

THE INFLUENCE OF PROTO-ONCOGENES ON TYPICAL PATTERNS OF GROWTH & DEVELOPMENT

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ABSTRACT

Proto-oncogenes, also known as cellular oncogenes, plays a vital role in regulating normal cell growth. Their malfunction can lead to cancer, highlighting their significance. Most oncogenes encode intracellular proteins involved in signal transduction pathways and belong to closely related gene families. Families like *erbB*, *ros*, and *fms* encode membrane receptors with tyrosine kinase activity. *Src* family oncogenes, also tyrosine kinases, act as kinase subunits for independent receptors. Intracellular signaling occurs through phosphorylation of substrates such as phosphatidylinositol pathway kinases and cytoplasmic kinases. *Ras* oncogenes, conserved GTP-binding proteins, modulate signaling from membrane kinases. Oncogenes coding for nuclear DNA-binding proteins, phosphorylated by kinases like *raf*, regulate gene expression through dimerization. DNA-binding proteins, such as helix-loop-helix proteins (*myc*, *MyoD*, *myogenin*) and leucine zipper proteins (*fos*, *jun*), influence cell growth. Antioncogenes, like *Rb* and *p53*, counteract growth by inhibiting it.

Keywords: *GTP-binding proteins, Helix-loop-helix proteins, Intracellular signaling, leucine zipper proteins, Tyrosine kinase*

activity

INTRODUCTION

Oncogenes code for proteins that play a vital role in cell growth regulation and are involved in the onset of cancer. Proto-oncogenes, or cellular oncogenes, ensure proper regulation of cell division and differentiation during normal growth. Alterations like mutations, translocations, or viral effects can lead to their dysfunction, resulting in abnormal cell growth—a hallmark of cancer.

HISTORICAL CONTEXT OF THE RETROVIRUS GENE

Retroviruses, which have RNA instead of DNA as their genetic material, were pivotal in the discovery of oncogenes. Upon infection, retroviruses replicate by converting their RNA into viral DNA (V-DNA) using a reverse transcription process. This V-DNA, flanked by long terminal repeats (LTRs), integrates randomly into the host genome as a “provirus.” The host then transcribes the viral DNA, producing viral RNA and proteins as though they were part of its genome. Occasionally, viral RNA may incorporate host DNA sequences, producing hybrid RNA and fusion proteins. This phenomenon, known as transduction, allows retroviruses to acquire and transmit host genetic material, some of which may have oncogenic potential. The discovery of cellular homologs to viral oncogenes revealed that normal regulatory genes, when disrupted, could drive cancer, thus offering a strategy to study cellular proliferation and differentiation.

TERMINOLOGY

Proto-oncogenes, also known as normal cellular oncogenes, are denoted as c-“onc.” However, transforming oncogenes are not labeled as c-“onc,” even if they originate from mutations, deletions, or other changes in cellular genes. When the function of a gene product is unknown, nomenclature often reflects the source (e.g., c- for cellular, v- for viral) and the viral homolog’s identity (e.g., v-src from the Rous sarcoma virus). Typically, the gene is better understood than the protein product, as researchers often focus on oncogene sequence homology to uncover regulatory mechanisms.

Proteins encoded by oncogenes are named after the oncogene or their molecular weight (e.g., Myc protein or pp60c-src). Similar names, like ras and ros, do not imply related genes.

CELLULAR CONTROL & THE PROCESS OF SIGNAL TRANSDUCTION

Cellular oncogenes typically encode proteins involved in intracellular signal transduction. These oncogene products facilitate the reception of extracellular signals, transmission across the cytoplasm, and modulation of gene expression in the nucleus to elicit a cellular response. While the understanding of these regulatory pathways is growing, significant uncertainties remain.

Oncogene families represent distinct components of signal transduction pathways, enabling tissue-specific responses to stimuli through differential gene family expression. This discussion explores these families at various signal transduction stages.

Signal transduction, often reliant on phosphorylation cascades, enables external stimuli to cross membranes, reach the nucleus, and influence gene expression. Receptors with tyrosine kinase activity or associated kinases initiate these cascades. Phosphorylated cytoplasmic kinases, including serine kinases, activate DNA-binding proteins.

The phosphatidylinositol (PI) pathway, involving lipid phosphorylation, offers an additional mechanism for membrane kinases to activate cytoplasmic kinases. Adrenergic pathways can regulate kinase activity through protein kinase C or protein kinase A. Similarly, oncogenes resembling G proteins, components of adrenergic pathways, contribute to transduction, albeit differently.

