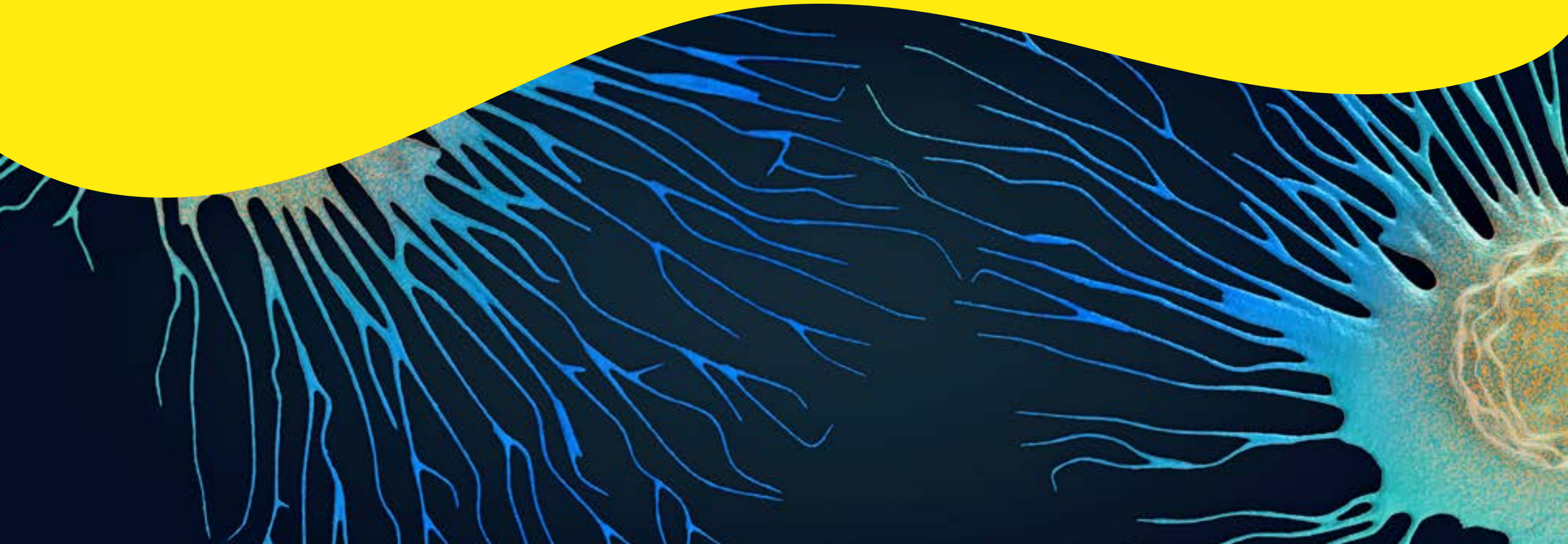
Oncology guide

Cellular signaling processes involved in cancer development and progression



INTRODUCTION

Purpose and scope

Molecular drivers of cancer pathogenesis

Cancer progression is associated with the interplay between tumor cells and the surrounding environment, which requires signal transduction pathways to relay messages throughout the cell.[1,2] Cell signaling pathways regulate everything from cell growth to proliferation to survival. PI3K/AKT/mTOR and Ras/MAPK are examples of the main pathways that are interconnected and mediate signals from receptor tyrosine kinases (RTKs) to intracellular effector proteins and cell cycle regulators.[3] The growth of breast, ovarian, and prostate cancers depend on the proliferative signal induced by their hormones since they express hormonal receptors.[4] Many of these pathways are altered in cancer and contribute to cancer progression.[3]

Genetic or epigenetic alterations in tumor cells are often the underlying cause of cancer. Genetic alterations to cellular genes may be inherited or arise spontaneously because of DNA damage from an environmental carcinogen or mutation from replication errors.[1] Many common genetic lesions in cancer involve signaling proteins. These mutations can either activate genes or result in loss of function. Hyperactivation of these pathways drives tumorigenesis and supports tumor growth.[2] Signaling pathway proteins that are commonly activated by physiological responses include growth factor receptor (e.g. EGFR), small GTPases (e.g. Ras), serine/threonine kinases (e.g. Raf and Akt), cytoplasmic tyrosine kinases (e.g. Src and Abl), lipid kinases (e.g. phosphoinositide 3-kinases, PI3Ks), as well as nuclear receptors (e.g. the estrogen receptor). The components of developmental signaling pathways such as Wnt, Hedgehog, Hippo, and Notch can also be altered. Finally, downstream nuclear targets of signaling pathways like the transcription factors Myc and NF-κB, chromatin remodelers, and cell cycle effectors are also commonly altered. Many of the genes commonly mutated encode components or targets of the PI3K/AKT and Ras/ERK pathways, causing dysregulation of cellular signaling.[1]

This dysregulation drives cancer progression by influencing the behavior of tumor cells through cell proliferation, survival, migration, differentiation, metabolism, polarity, angiogenesis, and the tumor microenvironment.

Why this guide?

Cancer is a complex entity and regardless of cancer type, there are frequently observed cellular changes involved in tumorigenesis, tumor growth, and metastasis. Decoding these cellular changes and correlating to molecular pathways are key to novel discoveries that will help develop the next generation of cancer treatments. This guide highlights a selection of the key events and pathways that are dysregulated and lead to pathogenesis. Discover scientific background and illustrations covering cellular changes associated with many of the hallmarks of cancer.

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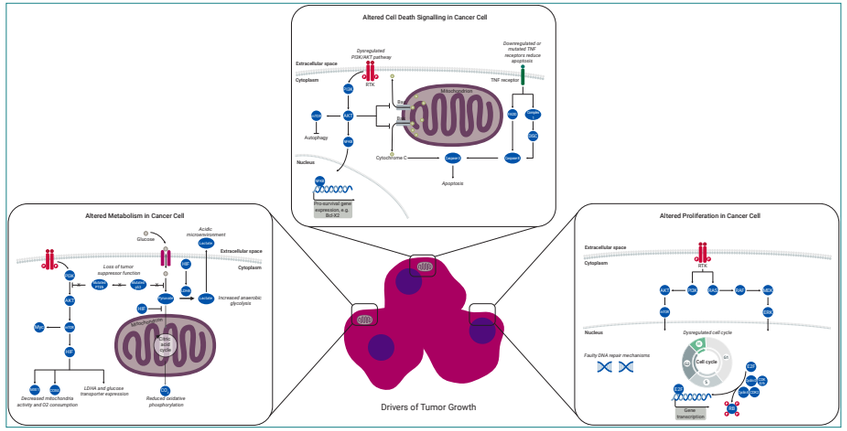
DRIVERS OF TUMORIGENESIS AND TUMOR GROWTH

