Review

An Overview of the Oncogenic Signaling Pathways in Different Types of Cancers

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Abstract: Cancer is a leading cause of death worldwide. It is theorized that underlying genetic and epigenetic changes enable cells to proliferate out of control by escaping regulatory mechanisms. The progression of cancer is associated with increased cell proliferation, metabolic modifications, resistance to apoptosis, genetic instability, induction of angiogenesis and augmented migratory capability. Recent developments in DNA and RNA analysis have made it possible to study these genetic changes systematically. These advances have enabled us to possess a deeper knowledge of the signaling pathways and involved processes. In-depth studies of the pathways involved in carcinogenesis have led to the identification of pathways that may be targeted for therapeutic purposes. In this review, we provide an overview of the relevant mechanisms and pathways involved in the development and progression of cancer.

Keywords: cancer, cell signaling, therapeutic targets, signaling pathways

1. Introduction

Cancer is the 2nd leading cause of death worldwide. It has been theorized that genetic and/or epigenetic modifications are the potential drivers of malignancy [1,2] The process of carcinogenesis is the result of increasing cell proliferation, resistance to apoptosis, genetic instability, induction of angiogenesis, metabolic modifications, and augmented migratory capability [3,4]. The trigger for most of these changes is the dysregulation of cellular signal transduction pathways [5]. Recent progress in DNA sequencing has made it possible to study these genetic changes systematically providing us with a deeper knowledge of the various signaling pathways and involved processes [6,7]. Several experiments have described various signaling components over the past decades that have helped build a molecular structure for the many types of signal transduction pathways [8]. As abovementioned, genetic or epigenetic alterations in tumor cells are the root cause of cancer. Furthermore, the tumor cells develop several well-defined characteristics [3] and in addition to augmented cell proliferation, these include resistance to apoptosis, metabolic changes, induction of angiogenesis, and genetic instability as well as enhanced migratory capacity. Most of these characteristics are based on the dysregulation of cellular signal transduction pathways [9]. In this review, the various pathways involved in many types of cancer are considered to identify all of cancer's tricks and also the roles of main related genes in the cancer pathways are evaluated.

2. Tumorigenesis and signaling pathways

An increasing number of studies have illustrated that numerous tumor suppressor- and proto-oncogenes contribute to tumorigenesis when inactivated or activated by mutations, respectively [10]. It is believed that the cells must acquire certain key properties, sometimes referred to as the signs of cancer, to shape a tumor [3,11,12]. These effective modifications include apoptosis prevention, angiogenesis, limitless potential for replication and invasion. In most cases, biological functions are preserved by one, or many, groups of genes that cooperate in functional pathways. It has been recognized that several signaling pathways contribute to carcinogenesis [13]. Genetic changes in cancer cells regulate signaling pathways that lead to tumorigenesis-related disruption of the control processes. Oncogenic mutations can affect proteins implicated in several signaling pathways, such as Hedgehog (Hh), Wnt and Hippo, which not only are frequently activated in many physiological responses but also in cancer development and invasiveness **[14–17]**. Wnt pathway cross talks with Hh and Hippo pathways, which has implications for theragnostic targets in cancers **[18–20]**. Several pieces of evidence indicate that association therapeutic approaches combining Wnt inhibitors and chemotherapy might enhance tumor shrinkage in several solid neoplasias, holding promise aimed at immune microenvironment targeting too **[21–23]**. Oncogenic mutations may affect downstream nuclear targets of signaling pathways, such as chromatin remodelers (e.g., EZH2), cell cycle effectors (e.g., cyclins), and transcription factors (e.g., NF-κB and Myc) [1]. Additionally, mutations and deletions may inactivate negative regulators that generally function as suppressors of tumors. P53, the so-called 'genome guardian', is one of the most frequently mutated genes in a tumor, resulting in the modulation of cell proliferation and stress signals, including DNA response and apoptosis [24,25]. An example of a mutation of another tumor suppressor that deregulates the cell cycle includes cyclin-dependent kinase inhibitors (CKIs), such as p16. Most of the tumor suppressors function as negative cytoplasmic signaling regulators, for instance, adenomatous polyposis coli protein (APC) is a negative modulator of the Wnt pathway while Phosphatase and tensin homolog (PTEN) is a negative phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-AKT pathway modulator [9]. It is noted that an overactive oncogene pathway could also 'undo' an irreversible cell cycle arrest, known as senescence **[26–28]**. This is a fail-safe mechanism for preventing proliferation triggered by abnormal oncoprotein stimulation in normal cells and is followed by modifications in cell structure, organization of chromatin, cytokine secretion, DNA damage, and gene expression. Oncogenesis requires changes, including loss of p53 or PTEN, which override senescence [26,27]. Another core signaling pathway relevant to tumorigenesis **[29–31]**

includes the Receptor Tyrosine Kinase (RTK)/Ras pathway, with the highest median frequency of changes across all types of cancers. In the RTK pathway, KRAS is the most frequently modified gene, followed by B-Raf proto-oncogene (BRAF) and finally, the epidermal growth factor receptor [32]. Cancers affected by this pathway include (in descending frequency): melanoma, the gnomically-stable subtype of colorectal cancer, HER2-enriched breast cancer, pancreatic cancer, IDH1-wild-type glioma, lung adenocarcinoma and thyroid carcinoma [1]. Despite great promise in the clinical practice **[33–35]**, overcoming target therapy resistance remains an unmet clinical need in the tailored therapy era, due to the underlying acquired mutation [36,37]. In addition, some types of tumors, such as lung cancer, EBV-positive esophagogastric cancer, squamous cell carcinoma, non-hypermutated uterine cancer, show high rates PI3K pathway changes. Another important pathway that is significantly altered in colorectal cancer is the Wnt signaling pathway. In some pathways, the alterations are distributed over many genes (e.g., cell cycle, PI3K), whereas in others, the modifications involve only limited genes (Wnt, Myc, and NRF2) [1]. Aberrations in the PI3K pathway [38] have been primarily noted to be activating events in PI3K catalytic subunit alpha (PIK3CA), less commonly in PI3K catalytic subunit beta (PIK3CB) and inactivating events in PIK3R1 or PTEN, with the most common PIK3CA and palterations occurring in breast cancer, head and neck cancer, gynecological and gastrointestinal tumors [2]. The transforming growth factor β (TGFβ) pathway (personal communication) has the highest rate of alteration in pancreatic and gastrointestinal cancers, whereas renal and brain cancers have almost no alterations in this pathway [3]. The Myc pathway [39] is most commonly modified in chromosome 8 amplified tumor types containing Myc, for instance, ovarian cancer and breast cancer. The role of signal transduction in cancer cell-associated processes is discussed in the next section.

