - TYROSINE KINASE –**

Receptor tyrosine kinase are trans membrane proteins that have an extra cellular ligand binding domain , a trans membrane domain and cytoplasmic tyrosine kinase domain. The ligands for these receptors are proteins or peptides. Activation of receptor tyrosine kinase generally requires tyrosine phosphorylation of the receptor.


**FIG 2- MODULATION OF PROTEIN ACTIVITY BY PHOSPHATE**

Receptors that activate tyrosine kinase-a number of receptors do have intrinsic enzymatic activity which stimulate associated tyrosine kinase, example of this type of receptors include the cytokine and interferon receptor that are associated continuously with member of the jak family of tyrosine kinase.

**SERINE – THREONINE KINASE RECEPTORS -**

The TGF- β family of receptors are basically transmembranal protein with intrinsic serine and threonine kinase activity.

**RECEPTORS PHOSPHOTYROSINE PHOSPHATASE –**
(RPTPS) receptor protein tyrosine phosphatase have an extra cellular domain,a signal trans membrane spanning domain and cytoplasmic catalytic domain, the extracellular domains of some receptor tyrosine phosphatase contain fibronectin and immunoglobulin receptors.

**G- PROTEIN – COUPLED RECEPTOR-**
GPCRS are by far the most numerous receptors. Almost 700 GPCRS are present in human genome. Wide variety of ligands bind with GPCRS including proteins and peptides, lipids, aminoacids and nucleotides.

**TUMOR NECROSIS RECEPTOR FAMILY-**
TNF family of receptor is has concerned Cystine rich region in the extracellular domain a trans membrane domain and a domain called " DEATH DOMAIN' in the cytoplasmic tail.

TNF receptor undergo oligomerization after ligand binding which is necessary for signaling stimulation of receptor leads to recruitment or cytoplasmic protein that bind to each other and the receptor through

" **Death domains** "there by activating a protein CAPASE-8 that initiates apoptosis, under the some conduction however TNF Rs stimulate anti apoptosis signals.

**NUCLEAR RECEPTORS –**
Ligands for nuclear receptors diffuse into the cell, bind their receptors present either in cytoplasm or in the nucleus , the ligands indulge steroids and radios, the ligands nether in cytoplasm or the nucleolus, the ligand include steroids and retinoids and thyroid hormone directly goes up to nucleolus hit DNA and its action starts.

**PROPAGATION OF SIGNALS TO THE CELL INTERIOR –**
Although mechanism of various receptors and ligands that initiate cell signaling are very different most receptors activate a set of common downstream molecule to transmit their signals, the molecules that transmit signals are, proteins lipid kinase / GTPase/ phospholipase/ protease / Adenylatecyclase , these molecules produce array of response including changes in transcription / translation / enzymatic activities and cell motility.

**REGLUATION OF PROTEIN KNASE -=**
The balance between protein kinase & phosphatase activities control protein phosphorylation, protein kinase themself, transcription factors, and cytoskeletal components are few example of proteins regulated by phosphorylation .

Most signal transduction pathways require protein tyrosine kinase, receptor that are not themselves tyrosine kinase, usually several cytoplasmic tyrosine kinase, inducing Src/ syk/ jak family. phosphorylation of protein and tyrosine can either stimulate or inhibit enzymatic activity.

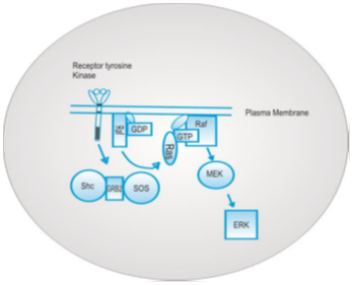


**FIG-3 TYROSIN KINASE RECEPTOR DIMERIZATION**

**REGULATION OF PHOSPHATASE –**

Protein phosphatase remove the phosphate residue from proteins which can either activate or inhabit signaling pathways.

**GUANOSINE TRIPHSPHATE- BINDING PROTEIN –**
Protein protein instruction is also important mechanism of signal transduction, G protein which binds GTP are the best studied protein, mediators that regulate other proteins by direct binding result in a conformal changes, GTP binding protein act as a digital switches GTP binding result in a conformational changes that allows G protein to bind to effector molecule and transmit signals. GTP hydrolyse to GDP ultimately returns the protein to its active conformation , Adenylate cyclase causing rotation of CIa domain which positions the catalytic residue more favorably for conversion of ATP to cAMP.

**SMALMOLICULE THE SECOND MFSSENGERS –**
Small molecules transmit signals by binding noncovalently to protein targets and affecting their functions. Theses molecules called as second massager such as growth factor binding to a cell surface receptor.