Introduction

The initiation and development of cancer is driven by a disruption in the balance of multiple cellular processes. In cancer cells, mutations in genes that control the cell cycle lead to errors in division, suppression, and death. Whether it's the disruption of defective cell clearing or an imbalance between self-renewal and differentiation, mutations within these processes that drive the modification of proteins and their associated signaling pathways can ultimately result in tumorigenesis. As cell proliferation increases, there are also associated metabolic changes that result in increased glucose uptake and lactate production that further promote tumor growth. Much research goes into elucidating basic biological processes that drive the early stages of cancer and its growth, with early-stage treatment being the best course of action for a patient. Identifying inhibitors that can mitigate the various imbalances within some of the key processes highlighted in this guide is an ongoing focus of oncology drug discovery.



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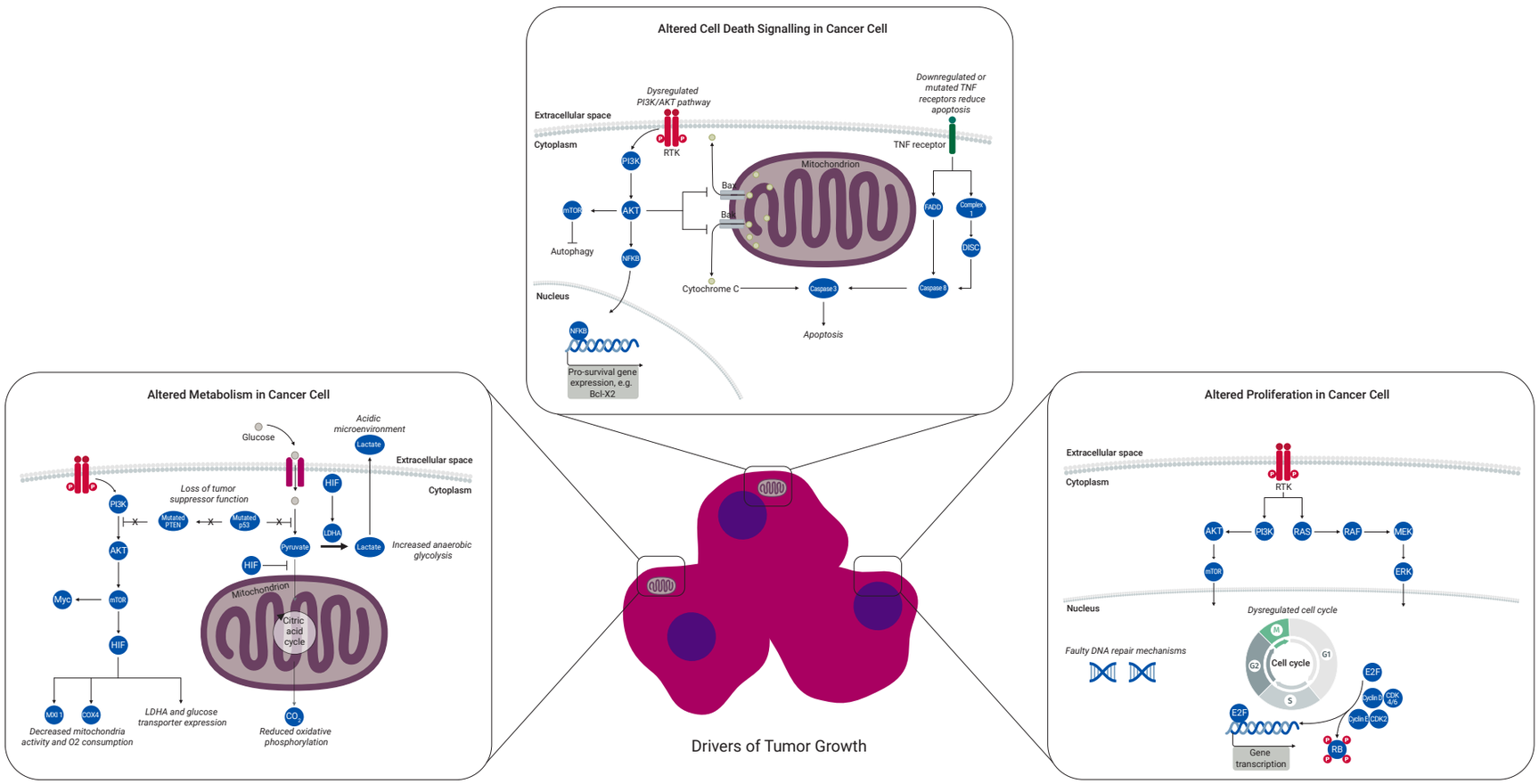

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Cell proliferation

Genes control the cell division process and regulate a balance between promoting cell proliferation, suppressing it, and inducing cellular death (apoptosis). In cancer, mutations lead to a disruption of this balance that results in unchecked cell growth. This results in unchecked cell growth.[1] The cause of cancer cell overgrowth is complex and often involves many different genes in different types of cancer.[2]

Normal cell growth is tightly regulated in a series of coordinated events that take place during the cell division cycle. In response to signals from growth factors (mitogens), chromosomes are replicated once in the S phase and segregated to create two genetically identical daughter cells in the mitosis or M phase. Growth and reorganization phases (G1 and G2) separate the S and M phase. Cells can enter the G_0 phase, or phase of quiescence where they stop cycling after division.[3]

Two types of cell cycle control mechanisms regulate the cell cycle. One is a cascade of protein phosphorylation events that relay a cell from one stage to the next. Protein phosphorylation involves protein kinases, which associate with a second subunit (cyclin) that is transiently expressed at the appropriate period of the cell cycle. The cyclin subunit associates with a cyclin-dependent kinase (CDK) to create an active complex. Regulatory phosphorylation and dephosphorylation controls the CDK-cyclin complex. The cyclins and CDK-cyclin complexes phosphorylate healthy proteins and move them into the next phase.[3] CDKs 1-6 associate with the cell cycle phases, while CDKs 7-11 regulate RNA transcription.[4] Growth signals trigger the growth phase and retinoblastoma (Rb) protein phosphorylation. The Ink4 family induces G1 phase arrest and inhibits CDK4 or CDK6 or the Cip/Kip family, suppressing CDK2 activity.[2]

