CHAPTER 34

Cellular Signaling Dynamics: Exploring MAPK, PI3K/AKT, and Wnt Pathways in Molecular Biology

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SUMMARY

Mitogen-activated protein kinase (MAPK) and Phosphatidylinositol-3 kinase/Akt (PI3K/Akt) signaling pathways regulate most cellular processes and play a critical role in metazoan life. During the past two decades, Molecular biologist focused on the crosstalk of different pathways within cells to investigate their individual and synergistic role in regulating diverse cellular functions. The proper functioning of these three pathways requires constitutive and extensive communication between them which leads to desired biological outcomes. The nature of this interaction is overwhelmingly complex and needs extensive research. We describe the recent state of the study of the individual molecular mechanism of Wnt, MAPK and PI3K/Akt and crosstalk between them. The PI3K pathway regulates Wnt and MAPK pathways through various nodal points, however, inhibition of MAPK promotes PI3K and vice versa. This complex cross talk enables cells to process and decode extracellular signals.

INTRODUCTION

Cells as a unit of life tend to communicate with neighboring cells and respond to environmental stresses through an innate communication system also referred to as cell signaling and signal transduction (Logan & Nusse, 2004). This cellular signaling is essential for the maintenance of homeostasis and cellular coordination balance between the cell and its environment. Signaling ligands bind to the surface of receptor proteins which induce conformational changes and start a cascade of reactions within the cellular cytoplasm transducing a specific cellular response (Nair et al., 2019). These signaling pathways do not control the cell system individually but rely on other factors and pathways and work together as a coordinated whole. Any irregulation or disruption in these pathways has been reported to cause serious abnormalities, including cancer, neurodegenerative disorders, and immune pathologies (Logan & Nusse, 2004).

The first discovery of internal secretion by Claude Bernard opened a new era of signaling study in molecular biology, since then there has been substantial progress in the understanding of cellular communication and the role of external factors in cellular interactions due to advancement in cell biology, molecular biology and cell physiology (Nair et al., 2019). These disciplines, coupled with the high throughput techniques including mass spectroscopy and CRISPR-Cas9 allowing us to move beyond mere observations and look deep into the intricate mechanisms of their internal complexities and their interconnected nature. This chapter highlights the nature of the Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), and Wnt pathways and potential crosstalk and their role in human pathologies.

WNT SIGNALING PATHWAY

Introduction to Wnt signaling:

The Wnt signaling pathway is an evolutionarily conserved pathway that is responsible for the regulation of multiple developmental and physiological responses of the body, including cell differentiation, fate determination, and embryonic development (Kikuchi et al., 2011). Its uncontrolled imbalance causes serious anomalies such as colorectal carcinoma (Nusse & Clevers, 2017) and birth abnormalities (Johnson & Rajamannan, 2006). This path is exquisitely stimulated when a signaling molecule (Wnt ligand) binds to the receptor cells of the receiving membrane, this binding triggers signal transduction within the cell that leads to cellular responses such as cell specification (Tepekoy et al., 2015), mitotic activity, or polarity establishment (Grainger & Willert 2018) Fig 1. Even after three decades of rigorous research on this fundamental pathway our knowledge of its molecular components and their interaction with other pathways is elusive. This pathway controls cell behavior in two main ways as well-known established Wnt/β-catenin pathway and the diverse non-canonical Wnt signaling pathway (Tepekoy et al., 2015).

How to Cite: Fatima T, U Aamir, A Fatima & E Riaz, 2024. Cellular signaling dynamics: Exploring MAPK, PI3K/AKT, and Wnt pathways in molecular biology. In: Zoology: Advancements and Research Trends (Ijaz MU, N Ehsan, M Imran & S Yousaf, eds): FahumSci, Lahore, Pakistan, pp: 267-277. ISBN: 978-627-7745-02-8. https://doi.org/10.61748/Zool.2024/34

Key components of the Wnt pathway

Both Wnt pathways (β-catenin-dependent and independent) have three basic key components that relay signal information from cell membrane to the nucleus. Wnt ligands are signaling proteins that attaches to membrane protein called Frizzled receptors and coactivator that initiate cascade of events activating Dishevelled (Dvl) protein, a central signaling hub (Rim et al., 2022). The type of Wnt protein and involved Frizzled receptor determines the type of pathway (Rulifson et al., 2000). In β-catenin-dependent pathway, recruitment of Dvl alleviates β-catenin protein level in the cytoplasm, β-catenin travels to the nucleus with other associated proteins and activate genes that regulate cell behavior and development (Prunier et al., 2004). In Non-canonical Wnt signaling Dvl bypasses β-catenin and directly interacts with other signaling molecules like JNK (c-Jun N-terminal kinase) (Wiese et al., 2018).

Wnt ligands: Wnt ligands comprise cysteine-rich glycoproteins that activate cell surface receptor to induce specific intracellular cascade. Since their initial discovery in 1982 (previously called int-1), Wnt genes have emerged as crucial players in animal development (Korzh, 2008). About 20 Wnt genes have been discovered that orchestrate diverse processes, from embryonic patterning to stem cell regulation. While Wnt gene expression is observed within all metazoan species, their number varies significantly for instance, the Hydra vulgaris genome carries thirteen independent genes, while humans carry 19 (Logan & Nusse, 2004).

