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Review Article

Signalling pathways in dermatology

Zonunsanga

Department of Skin and VD, RNT Medical college, Udaipur, Rajasthan-313001, India

Corresponding author: Dr. Zonunsanga, E-mail: jrkos04@gmail.com

ABSTRACT

Different signalling pathways are involved in cellular growth, differentiation, migration and maintenance of stem cells. These include EGF and EGFR, IGF-1R, Hedgehog, WNT, MAPK, PI3K and MC1R-MITF etc. Aberrations or overexpression of these signals result in abnormal proliferation of cells, which may leads to development of tumours. This review stress on different signaling pathways involved in growth, differentiation and maintenance of stem cells, which are important for pathogenesis of many diseases when the pathways are defective.

Key words: EGF; EGFR; MAPK; PI3K; MC1R-MITF; Janus kinase

INTRODUCTION

Human beings have several signalling pathways that are involved in cellular growth, differentiation, migration and maintenance of stem cells. These include EGF and EGFR, IGF-1R, Hedgehog, WNT, MAPK, PI3K, MC1R-MITF, JAK-STAT etc. Aberrations or overexpression of these signals result in abnormal proliferation of cells, which may leads to development of tumours.

EGF AND EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

Epidermal Growth Factor (EGF) 6.2kDa protein which stimulates the proliferation and differentiation and migration of epithelial cells and fibroblasts. The biological effects of EGF are mediated by a specific transmembrane receptor which is a 170kDa monomeric glycoprotein which has intrinsic tyrosine kinase activity. When EGF binds to the receptor, it results in autophosphorylation of the receptor and transduction of the EGF proliferative signal. This activated EGF receptor phosphorylates phospholipase C-γ1 (PLC-γ1) and other proteins involved in signal transduction. The activated PLC-γ1 hydrolyses inositol phospholipids and results in increase in intracellular calcium levels, which subsequently activate protein kinase C (PKC) which in turn, attenuates the tyrosine kinase activity of the EGF receptor [1,2].

EGFRs is known to play an important role in regulating the development of the epidermis and its appendages. EGFRs are predominantly expressed in the basal layer of epidermis. As the cell moves up, they are down-regulated as cells commit to terminally differentiate. EGFR has the ability to activate Ras-MAPK signaling, resulting incellular proliferation. It also activate PI3K–Akt signaling which is typically associated with cell survival. AP- epidermal keratinocytes had an inhibitory effect on EGFR promoter activity while the loss of AP-2β results in massive apoptosis. EGFR also activates other pathways such as phospholipase-C and small GTPases such as Rho and multiple signal transducer and activator of transcription (STAT) isoforms. Overexpression of EFGR is associated with tumorigenesis [1,3].

EGFR overexpression and activation results in increased migration of epithelial cells. Which is mediated by Matrix Metalloproteinase (MMP) which can regulate cell growth in different ways (e.g. the release of membrane-bound growth factors like tumor growth factor). E-cadherin and p120 also modulate EGFR Effects upon Cell Adhesion. By promoting increased migration, EGFR is decreases cell adhesion by its interaction with beta-catenin, as the phosphorylated catenin can no longer mediate the connection of the cadherin-catenin complex with the actin-cytoskeleton. EGFR also mediates increased cell aggregation

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through relocalization of p120 which is a component of adherens junctions [1-3].

Insulin-like growth factor 1 receptor (IGF1R)