CAMP use the first second manager discover adenylate cyclase activated by G proteins Catalyzes the synthesis of CAMP protein from ATP , the primary target of CAMP is protein kinase A is a telomere of two catalytic and two regularity subunits is the regulatory subunit inhibit the activates of the catalytic subunit Ip3 and binds to a calcium channel in the endoplasmic reticulum and stimulates the release of calcium from intracellular stores. The initial increase of calcium in cytoplasm is followed by an influx of extracellular calcium via capitative calcium channel at the plasma membrane in unstimulated cells cytosolic calcium is much lower than intracellular space therefore opening channels in ER (Enndoplasmic reticulum) or plasma membranes allows calcium to flood into cytoplasm, temporary raising the cytoplasm calcium level and ultimately returns to normal basic level as a result pumping action for calcium into intracellular comportments.

Calcium inside the cytosol having several effects like, directly regulating enzymatic activities, Ion channels and transcription activities.

**FORMATION OF MULTIPROTIEN SIGNALING COMPLEXS –**
The ability of signal transduction pathway to transmit signal is dependent on the probability that protein finds its target.

Recruiting a protein to a specific component of the cell markedly increase the local concentration of that protein, thereby enhancing the probability that it will interact with other protein or small molecule that are recruited to generate in the same compartment of the cell. Colonization of protein in a signaling pathway is achieved by recruitment to the same membrane surface or organelle (example plasma membrane or endoplasmic reticulum ER) by protein interaction, separating protein or second messenger are both into distinct compartment turn off signaling pathways, transport of singling proteins into nucleus is important in number of signal transduction pathways, nuclear transport proceeds through nuclear pores, proteins of less than 40 KD cross by simple diffusion into nucleus but transport of larger proteins molecules require a nuclear colonization signal to which the (importin protein bind) the importin target the protein to the nuclear pore the complex is transported into nucleus the Ran G protein dissociates the nuclear localizations of transcription factors, nuclear factors of activated T cells is NFAT which require is for it transcriptional activities response to T Cell activation and rise in intracellular calcium, NFAT is dephosphyralated calcium responsive phosphatase are

**CALCINEURIN** .

**DOMAINS THAT REGULATE PROTIEN BINDING –**
The regulated assembly of protein protein complexes has several functions in signal transduction including formations of complexes allowing protein to signal each other's forming a solid state molecule that does not require diffusion to transmit, protein protein interactions also localized an enzyme near its subtract, the binding of PLC $\gamma$ I to PDGF receptor brings the enzyme to plasma membrane where its subtract P tdins 4,5-P2 is concentrated their interactions are often mediated by conserved domain that recognizes the phosphorylated tyrosine or serine residue or protein rich sequences.

**Tyrosine kinase and phosphatase** regulate the formation of complexes involving the domain , tyrosine kinase themselves serve as docking sites for other proteins which is most evident with tyrosine kinase receptors next recruit PI.3 – kinase.

## REFERENCES


1- Perkins, N. D. Oncogenes, tumor suppressors and p52 NF-κB. Oncogene 22, 7553–7556 (2003).
2-. Lin, L., DeMartino, G. N. & Greene, W. C. Cotranslational biogenesis of NF-κB p50 by the 26S proteasome. Cell 92, 819–828 (1998).
3-. Cohen, S., Achbert-Weiner, H. & Ciechanover, A. Dual effects of IκB kinase β-mediated phosphorylation on p105 fate: SCF(β-TrCP)-dependent degradation and SCF(β-TrCP)-independent processing. Mol. Cell. Biol. 24, 475–486 (2004).
4- Druker Brian J., et al. "Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia." The New England Journal of Medicine 344, no. 14 (2001): 1031–1037.
5- Goldman, John M., and Junia V. Melo. "Targeting the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia." The New England Journal of Medicine 344, no. 14 (2001): 1084–1086.
6-. Nowell, P., J. Rowley, and A. Knudson. "Cancer Genetics, Cytogenetics—Defining the Enemy Within." Nature Medicine 4 (October 1998): 1107–1114.
7-. Gerondakis, S., Grossmann, M., Nakamura, Y., Pohl, T. & Grumont, R. Genetic approaches in mice to understand Rel/NF-κB and IκB function: transgenics and knockouts. Oncogene 18, 6888–6895 (1999).
8-. Pasparakis, M., Luedde, T. & Schmidt-Supprian, M. Dissection of the NF-κB signalling cascade in transgenic and knockout mice. Cell Death Differ. 13, 861–872 (2006). Genetic experiments in mice provide much of the basis for our understanding of the NF-9-κB and IKK pathway. Reference 3 summarizes fundamental information about different NF-κB-, IκB- and IKK-knockout mouse phenotypes. Reference 4 describes how these mice have been used to study the role of the NF-κB and IKK pathway in physiological processes and human diseases. These reviews are both essential reading.
10-. Pahl, H. L. Activators and target genes of Rel/NF-κB transcription factors. Oncogene 18, 6853–6866 (1999).
11-. Perkins, N. D. & Gilmore, T. D. Good cop, bad cop: the different faces of