2.1 Cell proliferation

Abnormal cell proliferation is a hallmark of most cancers and involves the modulation of multiple signaling pathways. For instance, Notch signaling can stimulate cell proliferation in T-cell acute lymphoblastic leukemia (T-ALL) via Notch1 signaling mediated hypoxia/HIF-1α [40]. Furthermore, when notch signaling is triggered, subsequently a ligand binds to a Notch receptor, for example, the binding of Jagged-2 (JAG2) to Notch2 upregulates cell proliferation [41]. Notch3 is also associated with tumor cell proliferation [42] and other studies have reported that the Hairy and enhancer of split 1 (Hes1) functions as a sequence-specific transcriptional binding factor involved in cell proliferation [43,44]. The Hh signaling pathway through glioma-associated oncogenes (GLI2) may increase tumor proliferation, suggesting that inactivation of the Hh pathway could significantly reduce the proliferation of SMMC-7721 cell lines in hepatocellular carcinoma (HCC) **[45–47]**. By regulating the mechanistic target of rapamycin complex, I (mTORC1), AKT controls cell growth in the progression of the cell cycle by suppressing tuberous sclerosis complex1-2 (TSC1–TSC2) GAP activity towards Rheb, thus causing mTORC1 to be activated by GTP-bound Rheb. So, phosphorylated eukaryotic translation initiation factor 4F (eIF4)-binding protein, releasing the cap-binding factor eIF4E and permitting these to attach mRNAs, as well as ribosomal S6 kinase (RSK) and ribosomal S6 kinase (p70 RSK). This supports improved protein synthesis, which is vital for cell growth after the development of the cell cycle [48]. AKT also phosphorylates the Glycogen synthase kinase 3 (GSK3), hampering its catalytic activity, whilst the GSK3 targets and phosphorylates cyclin D and Myc [49,50]. Moreover, AKT impairs many inhibitors of the cell cycle, like p21 (CIP1) and cyclin-dependent kinase inhibitors (CKIs) p27 (KIP1), whereas phosphorylation contributes to 14-3-3 proteins sequestration in the cytoplasm. Phosphorylation is often controlled for decay in the situation of p27. AKT mediated phosphorylation of p21 blocks the formation of a complex proliferating nuclear cell antigen (PCNA) to suppress DNA replication, decreases its attachment to cyclin-dependent protein kinases 2/4 (CDK2/CDK4) and decreases its down regulatory function to CDK2 [51]. Moreover, AKT inhibits the forkhead box (FoxO) reliant transcription of cell cycle inhibitors, including RBL2 (retinoblastoma-like protein 2) and p27 [52], thereby stimulating phosphorylation mouse double minute 2 homolog (MDM2) [53], the ubiquitin ligase, prompts p53