IGF1R is a transmembrane, ligand-activated tyrosine protein kinase which consists of Alpha-2 Beta-2 heterotetramers held together by disulfide bridges. Both IGF1 and IGF2 exhibit high-affinity binding to IGF1R. Most of the biological effects of IGF1 and IGF2 are mediated by IGF1R. IGF1R-mediated inhibition of apoptosis depends on the activation of PI3K (Phosphatidylinositol-3-Kinase) and Akt/PKB (Protein Kinase-B). The binding of IGF1 or IGF2 to IGF1R activates tyrosine kinase, resulting in the phosphorylation of the IRSs (Insulin Receptor Substrates) which further interacts with the cytoplasmic protein PI3K, leading to the transduction of the functional effects of IGFs, such as enhanced glucose transport, enhanced cardiomyocyte contractility and the inhibition of apoptosis by activating several downstream proteins and molecules. PIP3 binds to the Akt and PDK-1 (Phosphoinositide Dependent Kinase-1). PDK-1 then phosphorylates Akt. PDK-1 also phosphorylates PKC (Protein Kinase-C)[4]. These PKCs, along with Akt facilitate the GLUT4 (Glucose Transporter-4) translocation from the GLUT4 vesicle to the membrane, enhancing the rate of Glucose uptake by the cell. A primary target is the BAD. In its non-phosphorylated state, BAD locates at the mitochondrial membrane where it interacts with BCL2 (B-Cell CLL/Lymphoma-2) and prevents it from performing its anti-apoptotic functions. When Akt phosphorylates BAD, BAD associates with the cytosolic protein and is unable to interfere with BCL2. Akt can also phosphorylate and inactivate Caspase9, preventing the initiation of the Caspase cascade. Akt also phosphorylates several pro-apoptotic members of the forkhead transcription factor family, FKHRL1, FKHR and prevents their activity. Akt decreases expression of FasL (Fas Ligand), thereby decreasing Fas-mediated apoptosis. Akt not only inhibits pro-apoptotic transcription factors, but also increases the levels of anti-apoptotic proteins including BCL2 and BCL-X and several extracellular matrix adhesion molecules [5]. Phosphorylated Akt also stimulate expression of the anti-apoptotic transcription factor NF-Kappa B (by regulating I-Kappa B Kinases). This results in I-Kappa B degradation and allows NF-Kappa B to enter the nucleus and activate transcription of anti-apoptotic genes. Akt also inhibits GSK3 (Glycogen Synthase Kinase-3) which promotes the dephosphorylation and activation of Glycogen Synthase, leading to the stimulation of glycogen synthesis. GSK3 also catalyses the phosphorylation and inhibition of eIF2B (Eukaryotic Protein Synthesis Initiation Factor-2B), thereby inhibiting protein synthesis. Hence, by inhibiting GSK3, IGF1R stimulates the dephosphorylation and activation of eIF2B, leading to an increased rate of protein synthesis. IGF1 promotes protein synthesis by activating eIF4E (Eukaryotic Initiation Factor-4E)[6]. Akt also phosphorylate mTOR. Phosphorylated mTOR promotes phosphorylation and inhibition of 4EBP1 and promotes protein synthesis by relieving 4EBP-mediated inhibition of eIF4E. Upon phosphorylation by mTOR, the ribosomal p70S6K and S6 (Ribosomal Protein-S6) becomes activated and promotes protein synthesis [7].

IGF1R phosphorylation leads torecruitment of protein SHC (SH2 Containing Protein) to the receptor and which is then phosphorylated. Activated SHC then binds the adaptor GRB2 (Growth Factor Receptor Bound Protein-2), recruiting the SOS in an IRS-independent manner. This complex then activates Ras and initiates sequential phosphorylation cascades involving serine/threonine kinase Raf, MEK1/2 (MAP Kinase Kinases) and ERK1/2 (Extracellular Signal Regulated Kinases). This pathway of IGF1R signaling is associated with cell differentiation, migrationand regulation of the machinery of apoptosis [6-7].

Besides, the IGF1R also modify Calcium-dependent signaling pathways. Binding of ligand IGF1R leads to activation of voltage-dependent Calcium channels, thereby, causing large transient increases in the Ca2+ levels, which further regulate Calcium-dependent transcription factors such as MEF2 (Mads Box Transcription Enhancer Factor-2), NFAT (Nuclear Factors of Activated T-cells) and CREB. These transcription factors promote the expression of several anti-apoptotic proteins including BCL2. The increased Ca2+ levels in the cytoplasm disrupt the inhibitory effects of Calmodulin, thereby, activating the protein phosphatase Calcineurin. Calcineurin activation leads to the dephosphorylation of NFAT, allowing it to enter the nucleus, where it cooperates with other transcription factors to bind promoters. The CalmKs (Ca2+/Calm [Calmodulin]-dependent Protein Kinases), activated by the increased Ca2+ levels activate the CREB and the ERK1/2 pathway which promote cell survival [4-7].

HEDGEHOG (Hh) pathways

The Hedgehog signaling pathway is a biological signalling pathway which is important for regulation of

the normal cell-fate specification, tissue polarity and patterning and organogenesis during embryogenesis and tissue homeostasis after severe injuries. The Hh proteins include SHH, Indian hedgehog (IHH) and Desert hedgehog (DHH). All three Hh proteins are able to bind the PTCH1 receptor and activate the Hh pathway in a time and concentration dependent manner [6].