Steroid and thyroid hormones bypass typical pathways, directly entering cells due to their lipophilic nature and binding nuclear receptors that regulate gene expression. Cross-talk between kinase pathways and hormone-receptor interactions influences gene regulation through phosphorylation.

Protein-protein interactions, including transient complexes and dimers, are pivotal in signal transduction. These

interactions ultimately regulate DNA-binding protein activity in the nucleus, facilitating changes in gene expression.

ONCOGENE FAMILIES

TYROSINE KINASE MEMBRANE RECEPTORS

Certain oncogenes encode families of membrane receptors with tyrosine kinase activity that respond to peptide hormones or growth factors. These include receptors similar to the insulin receptor, platelet-derived growth factor (PDGF) receptor, epidermal growth factor (EGF) receptor, and fibroblast growth factor (FGF) receptor. These receptors share structural features, including glycosylated extracellular ligand-binding domains, a membrane-spanning domain, and a cytoplasmic tyrosine kinase domain. Ligand binding induces structural changes that activate tyrosine kinase activity, leading to signal transduction via tyrosine phosphorylation of intracellular substrates. Autophosphorylation of the receptor itself often further modifies receptor function.

The Insulin receptor-like family includes the insulin receptor, insulin-like growth factor (IGF) receptor, and oncogenes such as *ros*, *met*, and *trk*. These receptors consist of four subunits: two extracellular subunits for ligand binding and two transmembrane subunits with tyrosine kinase activity. The extracellular α -subunit has a cysteine-rich ligand-binding region, while the β -subunit's intracellular domain contains the tyrosine kinase and autophosphorylation sites. Autophosphorylation enhances kinase activity, removing insulin dependence, while phosphorylation by protein kinase C on serine and threonine residues reduces insulin binding and tyrosine kinase activity.

Another oncogene family encodes receptors similar to the EGF receptor, such as *neu*, *erbB2*, and *erbB3*. The EGF receptor is composed of a single polypeptide chain with cysteine-rich extracellular ligand-binding domains. Tyrosine phosphorylation of the cytoplasmic domain activates the kinase, similar to autophosphorylation in insulin receptors. Serine and threonine phosphorylation can inhibit EGF receptor kinase activity.

Additional families include PDGF and CSF receptors, as well as receptors for FGF and *flg* oncogenes. These receptors have extracellular domains resembling immunoglobulins, with the PDGF and FGF receptor families featuring interrupted tyrosine kinase domains. The interruptions are variable but do not impact kinase activity directly, though autophosphorylation in these regions may play a role in substrate interaction.

All tyrosine kinase membrane receptors form functional dimers. The insulin receptor exists as $\alpha\beta$ dimers, while EGF receptors form dimers upon ligand binding, facilitating autophosphorylation and receptor activation. Some ligands, like PDGF, form dimers (e.g., PDGF-A and PDGF-B), which bind to specific receptor isoforms with varying affinities. This dimer assembly allows cells to modulate their response to signals efficiently by controlling a few genes.

NON-RECEPTOR TYROSINE KINASES

Non-receptor tyrosine kinases, such as those from the *src* family (*src*, *fgf*, *fin*, *lyn*, *lck*, and *yes*), are membrane-associated proteins that share similarities with receptor tyrosine kinases, although they do not have intrinsic receptor activity. These kinases likely function as kinase subunits for receptors without their own kinase activity.

The *lck* oncogene serves as a representative model for *src* family tyrosine kinases. In T lymphocytes, the CD4 surface protein interacts with MHC II antigens, and when it binds with p56^{lck} (the product of *lck*), the complex activates the kinase activity of p56^{lck}, leading to the phosphorylation of the T cell receptor subunit. This activation only occurs when p56^{lck} is bound to CD4, not when CD4 is uncomplexed.

The *src* family proteins, like pp60^{src} and p56^{lck}, lack a transmembrane domain but are membrane-associated via myristic acid at their amino terminus. They have both serine and tyrosine phosphorylation sites, similar to receptor kinases. Tyrosine phosphorylation at two distinct sites regulates the activity of *src* proteins—one stimulates and the other inhibits kinase activity. These phosphorylation events are mainly intermolecular, involving *src* proteins or other kinases. The inhibition of pp60^{src} and p56^{lck} by tyrosine phosphorylation

near the catalytic domain is not fully understood, but the phosphatase CD45 plays a key role in regulating the activity of these kinases by dephosphorylating specific sites.