The second cell cycle control mechanism is a set of checkpoints that monitor event completion and delay progression to the next stage if necessary. Specific checkpoints detect mistakes in DNA replication and chromosome segregation and signal a delay in cycle progression until the mutation danger has passed.[3]

Cancer cells ignore all regulatory signals and freely circulate through the cell division cycle, even in the absence of growth signals due to mutations present in the regulatory genes. Normally, RB phosphorylation is triggered by growth signals, but in some cancer cells, pRB brakes are defective, which results in E2F-dependent G1-S expression. Other common mutations present in cancer cell genes often include those found in mitogenic signaling pathways like HER2/ErbB2/Neu receptors, and downstream signaling pathways like Ras-Raf-MAPK or PI3K-Akt. In addition, the cell cycle-regulation genes/proteins such as cyclin and CDK proteins are often dysregulated in cancer cells.[4,2]

In normal cells, specific cell cycle checkpoints detect DNA damage, which is then repaired by the DNA damage response. The DNA damage response includes lesion detection, temporary cell cycle arrest, and DNA damage repair.[5] The cell cycle checkpoints allow for the cell cycle machinery to coordinate biochemical pathways that respond to damaged DNA. Checkpoint control mechanisms arrest the cell replication phases of the cell cycle and allow for DNA damage repair. Loss of these checkpoints and failure of DNA repair due to mutations in the cell cycle machinery can lead to cancer phenotypes.[6]

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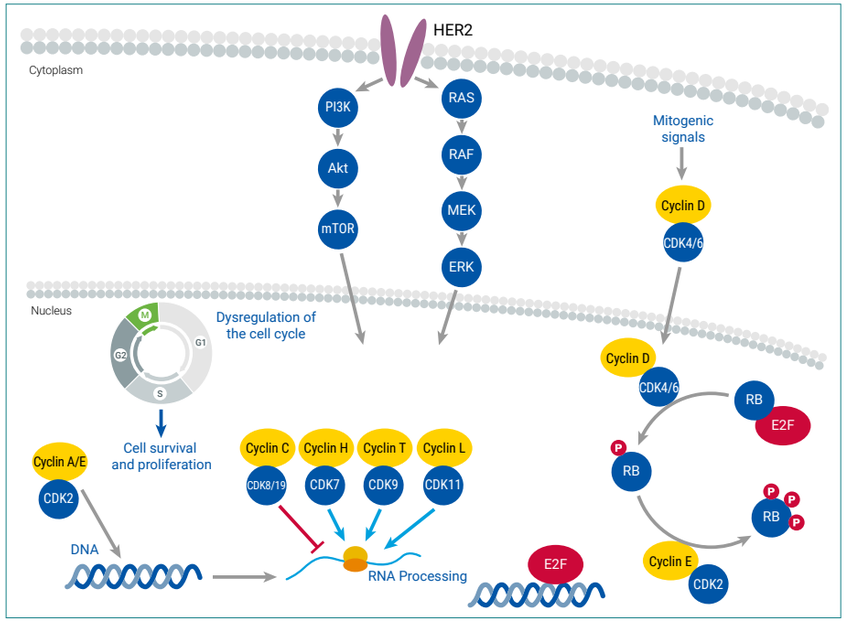
Cancer can develop as a result of defective DNA repair machinery. The DNA repair machinery mends genome modifications that occur as a result of deletions, translocations, loss of heterozygosity, and amplifications in the DNA. After DNA damage and depending on the type of damage, the following DNA repair pathways are recruited: nucleotide excision repair, base excision repair, mismatch repair, or DNA double strand break repair. Defects in any of these repair genes and pathways cause mutations to accumulate. For example, ineffective topoisomerase I and topoisomerase II promote DNA aberrations during replication where DNA strands break. As the mutation frequency increases, the amount of DNA damage increases and DNA repair enzymes decrease.[7] Thus, any loss in the DNA repair genes leads to genomic instability and drives tumor development.[8]



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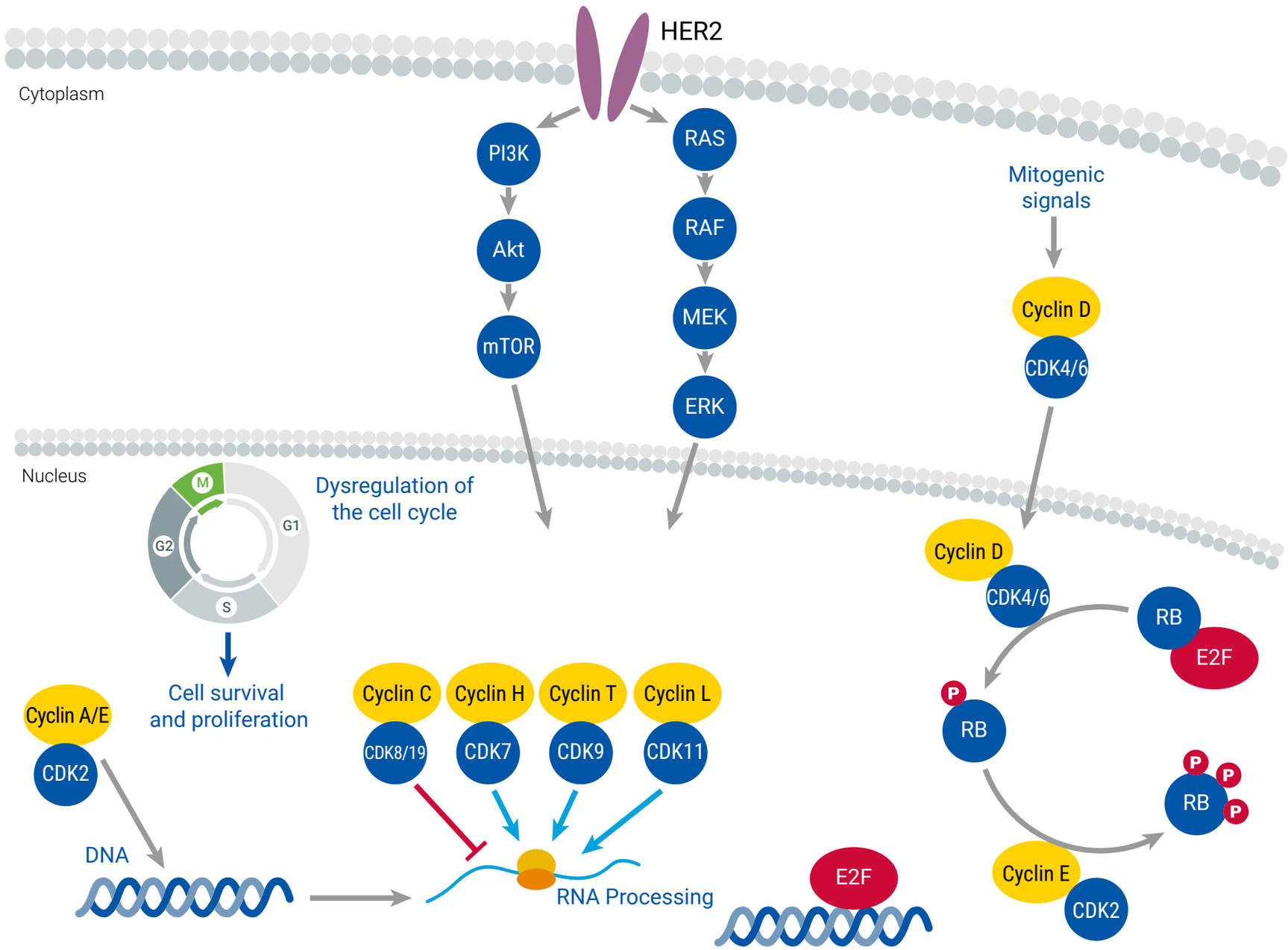