Wnt ligands, synthesized by ER-associated ribosomes, are post-translationally modified in the Golgi apparatus with glycosylation, palmitoylation, and acylation. These post-translational alterations are indispensable for their actions and secretions (Kurayoshi et al., 2007). The lipid modification of Wnts, mediated by Porcupine (a palmitoyl transferase), involves the attachment of palmitoleic acid moiety (Coombs et al., 2010). This lipid attachment acts as a binding motif facilitating the binding of Wnt signal to receptor FZD, rendering the Wnt protein hydrophobic and potentially anchoring it to the cell membrane (MacDonald & He, 2012). During Wnt protein maturation, Wntless/Evi (Wls) muddles to lipidated forms and facilitates their transport to the membranes for secretion (Franch-Marro et al., 2008) Fig 2. The whole mechanism of extracellular Wnt transfer to target cell is limited. Wnt proteins, along with Wntless (Wls) and other signaling components, are packaged by exosomes. This process ensures that some Wnt proteins are positioned on the outside of the vesicles for efficient receptor binding (Albrecht et al., 2021).

Frizzled receptors: Upon approaching the surface of cells, the Wnt ligand occupies in a complex formation through simultaneous interactions with receptors complex consisting of Frizzled (FZD) and LDL receptor-associated protein five-sixths (LRP5/6). Additionally, co-receptors i.e., glypican-3/4, ROR, and RYK may also participate in this intricate binding event. On the receptor cell surface Wnt protein simultaneously binds to a complex consist of Frizzled (FZD) and LDL receptor-associated protein five-sixths (LRP5/6) co-receptors such as glypican-3/4, ROR, and RYK may also participate in this intricate binding event (Liu et al., 2022). The FZDs belong to a unique class of G-protein receptors (GPCRs) and constitute two key domains: a seven-transmembrane domain and a cysteine-rich domain (CRD) (Bhanot et al., 1996). The CRD acts as a binding motif for Wnt's lipid surface (Hsieh et al., 1999). The Wnt binding triggers the dimerization of FZD and LRP5/6 (Janda et al., 2017) that causes conformational changes in them (Nusse & Clevers, 2017). The C-Terminus of FZDs binds to the Dsh that triggers subsequent intracellular signal cascade (Janda et al., 2012; MacDonald & He, 2012). The phosphorylation of cytoplasmic ends of LRP assists the scaffold protein Axin, one of which is interceded by GSK3 on a serine in a PPPSP ends (Stamos et al., 2014).

Disheveled: Dishevelled (Dvl) is an intracellular cytoplasmic protein that acts as signal transmitter from extracellular binding Wnt ligand to intracellular signaling pathway (Albrecht et al., 2021). Dvl protein has multiple domains essential for activation of multiple Wnt pathways including-terminal DIX, the central PDZ, and the C-terminal DEP domain (Wong et al., 2003). Without Wnt ligand binding, these three domains are tightly packed together limiting interaction with other proteins. The intracellular domain of Fz is responsible for downstream signaling cascade (Pan et al., 2004). For intracellular signal transduction Fz receptor has no enzymatic motif, so signal is transmitted by intracellular signaling molecule including Disheveled and heterotrimeric G protein (Albrecht et al., 2021). Upon Wnt ligand binding Dvl undergoes various conformational changes the PDZ domain and C-terminal domain move away from the central WD40 repeats, creating flexible docking sites for other proteins (Seidensticker & Behrens, 2000). The exposed docking site allows Dvl to interact with various signaling pathways depending upon the interacting protein. Wnt/β-catenin signaling involves Dvl interaction with Axin and casein kinase 1α (CK1α) (Cruciat, 2014). This disrupts Axin's ability to target β-catenin for degradation, leading to β-catenin accumulation and nuclear translocation, where it activates target gene transcription (Bikkavilli & Malbon, 2010). Dvl also interacts with calcium channel regulators, leading to intracellular calcium release and activation of Ca2+-dependent signaling (Katoh & Katoh, 2007).

In the absence of Wnt ligands, the β-catenin destruction complex, comprising APC, Axin1/2, CK1, GSK-3, and β-TrCP, targets β-catenin for ubiquitination and subsequent proteasomal degradation (Werner et al., 2023). Dvl competes with β-catenin for binding to Axin sequestering it away from the β-catenin destruction complex. This disrupts the GSK-3β-mediated phosphorylation and subsequent ubiquitination of β-catenin, leading to its stabilization and cytoplasmic accumulation (Stamos & Weis, 2013). Cytoplasmic β-catenin interacts with TCF/LEF factors in the nucleus, triggering Wnt target gene expression for cell growth, differentiation, and other processes (Liu et al., 2022).

Cellular responses and functions

Wnt signaling pathway determines the cell fate by developmental and physiological processes including cell proliferation, differentiation, specification of the anterior–posterior body axis, migration (Kahn, 2014). At the cellular

and organism levels Wnt protein provide information of entire body plan pattern plan and generation of cell and tissue diversity, tissue homeostasis, and damage repair (Grainger & Willert, 2018).

Cell fate determination: Wnt signaling pathway regulates stem cell fate after embryonic stage in mammals. Scientists inferred that role of Wnt in stem cell fate determination is an ancient process as Wnt cascade determine main body axes at embryonic stage in sea urchin (Angerer & Angerer, 2000), post-metamorphic development (Müller-Tidow et al., 2004) and stem cell fate determination in Hydractinia (Teo et al., 2006). Wnt signaling pathway guides vertebrate neural crest stem cells from growth to specialization, but its influence on invertebrate stem cells remains a mystery. Did this control evolve later in vertebrates, or is it an ancient inherited trait (Teo et al., 2006)?