degradation, thus triggering a main cell cycle brake. AKT could also control multiple enzymes engaged in the G2/M transformation later in the cell cycle [54]. In some cases, consequent inhibition and phosphorylation of GSK3 through AKT can put an end to nuclear translocation and stabilization of the Wnt target β-catenin [55,56], a transcriptional regulator, the deterioration of which, would be introduced by GSK3 [56,57]. This results in the induction of β-catenin target genes that control proliferation, such as those encoding cyclin D and Myc. Moreover, AKT can immediately phosphorylate β-catenin, which causes its dissociation from cadherin cell-cell adhesion complexes, thereby improving the β-catenin pool and transcription function [58]. Several signaling pathways could promote cancer cell proliferation. For instance, cytokine and RTK signaling activate Signal Transducer and Activator of Transcription 3 (STAT3), which also activates the synthesis of Myc and cyclin D [59] and also, transcription factor NF-κB which activate the expression of cyclin D. Several of these signals induce cyclin E in Estrogen signaling [9], which stimulate cell proliferation through the activation of the estrogen receptors subtypes alpha (ERα) subtype and this also stimulates Myc and cyclin D. Disruption of the ERα-ERβ balance or ERa mutations that produce truncated or activated proteins could dysregulate the above mechanism **[60–63]**. It is noted that both Ras-ERK and PI3K-AKT signaling improve signals from ERs and the androgen receptor (AR) [64,65]. The role of tumor suppressors is obviously critical that usually keep proliferative signals. Farthest downstream, pRB usually directly inhibits the E2F protein transcription activity until it is deactivated by CDKs through phosphorylation. P53, on the other hand, usually blocks cell proliferation by inhibiting CDK activity and by inducing CKIs in reaction to stress signals, such as DNA damage. Mutations in this tumor suppressor, thus, deregulate the proliferation of cells under hazardous circumstances that promote cancer. The CKIs themselves inhibit CDKs directly and in several cancers are also inactivated by mutation, the most prevalent example being p16. Upstream genes are pathway-specific tumor suppressors, such as APC and Ras-GAP NF1, which inactivate Wnt/β-catenin signaling by enhancing GSK3 phosphorylation and thus, the destruction of β-catenin by ubiquitin. In each case, tumor suppressor mutation removes a significant brake that allows the cells to proliferate regardless of the signals that would usually restrict them. The Hippo signaling pathway plays a pivotal role in controlling proliferation contact inhibition [66] and suppressing the transcriptional Yes-associated protein (YAP) co-activator as a major tumor suppressor system in many cancers [67]. Myc, which is phosphorylated by ERK, is a significant destination of the Ras-ERK pathway, which results in its stability by suppressing ubiquitylation [50]. Myc stimulates cell proliferation by regulating various cell proliferation proteins, including those encoding CDKs, G1/S cyclins and the cell cycle-driven E2F family transcriptional factors [68], as shown in Figure 1.
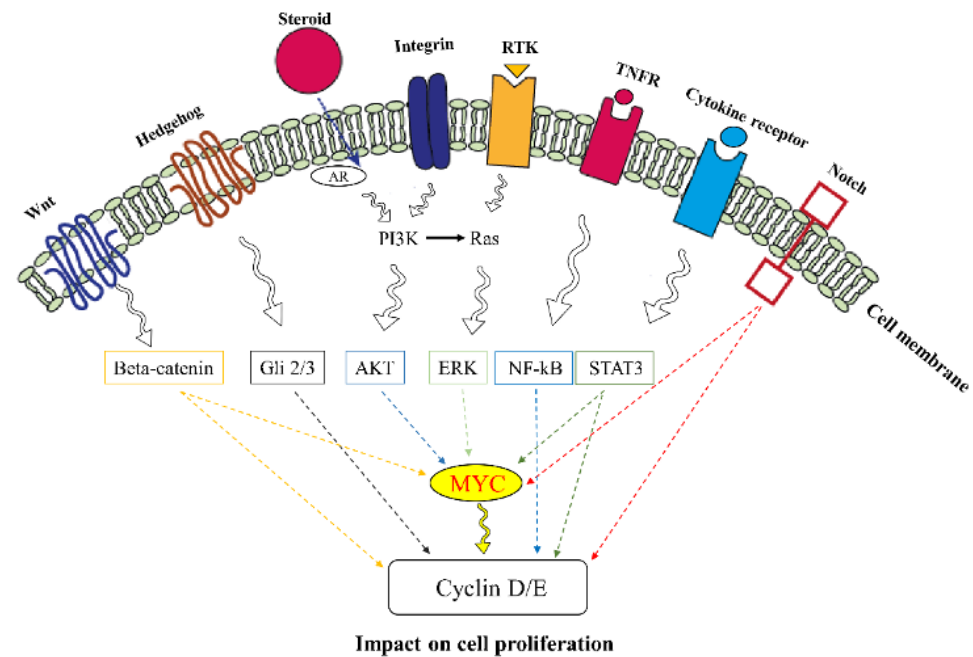
Figure 1. Signaling pathway and cell proliferation

2.2 Cell survival

Cell death performs as a homeostatic mechanism that usually regulates their number, but mutations can significantly disable cell death signals for cancer. For instance, Notch signaling can encourage cell survival through communication between Jagged-2 (JAG2) ligand and receptor Notch2 in cancer [69]. Moreover, studies have indicated that the Ras-ERK and PI3K-AKT pathways also control cell death in many aspects [70]. AKT itself interferes with the apoptotic signaling of mortality receptors at several stages. It phosphorylates forkhead-family transcription factors, including FoxO3A, which results in their cytoplasmic sequestration by 14-3-3 proteins. This stops the induction of proapoptotic B cell lymphoma 2 (Bcl2)-family member Bim and death ligands [e.g., Fas ligand (FasL) and TRAIL]. Also, ERK and AKT-regulated kinase RSK phosphorylate the Bcl2-family proapoptotic protein Bad, another target for 14-3-3 protein sequestration. Furthermore, AKT phosphorylates and stimulates the X-linked inhibitor-of-apoptosis protein apoptosis inhibitor (XIAP) [66]. AKT also activates NF-κB, which controls antiapoptotic enzymes (Bcl2, BCLxl, and Mcl1) and the FLIP inhibitor intracellular mortality receptor [71]. Furthermore, the ubiquitylation and degradation of p53 initiated by AKT repress apoptosis induced by p53 [53]. ERK phosphorylates Bim and the degradation targeting NF-κB inhibitor IκBα [72]. Additionally, RSK phosphorylates the caspase-9 scaffolding protein APAF, which inhibits the capacity of cytochrome c to nucleate apoptosome development and stimulates downstream apoptosis-driven caspases [73] (Figure 2).
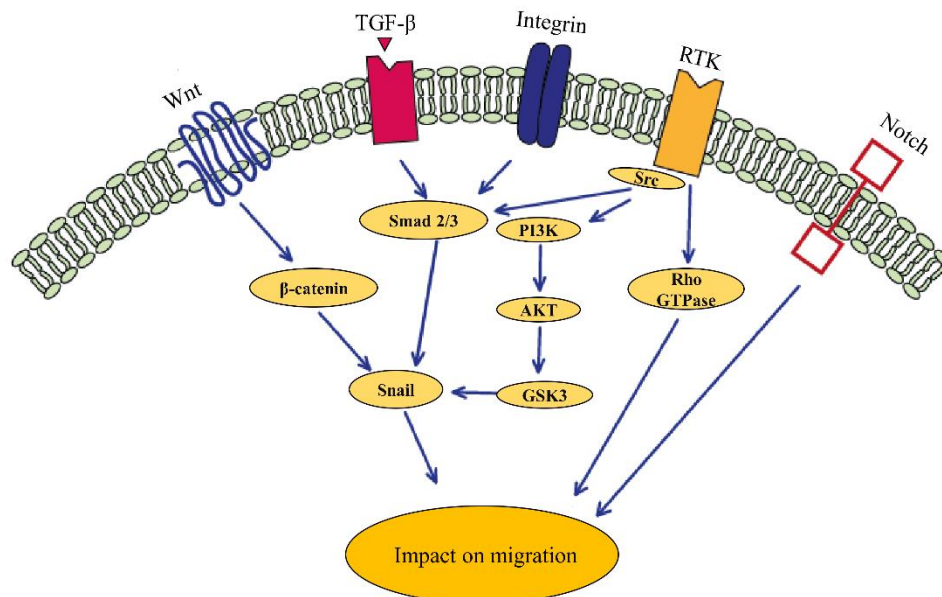
Figure 2. Signaling pathway and cell survival