Additionally, src proteins undergo serine phosphorylation at various sites, with minimal effect from protein kinase A and protein kinase C. However, cyclin-dependent kinase (p34cdc2) increases pp60src's tyrosine kinase activity through serine phosphorylation during mitosis. This phosphorylation may regulate the interaction between src proteins and receptor subunits.

The src family proteins also contain two regions, SH2 and SH3, which are crucial for their function and share similarities with other oncogene products and regulatory proteins. For example, the abl protein, a tyrosine kinase, contains SH2 and SH3 domains and can localize to the cytoplasm or nuclear membrane. These domains are also present in the regulatory regions of other proteins, such as ras GAP and phospholipase C. In src proteins, the SH2 domain activates kinase activity, while mutations in this region reduce activity. Conversely, mutations in the SH3 domain lead to oncogenic transformation, indicating its role in negatively regulating kinase activity. The presence of SH2 and SH3 domains in various proteins suggests a shared regulatory mechanism, potentially involving interactions between different proteins.

SUBSTRATE OF TYROSINE KINASE

Tyrosine phosphorylation, once considered a rare event, is now understood to occur in various proteins, even though it represents less than 0.1% of total phosphoproteins. While many proteins can be phosphorylated at low levels in vitro under non-physiological conditions, up to 50 proteins are phosphorylated in response to oncogenes that encode for tyrosine kinases. The challenge in identifying key tyrosine kinase substrates arises due to the overwhelming background of serine and threonine phosphorylation (90% and 10%, respectively) and the diversity of phospho-tyrosine proteins. This complexity is further compounded by the fact that proteins like the EGF receptor and erbB2, though structurally similar and both part of the same oncogene family, activate

distinct mitogenic pathways.

Membrane-associated tyrosine kinases phosphorylate several types of proteins. Common mechanisms include autophosphorylation by the kinase itself or intermolecular phosphorylation by another membrane-bound kinase. Membrane-bound proteins and cytoplasmic proteins such as serine kinases and metabolic enzymes may also be regulated by tyrosine phosphorylation. Phosphatases that dephosphorylate serine or tyrosine residues can be phosphorylated to reverse kinase activation. Since both receptor and non-receptor kinases are membrane-associated, membrane proteins are likely candidates for phosphorylation.

Enzymes in the phosphatidylinositol (PI) pathway are also substrates for tyrosine kinases, although the exact effects of their phosphorylation remain unclear. These include PI kinase, which produces phosphatidylinositol phosphate, and phospholipase C, which generates diacylglycerol and inositol triphosphate. Both enzymes are phosphorylated and form complexes with activated membrane receptors, such as the PDGF and EGF receptors. Activation of PI kinase or phospholipase C results in protein kinase C activation, a serine/threonine kinase that might inhibit receptor tyrosine kinase activity.

The protein pp85, a substrate for src or PDGF receptor-mediated tyrosine phosphorylation, has been linked to PI kinase activity in src-transformed cells. This protein exists in various forms in different tissues, and differential phosphorylation may lead to distinct activities. This could explain unexpected findings, such as pp85 generating novel PI phosphates not recognized by phospholipase.

Several cytoplasmic serine/threonine kinases are also phosphorylated by tyrosine kinases, including microtubule-associated protein kinase (MAP kinase) and casein kinase II. MAP kinase, activated by insulin-mediated phosphorylation, may be identical to pp42, a protein responsive to multiple growth factors. Casein kinase II, involved in various cell functions, is activated by insulin, IGF-I, and EGF and plays a role in Alzheimer's disease. It can phosphorylate various

cytoplasmic and nuclear enzymes, including the myc protein and the insulin receptor tyrosine kinase.

The raf protein, a serine kinase encoded by the raf oncogene, is phosphorylated by tyrosine kinases such as PDGF, EGF, or FGF receptors. Raf can form a complex with membrane receptor tyrosine kinases, PI kinase, and phospholipase C. This large complex may function as a multifunctional signal transfer particle, with various members binding at multiple sites, as deletions in the PDGF receptor gene can block PI kinase binding without affecting raf or phospholipase C binding.