Embryonic development: The Wnt signaling pathway has shown a key role in embryonic development, particularly in key endometrial events like decidualization and gland formation. It also governs the cyclic hormonal control of the endometrium (Tepekoy et al., 2015). Wnts regulate cell behavior by controlling cell proliferation, differentiation, and cell polarity. Wnt activity determines early cardiac mesoderm differentiation, vertebrate embryo lineage specification and regulate pluripotency in embryonic stem (ES) (Flaherty et al., 2012).

Tissue homeostasis: The internal maintenance of the body is especially important for the smooth running of the internal metabolism. Rigorous research on the Wnt pathway has shown the unique role of Wnt in regulating intra-cellular as well as extracellular homeostasis. Wnt ligand level in the cell cytoplasm determines the rate of stem cell proliferation and self-renewal (Gong et al., 2001). The genetic analysis highlighted the role of the Wnt-β-catenin cascade in bone tissue homeostasis as a change in components of this pathway leads to the significant fluctuation in the bone mass (Xi et al., 2015).

PI3K/AKT PATHWAY

Overview of PI3K/AKT signaling

The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is a key regulator in different cellular processes like metabolism, protein synthesis, cell survival and differentiation. Disruption of this pathway has been reported in many anomalies and pathologies, including cancer (Martini et al., 2014), osteoporosis (Xi et al., 2015), cardiac fibrosis (Qin et al., 2021). On activation PI3K molecule phosphorylate PIP2 and produce PIP3 which is responsible for the recruitment of other signaling proteins including a core protein of this pathway Ser/Thr kinase Akt (He et al., 2021). Activation of Akt further activate diverse cellular function like cell growth, depending on the substrate (Xi et al., 2015).

Molecular components and activation

The main components of this pathway are external signal transducer receptor tyrosine kinase (RTKs), a PI3K complex that convert PIP2 to PIP3 through phosphorylation and a key downstream regulator Akt (Behrooz et al., 2022).

AKT/protein kinase B: Receptor Tyrosine Kinase (RTKs) is a single pass extracellular receptor which is activated by the binding of various ligands including growth factors, cytokines, and hormones (Hubbard, 1999). RTK monomer has three functional domains, an extracellular ligand binding N-terminal domain, a cell-surface/ transmembrane that converts extracellular signal into intracellular signal and an intracellular cytoplasmic tyrosine kinase domain (Maruyama, 2014) as shown in Fig 3. The ligand binding to N-terminal domain triggers the activation of two RTK molecules which subsequently cause some conformational changes and two RTK molecules come close together to form a dimer (Schlessinger, 2000). On dimerization, these two receptor molecules phosphorylate each other which activates their intracellular tyrosine kinase domains (Regad, 2015).

Phosphoinositide 3-kinase (PI3K): PI3K is a crucial enzyme of the PI3K/Akt pathway which phosphorylates PtdIns on plasma membrane (Vanhaesebroeck et al., 2012). PI3K comprises of two main domains: the catalytic domain P110, which performs the phosphate addition, and the regulatory domain P85, which controls P110's activity (Cantley, 2002; Vanhaesebroeck et al., 2012). The p85 motif perform diverse functions in enzyme activation, receptor binding and localization (Mellor et al., 2012). The p110 domain consists of three subunits p110α and p110β that is responsible for insulin signaling and proliferation (Sopasakis et al., 2010), whereas third subunit p110δ shows a prominent part in immunology and inflammation (Costa et al., 2011). Activated receptors directly bind and activate P85, leading to P110 activation and PIP3 generation or through other adapter molecules that function as intermediaries, bridging activated receptors to P85 and triggering PI3K activation (West et al., 2002). By converting PIP2 to PIP3, PI3K initiates an array of signaling trials in the cells, influencing vital processes like growth, survival, and metabolism (He et al., 2021).

PIP2 and PIP3 are small phospholipid molecules in cell membranes. PIP3 acts like a special dock, which promote and recruited specific proteins to the membrane, and subsequently triggers a chain reaction within the cell (Mandal, 2020). This recruits AKT to the membrane, allowing PDK1 to modify it by adding a phosphate group (Li & Marshall, 2015). AKT needs another phosphate added at a different spot by either mTORC2 or DNA-PK to be fully activated. This full activation then allows AKT to perform the desired function (Ersahin et al., 2015).

Protein kinase B (AKT): Akt, a 60 kDa protein, shares a high resemblance with protein kinases A at 68% and C at 73% (PKA and PKC), it's also known as PKA and PKC-associated kinase (PKB) (Abeyrathna & Su, 2015). Akt controls vital functions like glucose metabolism, cell survival and death, cell proliferation, gene expression, and movement (Wang et al., 2008). Three Akt isoforms exist: Akt 1, widely expressed, Akt 2 especially in insulin-target tissues, and Akt 3 primarily in

brain and muscle tissues (Sharma & Dey, 2021). Despite sharing highly similar structures, including the N-terminal (PHD domain) and C-terminal regulatory domain (with Ser473 crucial for full activation) and the catalytic domain (activated by phosphorylation at Thr308, each isoform exhibits distinct tissue distribution and functional nuances (Datta et al., 1999; West et al., 2002).