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Cell survival

A balance between cell survival and death is crucial for multicellular organism survival. Organisms must eliminate damaged or infected cells to avoid interference with normal functions. Imbalances in this process can lead to uncontrolled cell growth and cancer development.

Apoptosis is a genetically programmed mechanism that results in cell death and removal of damaged cells. An anti-apoptotic cell phenotype is a hallmark characteristic for cells to become cancerous.[1] Apoptotic pathways are activated by death receptors on the cell surface, growth factor signal loss, or in response to lethal stimuli from inside the cell.[2]

Apoptotic pathways are extrinsic or intrinsic. The TP53 gene encodes p53, a tumor suppressor that activates both the extrinsic and intrinsic apoptotic pathways.[3] A sub-group of Tumor Necrosis Factor (TNF) receptors that include TNFR, Fas, and TRAIL mediate the extrinsic pathway. Activation of these receptors allows for recruitment and activation of caspases 8 and 10, which then forms and activates complexes such as the death inducing signaling complex (DISC). The complex then activates the effector caspase, caspase 3, which cleaves the death substrates that lead to apoptosis.[1] Upon ligand binding to the Fas receptor, FADD is recruited and caspase 8 is activated, triggering apoptosis execution. The FLIP protein inhibits FADD by binding to it and rendering it ineffective.[4] The intrinsic pathway involves the mitochondria and is initiated by stress. Upon stress initiation, the proteins of the Bcl-2 family, Bax and Bak, are activated and initiate cytochrome c release from the mitochondria. Cytochrome c release activates caspase 3, which then leads to apoptosis. Other pro-apoptotic proteins released by the mitochondria include Smac/Diablo (Second Mitochondrial derived activator of Caspase/ Direct IAP- Binding protein with a low pI) and the serine protease Omi/HtrA2.[1]

The PI3K/AKT pathway is indicated in tumor development and progression.[5] Mutations that occur in oncogenes and tumor suppressor genes lead to the dysregulation of the PI3K/AKT pathway, which promotes AKT interference with cell death signaling pathways. Receptor tyrosine kinases (RTK) are activated upon binding of epidermal growth factor I (EFG), fibroblast growth factor receptor (FGF), and insulin-like growth factor (IGF) to its N-terminal extracellular domain.[6] Upon binding of a ligand to RTK, tyrosine kinase phosphorylation is triggered and activates PI3K. Activated PI3K recruits AKT by phosphorylating the protein. Activated AKT inactivates proteins like Bax and Bad. AKT also activates NF-kB, resulting in transcription of pro-survival genes like Bcl-XL (B-cell lymphoma-extra-large).[5]

Evidence suggests that cancer also involves mechanisms of apoptosis resistance and that some cancers result from the lack of cell death. The p53 protein is commonly mutated in human cancers, which disturbs the levels of apoptosis regulation. In addition, the Fas receptor is downregulated in hepatomas. Further, altered TNF family receptors are identified in some cancers and FLIP is overexpressed in carcinomas. Bcl-2 is overexpressed in a variety of cancers, including multiple myeloma, acute lymphocytic leukemia, and chronic lymphocytic leukemia. Thus, pro-apoptotic receptors in cancer are targets of some therapies.[5]

Autophagy is another important cellular degradation pathway essential to cellular homeostasis. While apoptosis prevents cancer cell survival, autophagy removes oncogenic molecules and prevents cancer cell survival. Autophagy is divided into 5 stages: initiation, autophagosome nucleation, autophagosome membrane expansion and elongation, closure and fusion with the lysosome, and intravesicular product degradation.