2.3 Cell metabolism

Cancer-related mutations can contribute to increased metabolites in cancer cells [74], for instance, Isocitrate dehydrogenase 1 (IDH1) and Isocitrate dehydrogenase 2 (IDH2) mutations. This results in the production of 2-hydroxyglutarate (2HG), a metabolite that is not found in normal cells at high levels. 2HG inhibits α-ketoglutarate-dependent enzymes, including the DNA methylation-controlled TET family and histone demethylases of the Jumonji-C domain. This causes epigenetic dysregulation that can lead to tumorigenesis. Additionally, suppression of tumor suppressors and activation of oncogenes can control parts of normal metabolic pathways effectively, producing similar metabolic changes. The PI3K-AKT pathway, for instance, uses multiple substrates to support these alterations in metabolism [51,75]. AKT regulates the transport of glucose and hexokinase, which promotes glycolysis, resulting in the production of the nucleotides and amino acids necessary for development [76]. AKT2 mediates the transport of glucose by means of several processes, which is important for the circulation of homeostasis of glucose [77]. AKT2 also regulates transcription, accumulation [78,79] and Glucose transporter 1 (GLUT1) traffic, the main glucose transporter in most cells [80]. mTORC1 signaling causes the enhanced synthesis of the hypoxia-inducible transcription factor (HIF1), which promotes lactate dehydrogenase (LDH-A) and glycolytic enzymes to upregulate glycolysis. It also triggers pyruvate dehydrogenase protein (PDK), which deactivates pyruvate dehydrogenase (PDH) in the mitochondrion and thus, decreases glycolysis flux into the Krebs cycle [81,82]. Akt/mTORC1 enhances lipid synthesis by triggering the sterol-response-element-binding protein 1 transcription factor (SREBP), a main lipid synthesis modulator critical for tumorigenicity **[83–85]**. Loss of SREBP uncouples stearoyl-CoAdesaturase-1-mediated desaturation fatty acid synthase activity. Another target of AKT is ATP-citrate lyase (ACL), an enzyme vital to fatty acid, cholesterol, and isoprenoid synthesis for converting citric acid into Acetyl-CoA. mTORC1 also regulates the absorption of amino acids through promoting their translocation from intracellular vesicles to plasma membranes [86,87]. Ras-ERK signaling effects on many of metabolic impacts through Myc, which roles in glucose uptake, glycolysis and the pentose phosphate cycle [88] stimulating glutamine transporter production and glutaminase enzyme (GLS) that transforms glutamine to glutamate which can be metabolized in mitochondria [89,90]. Interestingly, in cancer cells is the glycolytic enzyme pyruvate kinase. Despite

the rate of glycolysis is generally higher than in non-cancer cells, many generate an alternative type of pyruvate kinase (PKM2), which is less effective than PKM1 [91]. PKM1 continues to be functional under most physiological circumstances; however, PKM2 could be switched off by signaling through tyrosine kinases, such as Ras-ERK and PI3K-AKT RTKs [92]. Consequently, cancer cells can redirect the glycolytic intermediates flux into anabolic pathways for the production of glutathione and NADPH required to reduce oxidative stress for ribose, serine, and glycine. PKM2 could also enter the nucleus and contribute to gene expression [93][94]. Other cancer silencers not only regulate the metabolism of the cells but also, loss of p53 may lead to cancer cell glycolytic phenotype. P53 often controls glutaminase 2, a metabolic enzyme that regulates the output of glutamate transformed into mitochondrial respiratory α-ketoglutarate and most importantly, glutathione, a critical cellular antioxidant. [95]. Loss of p53 contributes to higher oxidative damage and ROS concentrations. P53 also regulates the mevalonate pathway, which in turn, regulates the synthesis of cholesterol and produces the required intermediate protein geranylgeranylation and farnesylation [96] (Figure 3).
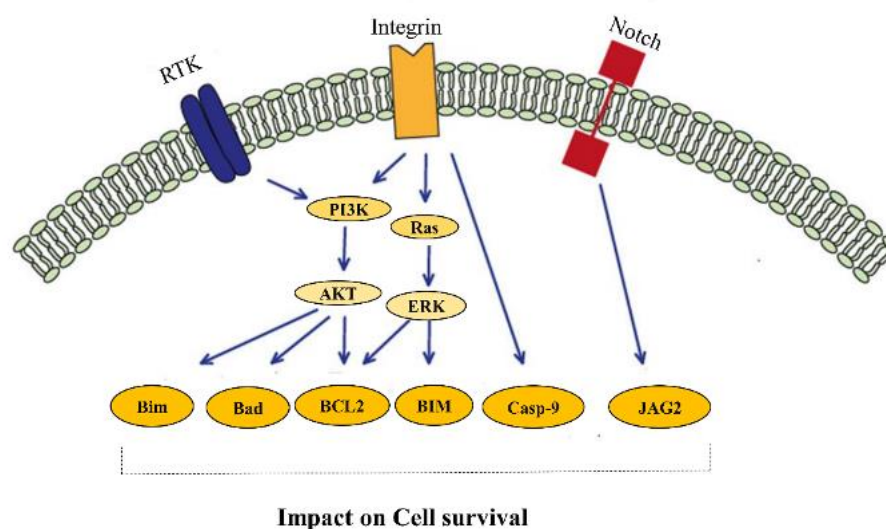