Full Akt initiation is primarily under the control of phosphoinositides, PIP2 and PIP3, generated by PI3K, these potent second messengers bind the Akt PH domain (Fig 4), prompting its positioning to the membranes (West et al., 2002). Subsequently, full Akt activation begins with a sequential phosphorylation process. PDK1, which is also regulated by PI3K, phosphorylate T308 at activation loop, however kinase responsible for phosphorylation at S473 in the C-terminus remained elusive, with possibilities including Akt itself or another upstream kinase. Although PI3K activates Akt, other PI3K-independent mechanisms can also activate Akt. Agonists of PKA or α-adrenergic receptors, along with intracellular calcium fluctuations, can all trigger Akt activation independently of PI3K, though some discrepancies in findings exist, requiring further investigation (Yusta et al., 2002). Interestingly, Akt's repertoire extends beyond growth factor and receptor signaling. Various forms of cellular stress can also ignite Akt activation Ouyang et al., 2000), this stress-induced activation might serve as a general protective mechanism against cell death, a crucial point for understanding cancer cells' response to chemotherapy and its cytotoxic ROS generation (Datta et al., 1999; Akbar & Ijaz, 2024; Hayat et al., 2024).

Functional outcomes

Cell growth and survival: PI3K/Akt pathway play a critical role in cell growth, survival, nutrient uptake, and metabolism (Xi et al., 2015). The genetic manipulation of its core components has shown the key role of this pathway in organismal growth and tissue formation (Amani et al., 2021). Their frequent hyper-activation of Akt and PI3Ks in various carcinomas have ascertained their role in cell progression and proliferation. The p110α and p110β are indispensable for the normal embryonic growth due to their kinase independent function (Świderska et al., 2018). The deficiency of PI3K subunit p85 results perinatal death but its complete eradication

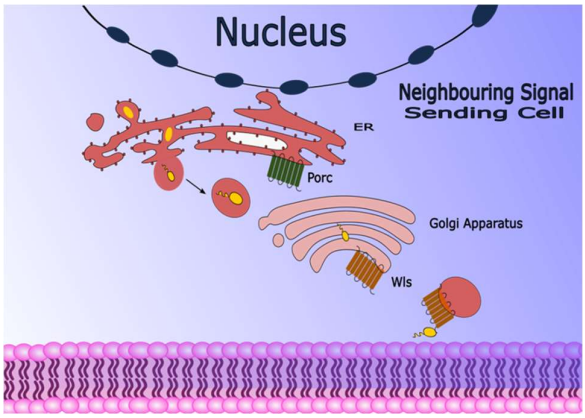

Fig 1. Wnt protein formation within cell

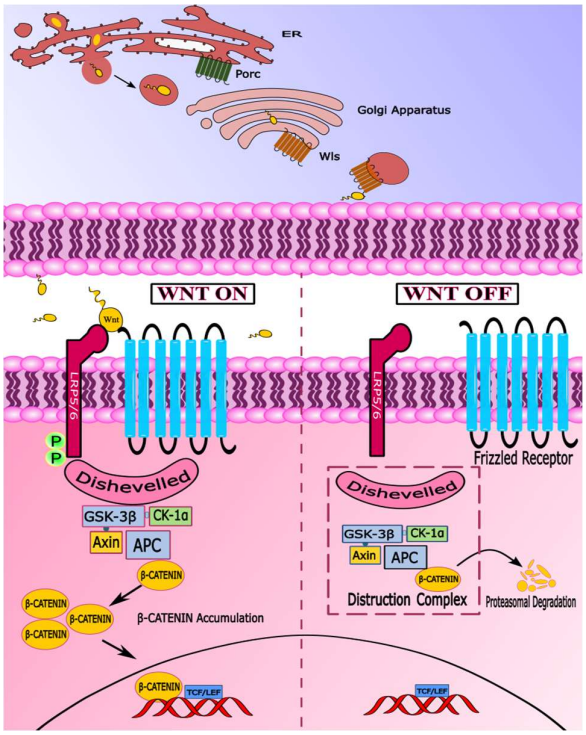

Fig 2. Overview of canonical Wnt signaling pathway

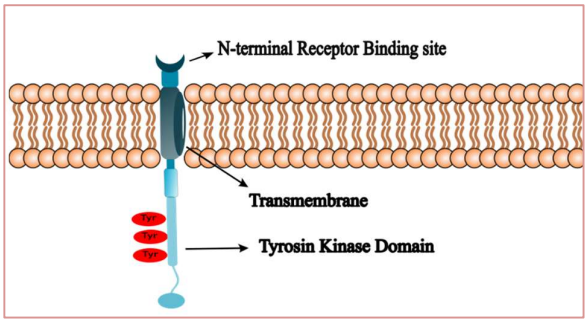

Fig 3. Functional domains of RTK monomer

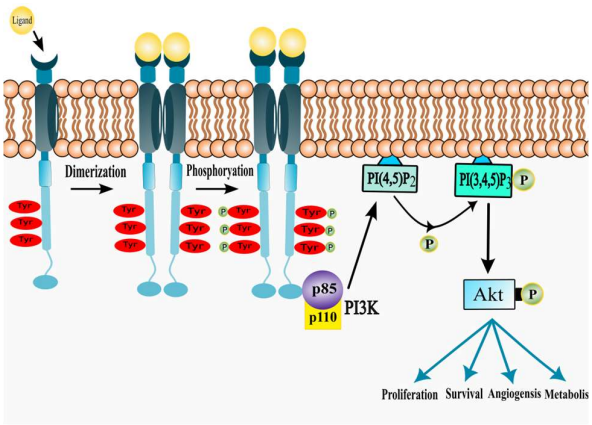

Fig 4. Schematic diagram of PI3K/AKT pathway

produces feasible mice suggesting its non-compensating role in early embryonic development (Jeong et al., 2008).