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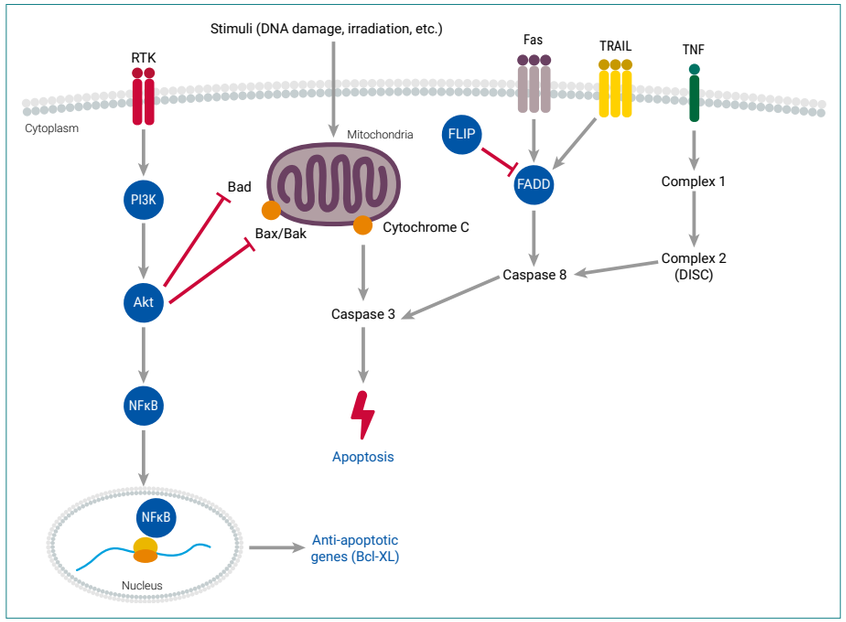
Initiation involves inactivation of mTOR in response to autophagy signals. PI3K/AKT/mTOR signaling controls autophagy, since mTOR activation inhibits the process. Subsequently, the Unc-51-like kinase 1 (ULK-1) complex is activated. This complex stimulates autophagosome nucleation by activating the class III P13K complex. This induces phagophore formation through production of PI3P and association with WIPI protein family members. During elongation, ATG12-ATG5-ATG16L1 and ATG4B-ATG7-ATG3 work together to activate LC3 into LC3I, lipidation with PE to form LC3II, and anchoring to the phagophore. LC3 and GABARAP mediate the collection of autophagic substrates before closure. Fusion of the lysosome occurs through the interaction between STX17 and VAMP8. During intravesicular product degradation, acidic lysosomal hydrolases degrade the substrates collected, generating nutrients that are then released to the cytoplasm and reused by the cell. Evidence suggests that autophagy and apoptosis are closely interconnected, since some proteins have dual roles in both processes. Autophagy facilitates apoptosis by degrading a negative regulator of Fas and modifies levels of Bcl-2. [7,8] Moreover, autophagy can be tumor-promoting or tumor-inhibiting. Tumors are exposed to stressful conditions and autophagy acts as a regulator of tumor promotion by helping them overcome these stresses. The process supplies nutrients to meet the metabolic demands of tumors, thus increasing cell survival, tumor growth, and oncogenesis. Autophagy is also a regulator of tumor suppression by offering protective effects for the cell and reducing the amount of damaged cellular parts and proteins, which maintains cellular homeostasis. Thus, an impaired autophagy process can lead to oncogenesis.[9]



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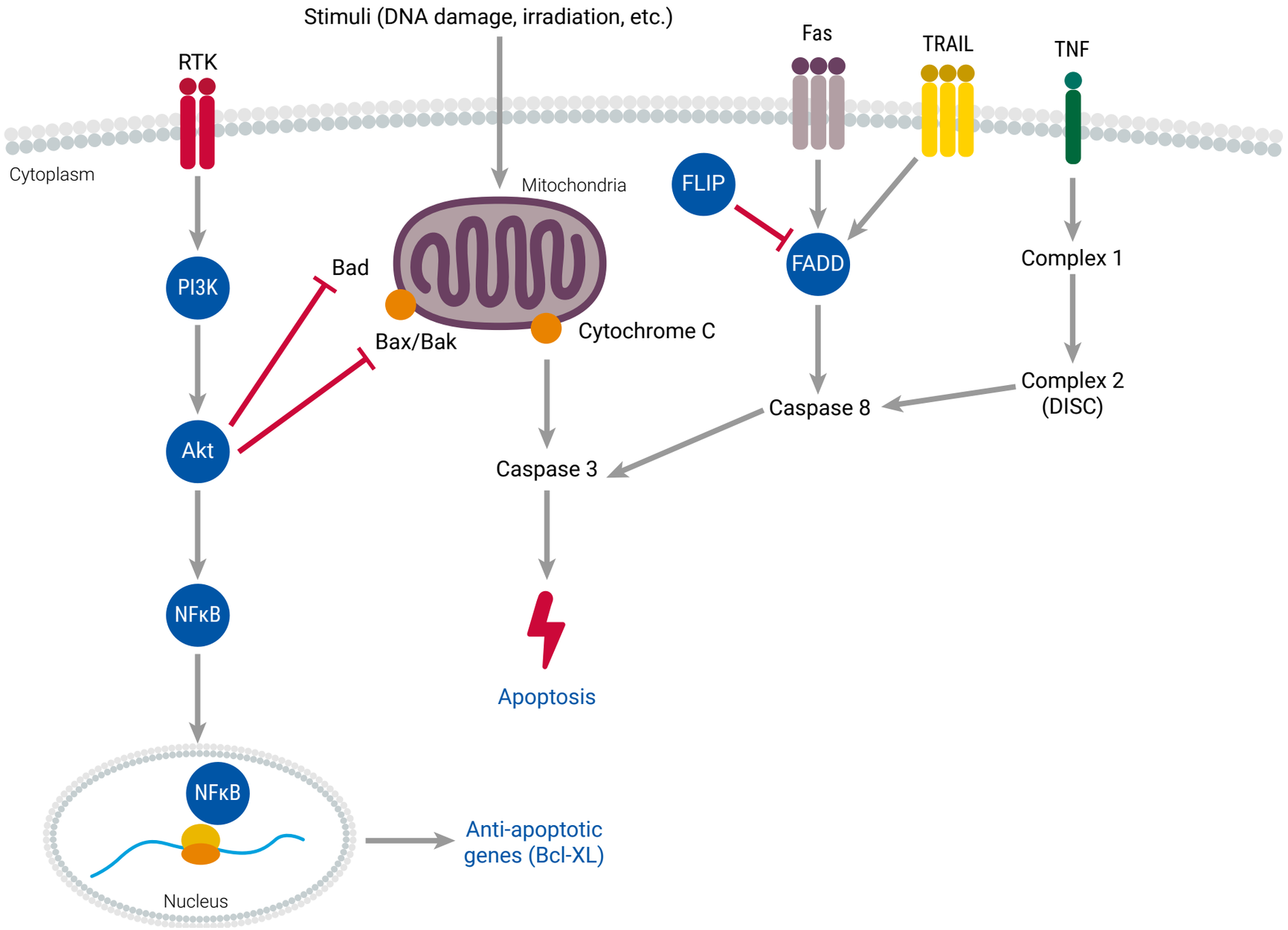