NUCLEOTIDE BINDING PROTEINS OF GUANINE

Guanine nucleotide-binding proteins, such as those in the ras family, play a significant role in cellular processes and are associated with the cell membrane. These proteins are not kinases but are involved in the activation of the ras oncogene product through the ras GTPase activating protein (GAP). The ras family includes several genes, such as ha-ras, ki-ras, N-ras, ral, and others, with high homology between them. Although their exact function is still unclear, ras proteins likely participate in cellular signal transduction between membrane-bound oncogenes like src or fms and cytoplasmic kinases like raf, possibly through activation of protein kinase C independently of the PI pathway.

Ras proteins are attached to the cell membrane via a carboxyl terminal palmitic acid, and this attachment site is crucial for their oncogenic activation. For example, exchanging palmitic acid for myristic acid at the amino terminal can activate ras oncogenically. These genes are highly conserved across species, with mammalian and yeast ras genes being functionally interchangeable. Ras overexpression leads to enhanced cell growth and lower serum requirements, resembling the behavior of transformed cells, though without full transformation. Ras overexpression also results in the production of PDGF and TGF- β , while reducing responsiveness to external PDGF. Such abnormalities are often seen in transformed cells, indicating that ras plays a role in transformation processes.

Ras proteins function through guanine nucleotide binding, much like G-proteins in adrenergic signaling. The active form, P21ras, binds GTP, while the inactive form binds GDP. The GTPase activity of P21ras is low but is activated by the GTPase Activating Protein (ras-GAP). Unlike adrenergic G-proteins, which release GDP in response to hormones, p21ras releases GDP with the help of a releasing factor (ras-GRF). The ras activation-deactivation cycle involves GTP, GAP, and GRF proteins. Although GAP is present in higher concentrations than P21ras, the regulatory role of GAP is still not fully understood, and it may be regulated by ras rather than the other way around.

A portion of GAP is phosphorylated, possibly indicating a regulatory function. GAP can be phosphorylated by src or by PDGF or EGF receptors in response to growth factors. Phosphorylated GAP can bind to the PDGF receptor and other proteins like PI kinase, phospholipase C, and raf. However, GAP binding is not essential for the interaction of these proteins, suggesting that GAP may influence their function. Additionally, GAP can form complexes with other tyrosine-phosphorylated proteins, pointing to complex interactions among membrane-bound oncogenes. Another ras family member, rap-1, can block v-ras oncogenic transformation, similar to how inhibitory and stimulatory G-proteins function. Rap protein has its own GTPase activity and is not activated by rap-GTPase activating protein

CYTOPLASMIC KINASES

Cytoplasmic kinases are important in the signal transduction pathway, linking the membrane to the nucleus. Several oncogenes encode cytoplasmic serine kinases, with raf (also known as mil). The mos oncogene, a cytoplasmic kinase, is expressed exclusively in germ cells and plays a role in oocyte meiosis. The abl oncogene, a cytoplasmic tyrosine kinase, may also associate with the nuclear membrane. Raf kinase is activated by PDGF through tyrosine phosphorylation and can also form a complex with the PDGF receptor. Interestingly, raf can also be activated by insulin (within 2 to 6 minutes) through serine phosphorylation, suggesting the involvement of an intermediate kinase like MAP or casein kinase. Although

raf substrates are not well-defined, cytoplasmic kinases may target nuclear oncogenes like *myc*, *fos*, *ski*, and *myb* for serine phosphorylation.

In addition to their role in activating signaling pathways, cytoplasmic kinases may also help deactivate receptors. Many membrane-bound tyrosine kinases interact with the PI pathway, leading to the activation of protein kinase C (PKC). Both PKC and protein kinase A can phosphorylate serine residues on receptors, causing their inactivation. Receptor deactivation can occur through various mechanisms, including decreased ligand binding affinity, inhibition of tyrosine kinase activity, or enhanced internalization of the receptors.

NUCLEAR BINDING PROTEINS

Nuclear binding proteins encoded by oncogenes plays a crucial role in the final stage of signal transduction, as they bind to DNA. These proteins are often serine phosphoproteins, and their phosphorylation carried out by cytoplasmic kinases like raf or nuclear kinases like abl. Oncogenes that produce DNA-binding proteins belong to various families with distinct mechanisms but share some key characteristics. Many of these genes, known as “immediate early genes,” are involved in regulating the expression of other genes. These genes are usually expressed at low levels in resting cells but are rapidly activated by growth factors or other mitotic signals. Their expression does not require protein synthesis, suggesting that the necessary regulatory pathways are already in place, allowing the cell to respond to stimuli and alter gene expression without needing new proteins to be made.