Metabolism: PI3K/Akt pathway is the chief regulator of cellular metabolism and its role in aerobic glycolysis is well established (Deshmukh, 2016). The activation of PI3K pathway has shown a significant uprise in glucose uptake by stimulating glycolytic enzymes and cell surface receptors. Akt activates ATP citrate lyase which promotes the acetyl-CoA production accelerating the metabolism (Li et al., 2019). Akt has also been reported to uphold the glucose uptake in insulin

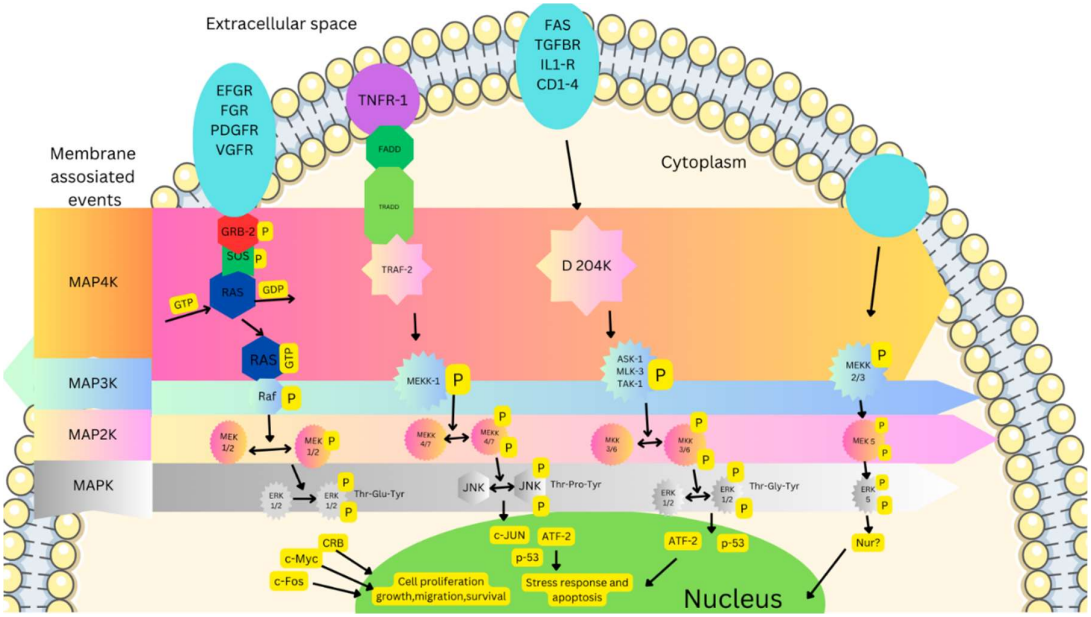

Fig 5. Schematic Representation of Conventional MAPKs

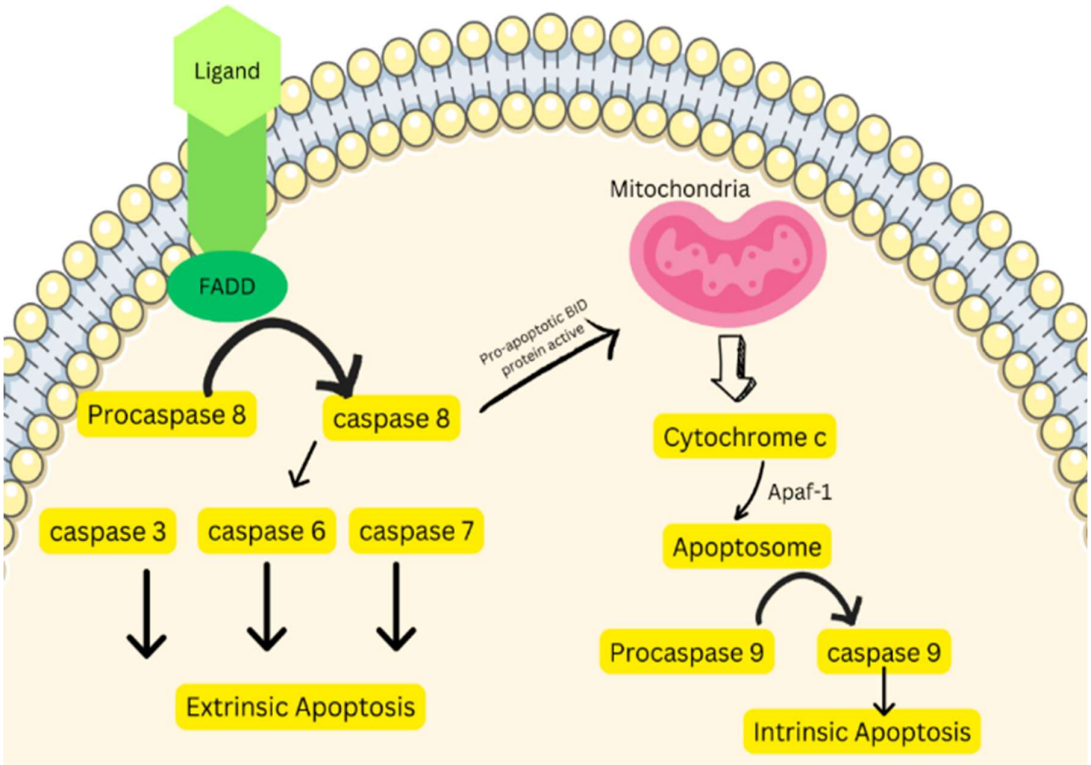

Fig 6. Role of MAPK in intrinsic and extrinsic apoptosis

sensitive tissues through glucose transporters (GLUTs) (Jiang et al., 2014). PI3K pathway also plays key role in fat metabolism, it activates acetyl-CoA carboxylase (ACC) in adipose tissues assisting fatty acid synthesis and triglyceride accumulation (Wang et al., 2022). Its role in mitochondrial biogenesis ensures effective energy extraction within cell (Rius-Pérez et al., 2020).