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Metabolism

Cancer cells alter metabolism to promote growth, survival, proliferation, and long-term maintenance by increasing glucose uptake and fermenting glucose to lactate. Glucose metabolism is essential for cells to generate energy. In a normal cell with optimal oxygen levels, full glucose oxidation occurs via respiration in the mitochondria. Glycolysis converts glucose into pyruvate that enters the mitochondria where it is oxidized by the citric acid cycle to generate ATP and CO_2. Tumors and other actively dividing cells switch from oxidative phosphorylation to aerobic glycolysis where glucose uptake increases and lactate is produced, even in the presence of oxygen and a functioning mitochondria. This process is also known as the Warburg Effect.[1] Pathways such as phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) and hypoxia-inducible factor-1 (HIF-1) are glycolysis regulators.[2] The Warburg Effect results from HIF-1 upregulation, oncogene (cMyc, Ras) activation, tumor suppressor (mutant-p53, mutant-phosphatase and tensin homolog deleted from chromosome 10 [PTEN]) loss of function, or P13K/Akt/mTOR activation.[3]

The P13K/Akt/mTOR pathway is commonly activated in cancers in response to glucose metabolism. When activated, receptor tyrosine kinases (RTK) lead to phosphorylation of the binding sites that recruit PI3K and Ras to the plasma membrane. Upon activation of PI3K, Akt is recruited and activated. mTOR is then activated and stimulates growth-related protein Myc translation and increases HIF transcriptional activity. Normally, the tumor suppressor p53 regulates PTEN, which down-regulates the PI3K pathway. Mutations in these genes in cancer cells cause loss-of-function. p53 also down-regulates glycolysis and enhances mitochondrial oxidative phosphorylation in normal cells. Loss of these tumor suppressors in cancer cells results in activating growth-promoting mechanisms.[4]

Key processes required for the Warburg effect are modulated by HIF-1 activation.[4] The expression of glucose transporters and activation of glycolytic enzymes are enhanced by HIF-1. HIF-1 also prevents the citric acid cycle and oxidative phosphorylation process by activating pyruvate dehydrogenase kinase 1 (PDK1), which prevents pyruvate dehydrogenase (PDH) from converting pyruvate into acetyl-CoA and limits entry of pyruvate into the citric acid cycle. Additionally, HIF-1 activates max interactor 1 (MXI 1) and cytochrome c oxidase subunit 4 (COX4). This results in a decrease in mitochondrial activities and oxygen consumption. Finally, HIF-1 stimulates lactate dehydrogenase (LDHA) expression, which results in an increase in lactate production.[5]

Additional lactate produced as a result of the Warburg effect reduces pH levels and creates an acidic microenvironment. This microenvironment can enhance tumor invasion and metastasis, while also increasing ionizing radiation resistance. Thus, the Warburg effect is another method in which cancer cells use cellular stress to progress.[6]

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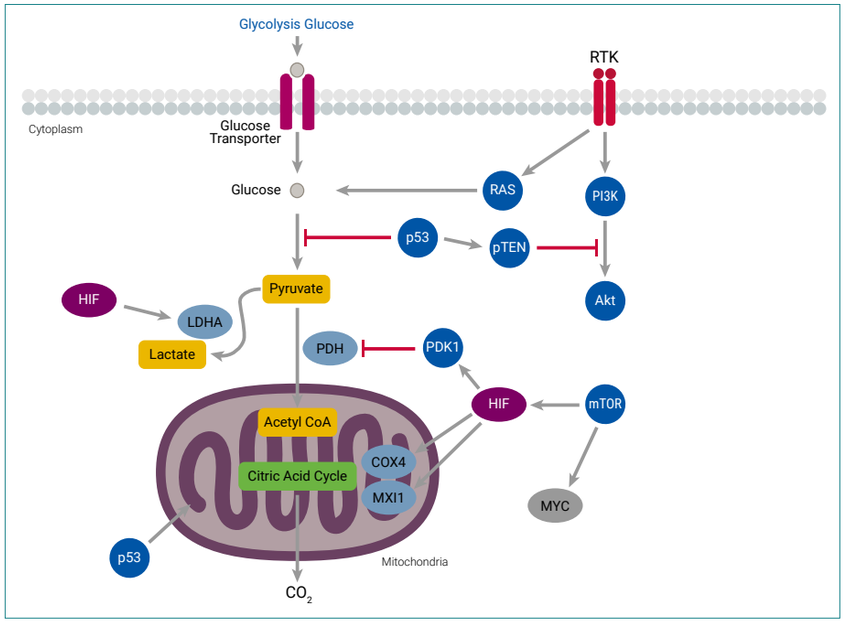

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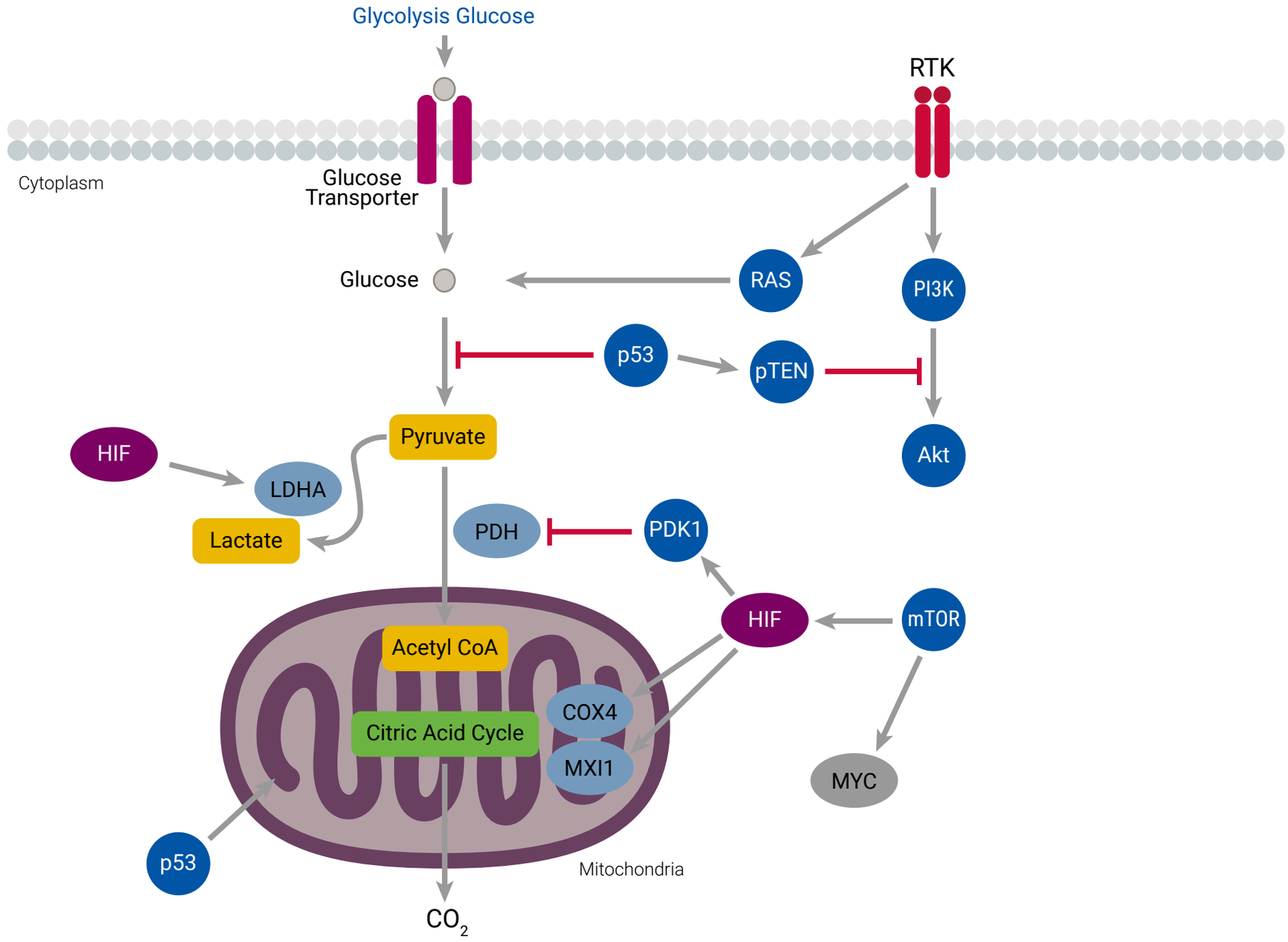