Figure 3. Signaling pathway and cell metabolism

2.4 Cell migration

Migration is regulated by adhesion receptors, chemokines, growth factors, and other stimulators [97,98], most of which are dysregulated in cancer signaling. The result of changes in these pathways is extremely contextual and isoform dependent, as with other procedures controlled by oncoprotein signaling. For instance, AKT1 explicitly represses migration by inhibiting ERK, the transcription factor NFAT, TSC2 or actin bundling induced by phosphopalladin, whilst AKT2 enhances migration by regulating integrin activity and also regulates epithelial-mesenchymal transition (EMT) [99]. It should be noted that EMT is not crucial for the dissemination of infection and tumor cells. EMT is associated with several physiological processes, such as wound regeneration, gastrulation and morphogenesis splitting [100]. This type of development is regulated by various highly organized processes, including TNF, Notch, Wnt, TGFβ and a number of growth factors **[101–103]**. EMT is characterized by the decrease of E-cadherin cell-cell adhesion molecules, which drives tumor progression [104,105], loss of apical-basal polarity, anchorage independence in some contexts, the adoption of a more fibroblast-like appearance and the acquisition of stem or progenitor-cell phenotypes as well. These would augment the capacity of the cell to invade other tissues and trigger tumors at distant sites. In certain circumstances, it is stipulated that the PI3K-AKT and Ras-ERK

pathways promote EMT when hyperactivated in conjunction with other pathways involved in (e.g., Notch, Wnt, and TGFβ signaling) [106]. Several transcription factors, such as Slug, Snail, ZEB, and Twist play pivotal roles in enhancing EMT, which are modulated by AKT and ERK. For instance, AKT could phosphorylate IκB kinases that control NF-κB, which is a transcription factor that stimulates Snail. Also, GSK3 is phosphorylated and inactivated by AKT, which increases Snail ubiquitin-dependent degradation [107], whilst activation of AKT stimulates Snail, further enhancing EMT. Furthermore, HNRNP E1, which is a protein that stimulates translational elongation on transcripts promoting EMT is phosphorylated by AKT2 [108]. In addition to other gene expression programs that regulate phenotypic modifications connected with EMT, AP1, which is modulated by the Ras-ERK pathway, can stimulate transcription factors that enhance EMT. RAS represents a pivotal pro-tumorigenic, but to date scanty effective approaches were clinically successful [109]. This includes the stimulation of E cadherin, fibronectin, vimentin, integrin heterodimers [e.g., aVb6 and a5b1], cytokeratin down-regulation polarity proteins (e.g., LGL, PATJ, and Crumbs), all of which the promote cell motility. Of particular interest, by inhibiting ERK (which stimulates ZEB1), the polarity protein Scribble retains cell-cell ties [110,111]. In addition, notch signaling could promote tumor migration through Notch3 activation [43]. Ultimately, aberrant regulation of both and PI3K-AKT and Ras-ERK, thus, has the ability to play a significant function in development of cancer, as shown in Figure 4.
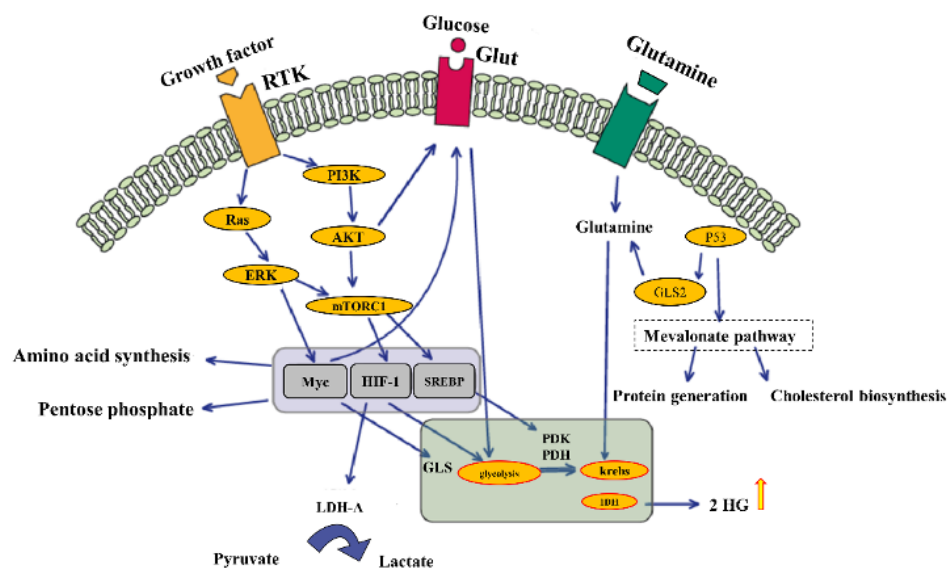

Figure 4. Signaling pathway and cell migration.

2.5 Cell polarity

Polarity proteins are essential for maintaining tissue architecture. Three complexes of proteins possess key functions in polarity control: the complex of Scribble, Par and Crumbs. Dysregulation of these processes is found in tumors, where aberrant expression of PI3K-AKT and Ras-ERK signaling pathways are involved. For instance, by functioning as a scaffold to link it to the protein phosphatase PP1G, Scribble inhibits ERK activity [111,112]. Loss of Scribble stimulates H-Ras activation, [113] whilst Ras and Myc stimulate tumor formation [114]. Moreover, loss of the Par3 polarity protein contributes to enhanced accumulation of several cell designs [115,116] through various mechanisms, including JAK/STAT3 signaling PKC-dependent activation. This stimulates a metalloproteinase, MMP9 expression with the consequent death of ECM, enhanced activation of Rac and invasion, resulting in reduced cell-cell adhesion **[116–118]**.