The Hh protein, including SHH, IHH or DHH ligand binds to its 12-pass transmembrane PTCH1 or PTCH2 receptor, relieving the repressive effect induced by this receptor on the activity of its signaling partner, a seven-pass transmembrane coreceptor, SMO. The stimulation of the SMO signaling transduction results in the activation of cytoplasmic GLIs and their translocation to the nucleus, where they participate in the transcription [6,7].

The positive regulatory signalling pathways include EGF/EGFR, Wnt/beta-catenin and TGF-beta, which can cooperate with the canonical Hh ligand-induced signaling to activate GLI proteins and Hh target gene expression. TGF-beta can up-regulate GLI1 and GLI2 expression, thereby contributing tumorigenesis. More specifically, the activation of TGF-beta/TGF-R1-ALK5 system results in the nuclear translocation of Smad3-Smad4 complexes that directly interact with the GLI2 promoter and promote the recruitment of beta-catenin. These nuclear factors can up-regulate the GLI2 expression, which in turn induce the transactivation of Hh target genes, including GLI1 [8-10].

MAPK signalling

MAPK pathways regulates proliferation, growth and migration of cells. When the ligand binds the receptor tyrosine kinase like KIT receptor on the cell surface, the kinase-mediated phosphorylation leads activation of the receptor. The phosphorylation of tyrosine residues give way for binding to adapter protein like GRB2, SOS etc, which initiate the signalling cascade that requires GTPase activity of NRAS and relayed to the kinase activities of BRAF, MEK and ERK. Within the nucleus, this results in transcription of genes involved in cellular proliferation, growth and migration [6,7,11-13].

PI3K signalling

Phosphoinositide 3 kinases are enzymes which regulate growth, proliferation, differentiation, motility and survival of cells. They are activated by RTKs and PIP2 is phosphorylated into PIP3 which act as 2nd messenger. This phsphorylate AKT thereby inhibiting apoptosis by further phosphorylating BAD, leading to loosing of its pro-apoptotic function, increasing transcription of genes, enhancing cell survival and accelerating cell growth via mTOR [6,7,11-13].

WNT signalling

WNT signals are involved in cellular differentiation, migration, proliferation and maintenance of stem cells. When the Frizzled/LRP receptor complexes are not bound by ligands, beta-catenin is phosphorylated which is ubiquitinated and destroyed by proteasome. When WNT binds Frizzled/FLR receptor complex, dishevelled (DSH) is activated and inhibit catenin destruction, thereby stabilizing catenin. The beta- catenin, then enter the nucleus and promotes transcription [12,13].

MC1R-MITF signalling

The Melanocortin-1 receptor(MC1R) is a G-protein coupled receptor. It is activated by Melanocortins (ACTH, alpha-MSH etc). MC1R activates adenylate cyclase, thereby increasing cAMP, which activates Protein kinase (PKA), which, in turn, activates cAMP responsive element binding protein(CREB), which is a transcription factor. MITF is also a trancription factor, which is regulated by MAPK and WNT signalling [6,7,11].

JANUS KINASE

Janus kinase (JAK) is a family of intracellular, non receptor tyrosine kinases. It mediates cellular signal called JAK-STAT pathway. JAK1, JAK2 and TYK2 genes have been mapped to chromosomes 1p13.3. Upon binding of ligand to the receptors, JAK kinase activates Src-kinase cascade, Ras-MAP kinase pathway, PI3K-AKT pathway and STAT signaling. Type I and type II cytokine receptor families possess no catalytic kinase activity, so they depend on the JAK family of tyrosine kinases to phosphorylate and activate proteins involved in their signal transduction pathways. Janus kinases phosphorylate activated cytokine receptors which in turn, recruit STAT transcription factors which modulate gene transcription [14,15].

JAK kinases are involved in signaling by interleukins such as IL-2, IL-4, IL-7, IL-9 and IL-15. Erythropoietin activates JAK 2. IL-3, GM-CSF and IL-5 activate JAK 1 and JAK 2. IL-12 stimulation activates. JAK2 and

TYK2 and plays a critical role in IL-12 mediated T-cell differentiation. IL-2 stimulation leads to the activation of JAK3. IL-2, IL-4, IL-7, IL-15 and IL-19 stimulation activate JAK 3. In short, JAK 1 and JAK 2 mediate Th1 response and JAK 3 mediates Th2 response. JAK kinases also mediate the signal transduction in response to stimulation by growth hormone, Prolactin and G-CSF [16,17].

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