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Cell differentiation

Stem cells have the ability to self-renew or maintain a stem cell population and differentiate into specialized cells, depending on responses to signals. A normal cell has the ability to maintain a balance between self-renewal and differentiation. Cellular differentiation involves alterations in gene expression that depend on chromatin changes, which are accomplished with chromatin-remodeling enzymes. These enzymes regulate differentiation through cell-type-specific and gene-specific roles. Chromatin-remodeling enzymes either use ATP hydrolysis to change DNA contacts or covalently modify histone proteins. ATP-dependent chromatin-remodeling enzymes regulate the balance between proliferation and differentiation. Chromatin remodeling is linked to other cellular processes during differentiation, recombination, genome organization, and the cell cycle.[1,2]

ATP-dependent chromatin-remodeling enzymes are a part of the SNF2 family of DNA-dependent ATPases. The classes of ATP-dependent chromatin-remodeling enzymes include the SWI/SNF, imitation SWI (ISWI), and chromodomain and helicase-like domain (CHD) families. The SWI/SNF protein complexes can include either the ATPase brahma (BRM)- or brahma-like 1 (BRG1)-containing enzyme, which binds to the bromodomain. The complex binds to acetylated (Ac) histones. The SWI/SNF complex is involved in embryonic and extraembryonic lineage segregation during preimplantation development. During this stage, the SWI/SNF-BRG1 complex maintains chromatin accessibility at STAT-3 binding targets by preventing PcG-mediated expression.[1] This enhances leukemia inhibitory factor (LIF) signaling, which is involved in cell differentiation. LIF binding to its receptor activates Janus kinases (JAKs), phosphorylating receptor docking sites and recruiting proteins like signal transducer and activator of transcription 3 (STAT3).[3] LIF binding initiates the transcription of differentiation, self-renewal, and survival genes.[1] The SWI/SNF complex also prevents Polycomb complex (PRC2), a transcription repressor, from binding. This allows for transcription to occur.[4]

Approximately 25% of all cancers have mutations in one or more of the genes encoding the SWI/SNF chromatin-remodeling complexes. At least 9 different genes encoding the SWI/SNF subunits can be mutated in cancer.[5] Many gene mutations in the SWI/SNF complex are loss-of-function mutations. Inactivating SWI/SNF subunits through mutations or deletions cause defective complex assembly and failure to oppose PRC1/2, resulting in an imbalance between differentiation and self-renewal. This imbalance impairs differentiation and allows expansion of progenitor cells and tumorigenesis.[6] Mutation of a gene encoding SWI/SNF complex subunit components allows for the formation of a residual complex that is dependent on other subunits and necessary for cancer growth.[7] The SWI/SNF complex is also involved in cell cycle regulation and cellular invasion in vivo.[8] As discussed in the cell proliferation section, the cell cycle is disrupted in some cancers. Thus, SWI/SNF regulation is also affected in these cases.

Chromatin remodelers make DNA accessible for transcription factors and basal transcription machinery. The SWI/SNF complex remodels chromatin so genes can be activated or repressed, depending on the interaction between a variety of transcription factors and other chromatin modifiers. It is essential for maintaining correct nucleosome positions and any alterations or disruptions in SWI/SNF function can result in incorrect transcription factor binding, leading to atypical gene expression patterns. Thus, mutations in or inactivation of chromatin remodelers can lead to an imbalance between self-renewal and differentiation, leading to expansion of progenitor cells and tumorigenesis.[2,6]

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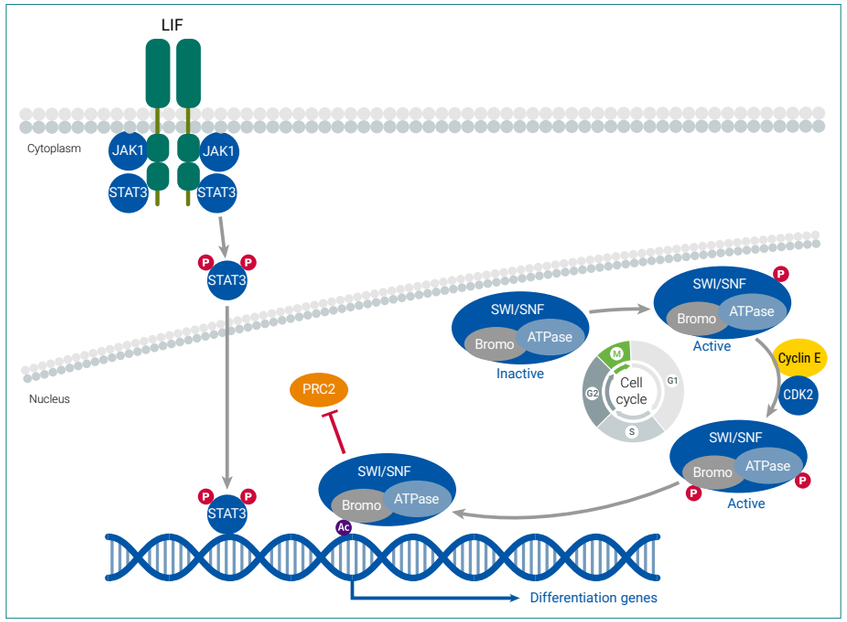