2.6 Cell differentiation

In the several cancers that disrupt the equilibrium between cell differentiation and proliferation, for example, in acute promyelocytic cancer, myeloblasts are decreased to differentiate into mature erythrocytes due to a translocation that creates a protein fusion component called PML and a receptor of retinoic acid [119]. The PML-RAR fusion protein inhibits and targets RAR genes that generally trigger differentiation, therefore blocking the RAR signal. Additional mutations then cause the over proliferation of undifferentiated myeloblasts [109]. Similarly, in colon crypts, Wnt/β-catenin signaling [120] usually keeps enterocytes in an undifferentiated state in colon cancer, but these are blocked by β-catenin degradation caused by APC as cells migrate up to the luminous intestine surface. However, the APC tumor suppressor mutation implies that β-catenin is not demolished and can retain cells in an undifferentiated state as they die. Developmental signals may also enhance the development of cancer since they promote the proliferation of cells. For instance, mutations that trigger notch leading to acute lymphocytic leukemia [121] can promote the cell cycle and also suppress T cell apoptosis. Remarkably, notch functions in some other tissues as a tumor suppressor [122], illustrating the significance of this signaling pathway. Hh signaling pathway activation [46,123] through mutations in the patched receptor occurs in medulloblastomas and basal cell carcinomas, thereby promoting cell proliferation. Hh signaling is upregulated in several malignancies through autocrine loops that influence embryonic gut tissues. As the signaling mechanisms of PI3K-AKT and Ras-ERK are triggered by fibroblast growth factor [FGF that performs a significant role in controlling cell fate], IGF and EGF and they can be regarded as behavioral signaling mechanisms. For instance, FGF4/8 signaling stimulates the Ras-ERK pathway to promote EMT and multiple cancers recapitulate this pathway throughout gastrulation [124]. Furthermore, the background is crucial. That is, whilst FGF signaling might influence angiogenesis [see below] as well as cell growth, migration, and apoptosis [see above], it may also have tumor repressive effects, retaining cells in a distinguished, non-proliferative state. The expression of FGFR2 is decreased in prostate and bladder cancer, while its expression is increased in gastric cancers [2]. In addition, notch signaling could affect cellular differentiation through Hes1 [43,44] and glioma-associated oncogenes (Gli2). The Hh signaling pathway can also promote tumor differentiation [69,125].

3. Cancer and Extracellular matrix [ECM] signaling

The ECM is a scaffold that supports tissues and provides a cell migration and adhesion substrate along with a bioactive molecules source. It is constantly being renovated away from a static framework and its conformation plays a pivotal role in controlling the behavior of the cell. Collagen, laminin, and fibronectin several other elements of the ECM act as ligands that trigger the development of the integrin. ECM signaling results in the activation of canonical processes, including PI3K-AKT and Ras-ERK signaling, in addition to other proteins, such as tyrosine kinase FAK. This is a scaffold that connects integrins with cytoskeletal proteins, adapters, and enzymes, which transmit signals from complex matrix adhesion. Also, FAK controls p53 and microRNA family members, which regulate apoptosis and the epithelial phenotype [126].

3.1 Integrins and tumorigenesis

Integrins are heterodimeric receptors of the cell surface that mediate ECM interactions and play a major role in the tumor microenvironment. Transmembrane structures in the cytoskeleton, specifically connect to both α and β subunits in both solid [127,128] and haematological cancers [129]. Integrins are present on virtually all the surfaces of nucleated cells, thus being active in tumor cells and stromal cells and recent thorough assessments of integrin functions in tumor progression have been conducted [130,131]. Cancer-associated fibroblasts (CAFs) are the major producers that promote tumorigenic characteristics by initiating the remodeling of the ECM in the tumor, which

triggers the survival, migration, and proliferation of the tumor cells. Also, the ECM functions as a reservoir of cytokines and growth factors that contribute to the bidirectional communication of tumor cells and stoma [132,133]. Recent studies have also illustrated the correlation between CAF and ECM in the regulation of the metastatic niche and chemoresistance [134]. Cancer associated fibroblasts broadly infiltrate tumor stroma, comprising two different cellular populations (PMID: 15549095), namely cells ancillary to ephitelium and cells with myofibroblastic differentiation, whose phenotype is characterized by alpha-SMA expression and exert a direct modulation to cancer proliferative potential, tumoral angiogenesis and disseminative potential and aggressiveness, in both solid [135,136] and hematological malignancies [137,138].