MAPK PATHWAY

Introduction to MAPK signaling

MAPK pathway chiefly comprise of MAPKs, which transduce extracellular signals into cellular response. This cascade is responsible for a myriad of cellular functions including, cell proliferation, division, differentiation, and apoptosis (Lefloch et al., 2009). This signaling cascade

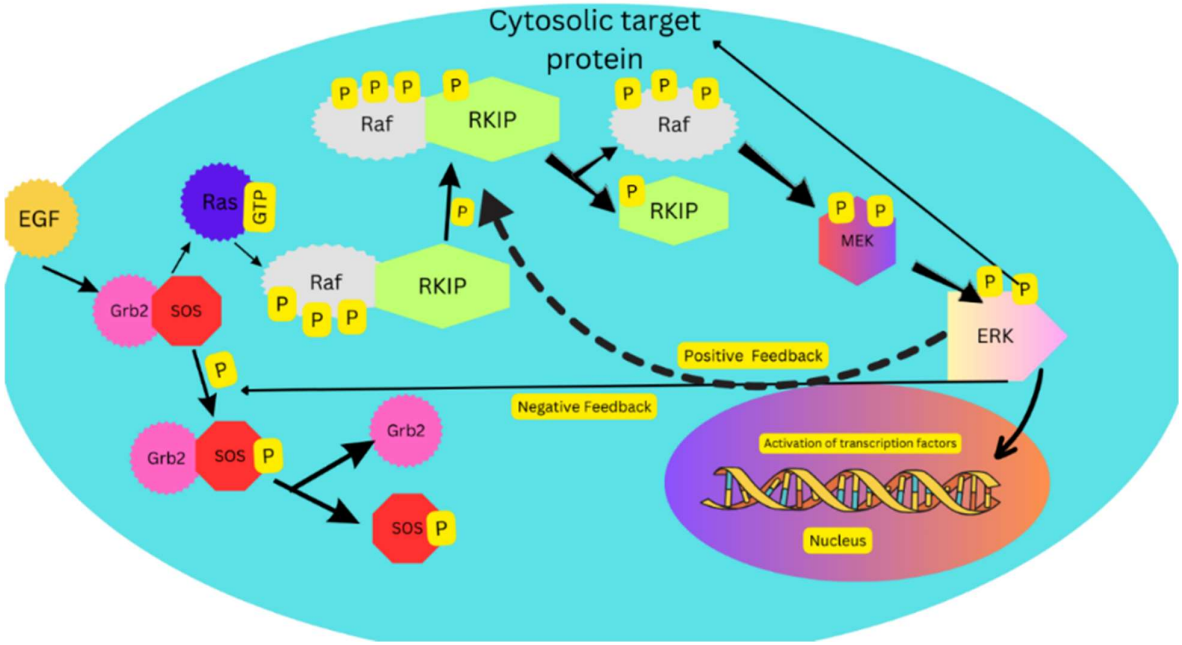

Fig 7. Positive and Negative Feedback Control of ERK Pathway

Table 1. Frequencies (%) of mutations in different components of MAPK and the resulting tumors arising from them

Tumor	GRB2	SOS	KRAS	NRAS	HRAS	BRAF	ARAF	MEK	ERK	References
Melanoma	1.2	2.4	15-29	20.0	0.3	90%	0.2%	3-8	67-90	Colombino et al., 2012
Non-small cell lung carcinoma	0.5	3.3	35	1.2	0.4	4.0	3.0	1.8	40-55	Nikolaev et al., 2012; Seo et al., 2012; Cardarella et al., 2013
Colorectal	0.6	3.5	32.4	3.7	0.9	12.3	2.0	1.9	1.0	Mlakar et al., 2021
Neuroblastoma	0.1	1.5	2.3	0.7	1.7	0.1	0.3	1.3	0.1	Mlakar et al., 2021
Brain Tumor	0.4	0.7	0.8	1.0	0.0	4.7	0.2	0.3	0.1	Mlakar et al., 2021
Blood cancer	1.0	1.3	4.9	9.5	0.2	8.2	0.3	2.2	0.2	Mlakar et al., 2021
Breast Cancer	2.2	3.3	1.4	0.5	0.6	2.1	0.6	1.8	0.4	Mlakar et al., 2021
Thyroid carcinoma	1.2	2.2	9-27	9-27	9-27	10-70	0.1	1.2	0.2	Cardarella et al., 2013; Bansal et al., 2013

proceeds by simultaneous activation of MAP4K, MAP3K, and MAP2K which activate MAPKs by phosphorylation. The activated MAPKs further phosphorylate and activate a diverse array of MAPKAPKs, which can be further categorized based on their functions and sequence homology into five subgroups: RSKs, MNKs, MSKs, MK5, and MK2/3 (Cargnello & Roux, 2011).