The Induction of these “immediate early genes” can occur within 1 to 2 hours after a stimulus, and their response is brief. The mRNA for these genes has a short half-life, typically around 15 to 30 minutes, with the level of mRNA being regulated by changes in transcription or reduced stability, often due to AT-rich 3' ends. The protein products from these genes also have short half-lives, ranging from 15 to 90 minutes

A useful way to categorize DNA-binding proteins is based on their binding mechanism. These categories include helix-

loop-helix (HLH) proteins, leucine zipper proteins, and zinc finger proteins. A key regulatory feature within these classes is the ability to form homodimers or heterodimers. Heterodimers regulate target gene expression differently from homodimers, and various heterodimers exhibit distinct activities. The formation of symmetrical dimers-almost but not entirely symmetrical in the case of heterodimers-aligns with the frequent presence of palindromic consensus binding sequences for these DNA-binding proteins.

HELIX-LOOP-HELIX PROTEINS

Helix-Loop-Helix (HLH) proteins, such as myc, myf, MyoD, myogenin, CEBP, and E12, belong to a class of oncogenes. These proteins have two regions that form amphipathic helices, separated by a loop. These regions are important for dimer formation, which influences DNA binding specificity, though the regions themselves do not directly bind DNA. The DNA binding region is highly basic and essential for the protein's function, and in some cases, proteins lacking this region are inhibitory. For example, a dimer missing a basic DNA-binding region (like ID:myoD) would not be active because the DNA-binding region would be asymmetrical.

Some HLH proteins, such as MyoD and myogenin, are crucial in muscle development, while others, like CEBP, are expressed in tissues related to lipid or cholesterol metabolism. Myc, one of the most studied HLH proteins, is highly expressed in proliferating cells and overexpression leads to hyperplasia. Although myc expression decreases during differentiation, this decrease is not required for differentiation, as cells can still differentiate with overexpressed myc. The relationship between HLH gene expression and differentiation is complex, likely due to dimer formation. For example, MyoD, although highly expressed in myoblasts, does not initiate muscle protein synthesis until it forms a homodimer. This is facilitated by the ID protein, which lacks the basic DNA binding region and forms a heterodimer with MyoD, allowing for the homodimer to form once ID levels decrease during differentiation. Alternatively, other HLH heterodimers, like MyoD-E12, can enhance DNA binding and promote muscle protein synthesis.

LEUCINE ZIPPER PROTEINS

Leucine zipper proteins, including fos and various jun proteins, are part of a family that forms dimers through interactions in a region with high homology, known as the leucine zipper. This region contains four to five leucine heptad repeats. The DNA binding domain is highly basic, similar to that in HLH proteins. Although these leucine zipper proteins share structural similarities, their effects on DNA binding can vary. They may be expressed in response to signals from protein kinase C or protein kinase A. Expression is also regulated by the proteins themselves, though the nature of this regulation differs. For instance, fos protein inhibits its own expression, while jun protein promotes its own. Both fos and jun are phosphoproteins, but the specific role of phosphorylation in their regulation is not fully understood.

Proteins encoded by the fos and jun oncogenes share significant homology with the AP-1 transcription factor and may bind to AP-1 or related proteins. AP-1 is a key member of a large family of transcription regulators. Fos and jun proteins can activate genes with AP-1 binding sites, and the fos gene regulates its own expression through AP-1 sites. Additionally, fos and jun proteins activate fat-specific element 2 (fse2), which is involved in glycerol phosphate dehydrogenase expression during early adipocyte differentiation. The impact of fos protein binding to AP-1 sites varies depending on the dimer formed. A jun:fos dimer activates transcription at AP-1 sites, while a jun:fos dimer represses it. This illustrates how different heterodimers can have opposing effects, particularly since jun and junB levels can fluctuate significantly. For example, in BC3H1 muscle cells treated with TGF- β , jun protein levels increase 2.5 times within 15 minutes, but junB levels rise about 20-fold, favoring the formation of the repressive junB:fos complex despite an increase in jun protein.

ZINC FINGER PROTEIN: HORMONE RECEPTORS FOR STEROIDS AND THYROID

Steroid and thyroid hormone receptors belong to a group of DNA-binding proteins that form dimers. This family includes receptors like the glucocorticoid, mineralocorticoid,

progesterone, estrogen, androgen, vitamin D3, and thyroid hormone receptors, among others. These proteins have separate regions for DNA binding, hormone binding, and a domain that regulates their activity. Unlike HLH or leucine zipper proteins, the zinc-containing domain in these receptors is responsible for DNA binding, not dimer formation. The binding consensus sequence of these proteins is longer than that of HLH or leucine zipper proteins, and different members of the family have varied effects when binding to this sequence. The v-erb-A oncogene, a fusion protein from a virus, is a well-known example of an oncogenic member of this family, as it shares DNA binding and hormone binding domains with thyroid hormone receptors.