3.2 Collagen-binding integrins

The α1 and α2 integrin chains have also been delineated in dermal myofibroblasts, but there is limited data on their CAF activity [139,140]. These chains are generally dispersed and may also be found in cancer cells, immune cells and vascular tissue **[141–143]**. In collagen gels, it has been shown that α11-mediated features that synergize through TGFβ depend on JNK signals [144]. Studies have shown a significant function for α11 in the endogenous stroma in cancer metastasis and development [145]. As α11β1 is limited to mesenchymally shaped fibroblasts, α11 may be a component of a gene pattern causing, the incursion of metastasizing neurons of breast cancer [146]. Moreover, it was illustrated that the siRNA knockdown of α11 decreases the invasion of cancer cells, as seen in Figure 5.
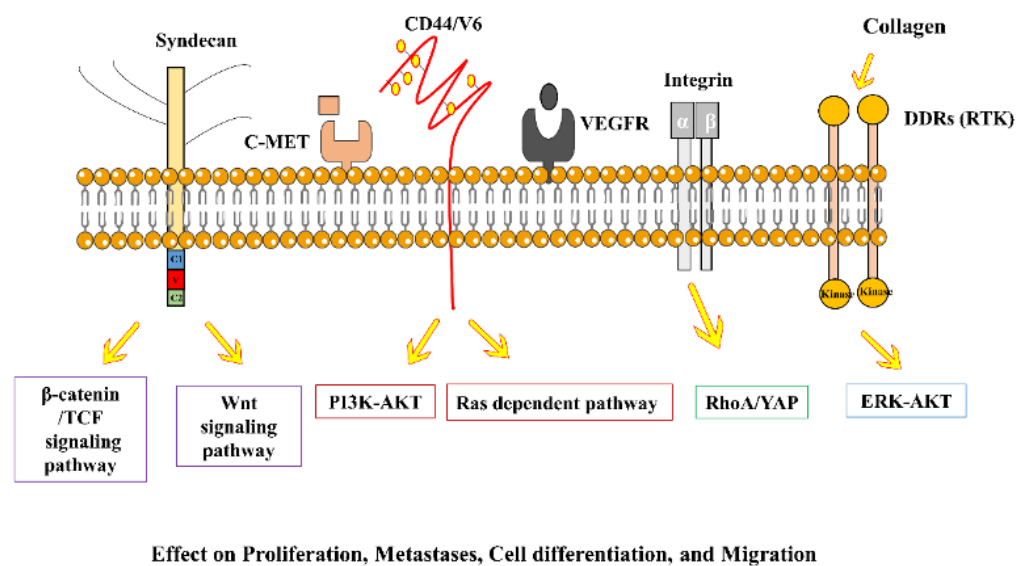

Figure 5. Extracellular matrix [ECM] and cancer signaling

3.3 EDA+ fibronectin-binding integrins

Extra domain A-containing (EDA+) fibronectin, functions as a biomarker of activated fibroblasts in cancer stroma, scar regeneration and fibrosis [147,148]. Many receptors have been suggested for the addition of EDA+ fibronectin in fibroblasts, such as α4β1 and α9β1, which bind at a cryptic site [149]. TGFβ triggered myofibroblast differentiation was shown to require EDA+ Fibronectin [150].

3.4 Integrin function and CAF differentiation

Regardless of the stroma role, fibroblasts are most frequently activated in tumor stroma. Fibroblasts are differentiated into myofibroblasts characterized by α-SMA and EDA+ fibronectin expression [133,147]. Two processes for the differentiation of progenitors into myofibroblasts are of major importance: cell contraction followed by a reorganization of the ECM and TGFβ signaling [151].

3.5 CAF integrins and tumor cell proliferation

Two other main loops maintain the activated state of CAFs, other paracrine processes influencing tumor cells or stem angiogenesis. For instance, tumor-secreted bidirectional PDGF-CC, which attracts PDGF αR-positive fibroblasts, thus influencing the production of FGF-7 and FGF-2 by CAFs, which plays a role in cell angiogenesis [152].

3.6 CAF integrins and tumor stiffness

The role of matrix stiffness may possibly be to modulate the activation of TGFβ on CAFs. It is probable that the latter has a fundamental role in the activation of the former in the tumor stroma. Accumulating evidence has demonstrated how a stiff matrix sensitizes the TGFβ-LAP complex for activation [153,154].

3.7 Integrin function in CAF-promoted metastasis and invasion

In vivo research has indicated that integrins on contractile CAFs are an incorporated component of matrix tunneling, thereby clearing the path for tumor cells to be invaded [155,156]. This method is accompanied by tissue, tumor and stage-specific induction of various MMPs [155,157,158].

3.8 Discoidin domain receptors

 Discoidin domain receptors (DDRs) are the tyrosine kinases receptors [RTKs] that their function is to bind to various collagens and MMP [159,160]. In this RTK class, there are two strongly associated receptors: DDR1 and DDR2 [161]. The DDRs also regulate basic procedures at the cellular stage, such as cell differentiation, proliferation, migration, and survival, typically controlled through RTKs. They also lead to the remodeling of ECM by regulating cell metalloproteinases' expression and function [160,162,163].

3.8.1 DDRs and cancer

Several malignancies are defined by dysregulation or activity of one or more RTKs, which their dysregulated activity could promote the development of cancer. Thus, it is not unusual that cancer has changed the activity of DDRs. Dysregulated DDR signaling is believed to lead to a broad spectrum of cancers being malignant, including solid tumors and blood cancers, such as the brain, head, and neck, lung, prostate, breast, ovarian, head and neck, kidney, pancreatic cancer, lymphoma and leukemia [162]. As several separate functions have emerged, the role that is played by DDRs in malignancy is probably multifaceted. For example, DDR1 can regulate tissue migration, metastasis, and chemoresistance [162,164,165]. Correspondingly, DDR2 is essential for the promotion of metastasis [166] and may be an oncogenic trigger in pulmonary disease [167].

3.9 Cell surface proteoglycans

Studies have indicated that proteoglycans comprise a core protein that is covalently connected to one or more glycosaminoglycan chains. Only a small number of types of glycosaminoglycans have been identified in mammals, such as keratan sulfate (KS), hyaluronan (HA), heparan sulfate (HS) and chondroitin sulfate (CS) with closely-related dermatan phosphate (DS) [168]. HA is not sulfated or connected to a core protein and can be cross-linked with ECM proteins [157]. It is recognized as an important ECM component for tumor biology [169], as indicated in Fig5.