The following are the main components of the MAPK pathway

1. Receptor Tyrosine Kinases
2. Guanine Nucleotide Exchange Factors (GEFs)
3. Small GTPases (Ras)
4. Raf Kinases (e.g., c-Raf)
5. MEK (Mitogen-Activated Protein Kinase Kinase)
6. ERK (Extracellular signal-regulated Kinase)

MAPKs may be atypical including ERK3/4, ERK7, and NLK, or conventional MAPKs which include:

The ERK1/2 pathway: Tyrosine Kinase Receptors are activated by growth factor stimuli such as PDGF and EGF. ERK1 and The GRB2 possess both SH2 and SH3 domains as illustrated in Fig 5. Particular phosphotyrosine residues of active Tyrosine Kinase Receptors are recognized by its SH2 domain. As a result, a GDP–GTP exchange factor (GEF) recruits at the membrane and replaces GDP with GTP acting as a ligand of the membrane protein RAS having three isoforms Hras, Kras, and Nras (Prior & Hancock, 2001). Stimulation of three Ras isoforms (A-Raf, B-Raf, C-Raf) primarily activates Raf and PI3K pathways, with these Raf proteins translocating to the plasma membrane upon activation (Baljuls et al., 2008) as demonstrated in Fig 5.

Role in cellular processes

Cell Proliferation and Differentiation: The MAPK/ERK pathway differentiates adipocytes, the visual cortex, (Hsu et al., 2007), Schwann cells, and the control myelination in the Peripheral Nervous system. The MAPK/ERK pathway helps in organ regeneration in a variety of ways (Lefloch et al., 2009).The generation of vascular progenitor cells and determination of the fate of endothelial cells occurs through the control of ERG and FLI oncogenes (Harding et al., 2017). The ontogenetic processes of gastrulation (Kristensen et al., 2005) and osteogenic differentiation occurs through ERK signaling (Ishii et al., 2021).

Apoptosis: JNK and p38 plays a critical role in apoptosis through downregulation of anti-apoptotic proteins (Cuenda & Rousseau, 2007). The extrinsic pathway is independent of Bcl-2 family members, and activate caspase-8 (Youle & Strasser, 2008) in some cells it also cleaves BH3-only protein named Bid (BH3 interacting-domain death agonist) from caspase 8 (Fig 6). In intrinsic pathway C-terminal Bid (tBid) releases cytochrome c from mitochondria which activate caspase-3,6,7,9 that may result in autophagy (Slobodnyuk et al., 2019).

Regulation Of the MAPK Pathway: Regulation of this pathway may occur with the help of, a scaffold protein, which amplifies ERK activation (Nguyen et al., 2009). Inhibitory phosphatases like PP2A and PP2Ca regulate MAPK activity in an antagonistic manner (Zhou et al., 2002). In activated state, the complex binds the RAS protein, and the kinase cascade begins (Colombino et al., 2012). The positive and negative feedback mechanisms of the MAPK pathway are demonstrated in Fig 7.

Dysregulation of MAPK and resulting tumors: Table 1. provides a brief summary of mutations in various components of MAPK along with resulting tumors arising from them.

INTERPLAY AND CROSSTALK

Integration of MAPK, PI3K/AKT, and Wnt pathways

Classical schemes of signaling pathways display Wnt, PI3K/Akt and MAPK as individual and isolated pathways, however, they are tightly intertwined with multiple crosstalk nodes and routes between them which determine cell fate through coordinated actions. These pathways possess interactive proteins as PI3K cascade 802 (Pilot-Storck et al., 2010), 2000 interactions to MAPK pathway. These broad interactomes suggest there must be a relation between these three pathways that positively and negatively influence at different stages, resulting in dynamic and complex crosstalk (Aksamitiene et al., 2012).

Crosstalk among cellular signaling pathways has emerged as a complex and dynamic subject of research that potentiates the regulation and maintenance of multiple cellular processes. A particularly intricate nexus of signaling pathways involves the integration of the MAPK, PI3K/AKT, and Wnt pathways due to their dynamic role in cell fate determination through precise control of proliferation, survival, differentiation, and apoptosis (van Amerongen & Nusse, 2009). Inhibition of PI3K can activate pathways like Wnt/β-catenin which proposes that co-inhibition and drug blocking may be an effective therapeutic strategy in various diseases (Behrooz et al., 2022). Delineating the complexity of the signaling pathway interaction with other signaling cascades is crucial for understanding normal mechanisms as well as for the discovery of new, personalized treatment approach for multiple diseases like cancer.

Cross-regulation and synergy

PI3K-AKT pathway regulates β-catenin activation by phosphorylating at the S552 site (Sastre-Perona et al., 2016), whereas PI3K inhibition impairs β-Catenin binding to targeted gene promoter and decreases Wnt target gene expression. PI3K dependent activation of Wnt pathway relies on events beyond phosphorylation at AKT target site as evidence suggest additional regulatory steps are needed, as S552D-phosphomimetic β-Catenin mutants exhibit impaired restoration of WNT signaling (Ormanns et al., 2014). Akt phosphorylated at T308 and S473 activate mTORC1 and 2 respectively and inhibition of mTORC1 rescue disheveled leading to the activation of Wnt pathway (Vadlakonda et al., 2013).