These receptors are regulated by phosphorylation, similar to HLH and leucine zipper proteins. Phosphorylation, potentially mediated by nuclear serine kinases like the abl protein, usually enhances hormone binding and is induced by hormones, though this has not been fully confirmed. Hormone binding also triggers dimer formation, suggesting that phosphorylation and dimerization may be linked. Multiple phosphorylation sites can lead to different receptor forms with varying binding affinities, which may prevent functional dimer formation. The physiological significance of this regulation is clearer for steroid and thyroid hormone receptors, as they are involved in well-understood endocrine pathways. For instance, insulin or EGF can increase estradiol-induced progesterone receptor induction, possibly through phosphorylation of the estrogen receptor. This process typically occurs during the estrous cycle but is inhibited during starvation, when insulin is low, and estrous cycling is inappropriate.

Several oncogenes are involved in the response to steroid or thyroid hormone receptors, explaining the role of steroids in tumor promotion. For example, glucocorticoids affect Ras and abl, while estrogen increases the expression of proteins like fos, myc, H-ras, and erb B. On the other hand, thyroid hormones reduce the levels of fos, myc, and ras in cardiac muscle.

Myb : DNA-BINDING PROTEIN

The myb oncogene product is mainly expressed in hematopoietic cells and functions as a DNA-binding protein, with no evidence of dimer formation. Phosphorylation directly regulates its DNA-binding ability. Specifically, a serine phosphorylation, mediated by casein kinase II, inhibits DNA binding in a reversible manner. Casein kinase II plays critical roles in both the cytoplasm and nucleus and is inhibited by phosphorylation. This suggests that when a growth factor activates a receptor tyrosine kinase, it phosphorylates and inhibits casein kinase II. As a result, reduced casein kinase II activity leads to dephosphorylation of myb protein by nuclear phosphatases, enabling it to bind DNA and promote transcription for protein synthesis from a target gene.

ANTI-ONCOGENES : TUMOUR SUPPRESSING GENES

Tumor suppressor genes, also known as anti-oncogenes, have the opposite function of oncogenes by inhibiting growth rather than promoting it. While oncogenes stimulate cell growth and must be carefully regulated for normal cell function, mutations or deletions in tumor suppressor genes can lead to uncontrolled cell growth, a hallmark of cancer. For instance, the retinoblastoma gene (Rb) and p53 gene both serve to inhibit growth, and mutations or deletions in these genes can result in cancerous transformation. The Rb gene is crucial for preventing growth in certain cancers like retinoblastoma, and p53 is involved in regulating cell cycles, with mutations found in a significant number of colon cancers.

Both Rb and p53 are proteins that bind to DNA and can act as transcriptional inhibitors to suppress growth-related genes. They interact with transforming viral proteins, indicating a shared regulatory mechanism. Rb can be phosphorylated, but only its dephosphorylated form can bind to viral proteins like large T antigen, which prevents cell growth. Phosphorylation of Rb in normal cells removes this inhibition and promotes cell cycle progression, supporting the idea of phosphorylation playing a key role in regulating growth signals, especially as cells transition from the G1 to S phase.

CONCLUSION

The review paper offers a detailed overview of the role oncogenes that plays in cellular regulation and signal transduction. It highlights how oncogenes are involved in essential cellular processes like cell growth and differentiation, and how their malfunction can contribute to cancer. The review also underscores the complexity of oncogene activity, with various oncogene families playing roles at different stages of signal transduction.

The paper discusses several families of oncogenes, such as tyrosine kinase membrane receptors, non-receptor tyrosine kinases, guanine nucleotide-binding proteins, cytoplasmic kinases, and nuclear binding proteins. These families are integral to signal transduction, and their disruption can lead to oncogenic transformation.

A central theme of the paper is the significance of protein-protein interactions in oncogene function. It highlights how processes like dimerization, phosphorylation, and other post-translational modifications regulate oncogene activity. The review also points out the intricate nature of oncogene regulation, with numerous feedback loops and regulatory pathways involved.

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