3.9.1 The classes of cell surface proteoglycans

There are two main types of cell surface proteoglycan, namely, syndecans and glypicans, both of which have a history of evolution. Syndecans are connected via a phospholipid anchor [170,171] to the cell membrane and also, ECM macromolecules with heparin-binding characteristics have been

discovered in all types of matrices. In wound repair processes, glycoproteins, like fibringen and fibronectin, the Von Willebrand factor, is critical and may be obtained from the circulation [172]. Others, including thrombospondins, tenascins, and CTGF/Cyr61/NOV (CCN) genes, such as matricellular proteins, are also produced in disease or response to tissue harm, such as tumors [173,174]. The processes require engagement and integration of RTKs with continuous ERK1,2 signaling [175]. This motif is prevalent in other proteoglycans on the cell surface, such as CD44 and syndecans. The enhanced manifestation of CSPG4 (with upregulated collagen VI) in individuals with soft tissue sarcoma is considered a prognostic factor [176].

3.9.2 CD44-specific signaling

CD44 has drawn much attention in tumor biology because tumor progression is strongly linked with the manifestation of some splice variants[32]. The version CD44v6 may function as a co-receptor by a receptor of the c-Met or vascular endothelial growth factor, where the ligand of the hepatocyte growth factor binds to both receptors [177]. In these examples, downstream signaling is complicated, incorporating Ras-dependent signals for preservation and opposition to apoptosis and Rac-1, which could enhance invasion and migration as well as actin cytoskeletal organization [178]. In reaction to the ECM relationships [179], the CD44v6 isoform can also detect the PI3K/AKT mechanism. CD44 is also of great importance as a cancer stem cell indicator in breast, prostate, pancreatic and colon cancer [180].

3.9.3 Syndecans and cancer

Even though there is little evidence that syndecans mutations play a key role in tumor progression, several trials have revealed changes in syndecan activity in solid and blood cancers [181,182]. However, it is uncertain whether expressed syndecans have a critical role in tumor progression participants or are bystanders. Moreover, syndecan-1 activation has been correlated to tumor development and malignancy in myeloma [183,184]. In research regarding a mammalian carcinogenesis model of the mouse, it was elucidated that syndecan-1 is necessary for Wnt1 to promote tumor formation [185], which seems to be associated with β-catenin/TCF signaling [185].

4. Angiogenesis

Like all tissues, tumor cells require a blood flow. By creating fresh blood vessels [angiogenesis] through the growth and incorporation of endothelial cells, they acquire co-opting procedures that frequently operate in wound healing. Signals for angiogenesis include angiopoietin, interleukin (IL) 8, FGF, VEGF, and PDGF. PI3K-AKT signaling pathway regulates angiogenesis induction and stabilization of the vessel [119], with potential multifaced therapeutic windows in a broad spectrum of malignancies [186,187]. In addition, HIF1 stimulates the synthesis and secretion of VEGF in cancer cells. PI3K-AKT signaling increases HIF1 intensity and hyperactivation is also a significant element of angiogenesis. The HIF1 function is regulated by the Von Hippel–Lindau (VHL) core, an E3 ligase element that stimulates its ubiquitin-dependent degradation under normoxic conditions. VHL acts as a cancer suppressor and a diversity of tumors is involved in inactivating its genes. The PI3K-AKT pathway also regulates other angiogenic factors, like angiopoietins and nitric acid. The structure of unusual blood vessels has been shown to cause constitutive endothelial stimulation of AKT1. VEGF is sequestered in the ECM after its secretion and cannot exert its impact on endothelial cells until released by MMP9. These are secreted by macrophages and monocytes in the microenvironment of the tumor, thus highlighting the significance of immune cells in angiogenesis and the presence of a broader signaling network involving cancer cells. For angiogenesis to occur, thrombospondin 1 (Tsp1) is another variable that must be inhibited [188]. Angiogenesis is also orchestrated by bone marrow derived cellular population. In the last years, bone marrow niche emerged as a major determinant of tumor angiogenesis, representing a major source of several cytotypes **[189–191]**. Macrophages, neutrophils, mast cells, myeloid-lineage derived precursors actively participate in

cancer-related inflammation, by providing a nursing environment orchestrated by the innate immunity, resulting in dynamic interaction with the angiogenic process within the tumor microenvironment. Additionally, several cell types cooperate in preventing the antiangiogenic drug activity on the endothelium [192]. Furthermore, a plethora of bone marrow-derived progenitors migrate within the cancer milieu actively participating in the neovascular wall, assuming endothelial or perycitic differentiation and functions **[193–195]**, and modulating immune response[196,197].

5. Inflammation

Inflammatory cells can secrete FGF and EGF, which are essential to PI3K-AKT and Ras-ERK signaling regulators in cancer cells. They also generate colony-stimulating factor 1 (CSF1), a key signal that induces macrophages to secrete more EGF. VEGF and MMPs are also produced by immune cells that stimulate angiogenesis [198]. Furthermore, in both tumor-associated inflammatory cells and cancer cells, signaling via the transcription factor NF-κB [199] is essential, because it can support cell proliferation and growth, thus promoting cytokine production, like TNF. In some lymphoid malignancies, oncogenic diseases influence NF-κB or downstream effecters, like MALT1 and Bcl10. Moreover, in most tumors, cytokine activation usually increases NF-κB production. For instance, macrophage-produced TNF in colon cancer increases NF-κB production in intestinal epithelial cells, thereby promoting tumor preservation. Meanwhile, other cytokines, including IL-6 and IL-11, enhance concentrations of phospho-STAT3 [59], thus promoting cell proliferation. A similar process occurs in HCC and prostate cancer [200]. Activation of NF-kB also contributes to more TNF and prostaglandin E2 synthesis, which then promotes cell proliferation and cell polarity.

6. Conclusion

There seems to be no doubt that the knowledge and experience of cell signaling in cancers have significantly improved over the last 20 years. Furthermore, the cross-talk is known about in terms of how it could influence the treatment options and therapeutic combinations and contribute to drug resistance in the near future. Much more awareness of intracellular signaling networks and also cross-discussion among pathways and extracellular is needed if this approach is to continue to thrive in the coming decades.

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