Wnt, MAPK and PI3K/AKT pathways converge in a complex network, activated by upstream signaling activators and are tightly regulated by phosphatases and bidirectional

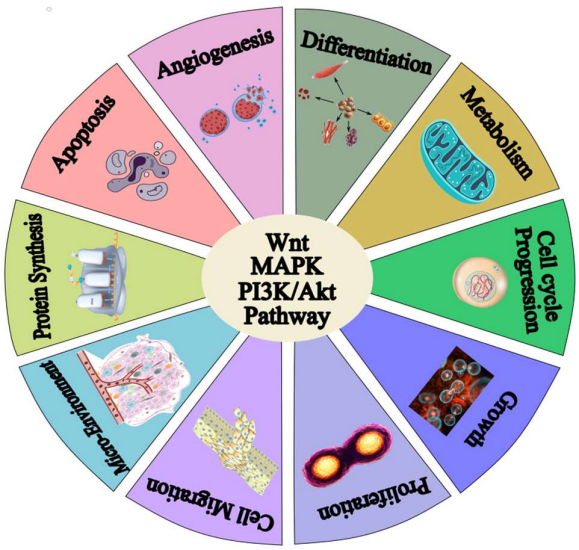

Fig 8. Cellular Functions of Wnt, MAPK and PI3K/AKT Pathway

crosstalk (Burotto et al., 2014). PI3K positively regulates MAPK pathway to physiological stimuli leading to a negative feedback loop on PI3K/AKT activity (Kiyatkin et al., 2006). Context dependent crosstalk between MAPK and PI3K/Akt pathway has also been recorded at multiple signaling routes and nodes, PIP3-mediated RasGEF and RasGAP signaling being major node (Rodrigues et al., 2000). Inhibition of MAPK induces a downregulation in PI3K activity (Yu et al., 2001) whereas, PI3K inhibition boosts MEK and ERK activation (Serra et al., 2011). These growth factor-activated pathways, MAPK and PI3K/AKT, constitute a well-studied signaling network with established roles in regulating cell proliferation and differentiation through specific protein cascades (RAF-MEK-ERK and PI3K-AKT, respectively) (Ishii et al., 2021). The Wnt signaling pathway also direct the regulation of RAS-ERK pathway and these both pathways play a pivotal role in proliferation and cell transformation. This complex crosstalk between WNT, MAPK and PI3K cascade has been observed at multiple nodal points and influence each other with feedback loop and mutual regulation (Kim & Choi, 2007; Park et al., 2006). As Disheveled (Dvl) phosphorylation by ERK can modulate Wnt signaling response (Harding et al., 2017) and PI3K/AKT influence Wnt cascade by regulating GSK-3β. This intricate regulation ensures the smooth running of cellular responses and show that each pathway have a regulatory role on the other (Burotto et al., 2014).

Cellular responses in the presence of combined pathway activation

A diverse array of cellular responses comprehended by the convergence of MAPK, PI3K/AKT and Wnt pathway including cell fate determination, proliferation, metabolism and apoptosis. Cell cycle progression and proliferation are regulated by Wnt and PI3K/Akt pathway through various mediators and regulate cell cycle at G0/G1 to S phase (Mydin et al., 2024). Cyclin D1 and c-Myc are also under the influence of Wnt pathway, which is essential for metabolic reprogramming of G1 phase (Ormanns et al., 2014). Thus, these three-pathway pathway ensures the proliferative signal recognition and controlled cell division (Mydin et al., 2024).

Apoptosis is induced by the abrogation of ERK/MAPK, Wnt/β-catenin and PI3K/Akt pathway. The apoptotic genes are the main downstream targets of the Wnt pathway and blockage of GSK3β is mediated by the downregulation of MAPK and PI3K/Akt pathway. Thus, these three pathways ensure the pro and anti-apoptotic balance. Inactivation of Akt inhibits the anti-apoptotic protein Bcl-2 by de-phosphorylation of Bad (Aksamitiene et al., 2012). This cellular communication synergistically plays a critical role in pathologies, including multiple carcinomas (Van Camp et al., 2014). A summary of all the processes controlled by the integration of Wnt, MAPK and PI3K/Akt pathway is depicted in Fig 8.

FUTURE PERSPECTIVES AND CONCLUSION

There has been a rapid advancement in the study of Wnt, PI3K/Akt and MAPK pathways in therapeutic approaches and their synergistic role in normal cell growth and functioning (Seidensticker & Behrens, 2000). Most crosstalk studies involve the use of computational methods to systemically predict cross relation between pathways (Tegge et al., 2016). Most approaches involve the inhibition of pathway mediator genes to detect the role of one pathway mediator in different cellular processes (Wang & Buck, 2012). Another common approach is NIC (nodes in common) to observe any protein shared between two pathways, BPLN (Biological process linkage networks) is used for interaction-based studies (Cargnello & Roux, 2011). Promising results have been obtained through these approaches and many nodal points have been identified which are important for therapeutics of different pathologies (Nusse & Clevers, 2017). However, these methods have their drawbacks as NIC cannot work in if two pathways lack common proteins or don't have any commonalities (Purvis & Lahav, 2013). They are also uncle to detect complex mechanisms or interaction between proteins of two pathways. Although all other methods show enormous potential for realistic crosstalk between different pathways in the future, there is also a need for a better understanding of the role of each pathway paralogue in different cellular responses and their interaction with other pathways. Biomarker study can also play a critical role in understanding the effect of other signaling pathways in signaling-associated carcinomas, thereby can help to select the most effective therapeutic approach (Aksamitiene et al., 2010; Serra et al., 2011).

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