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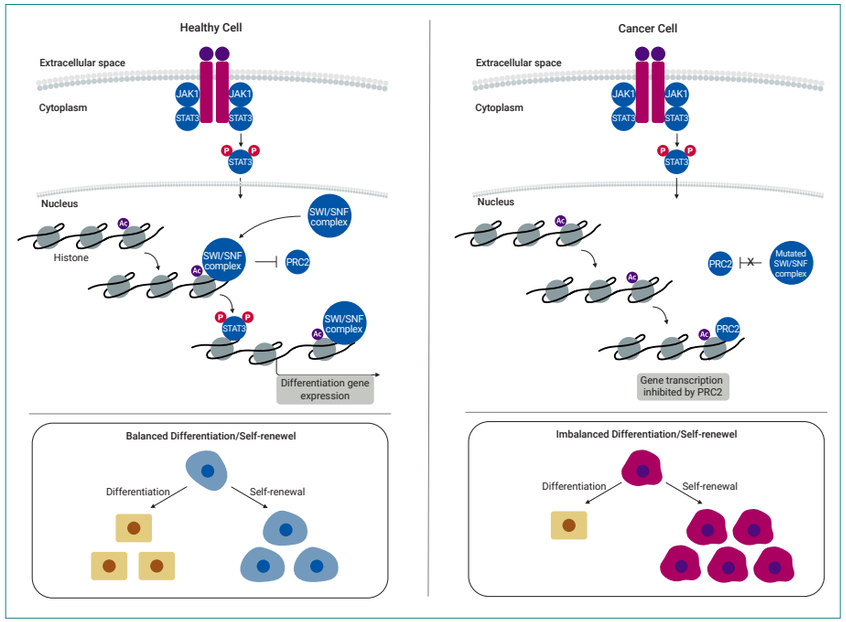

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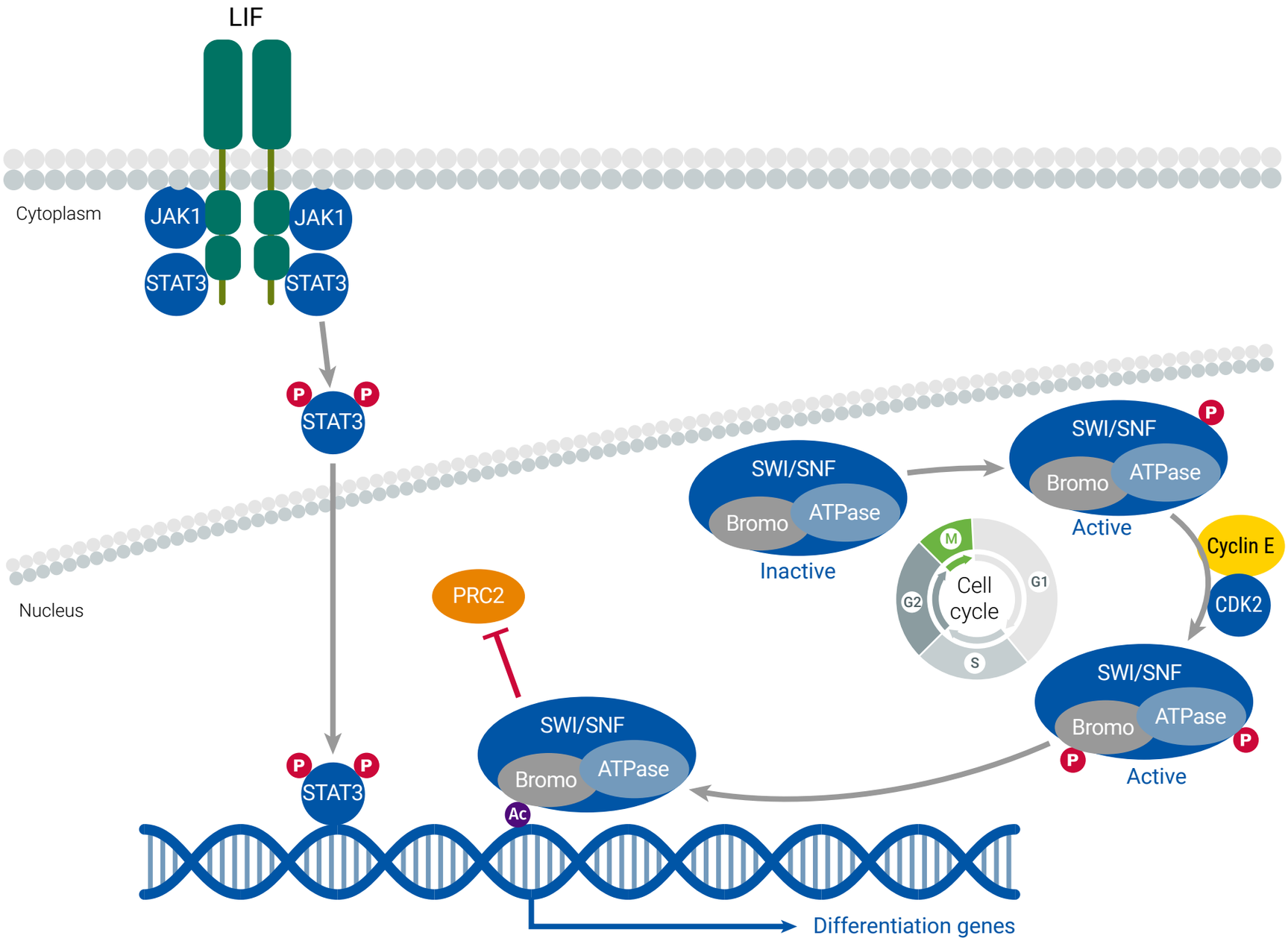

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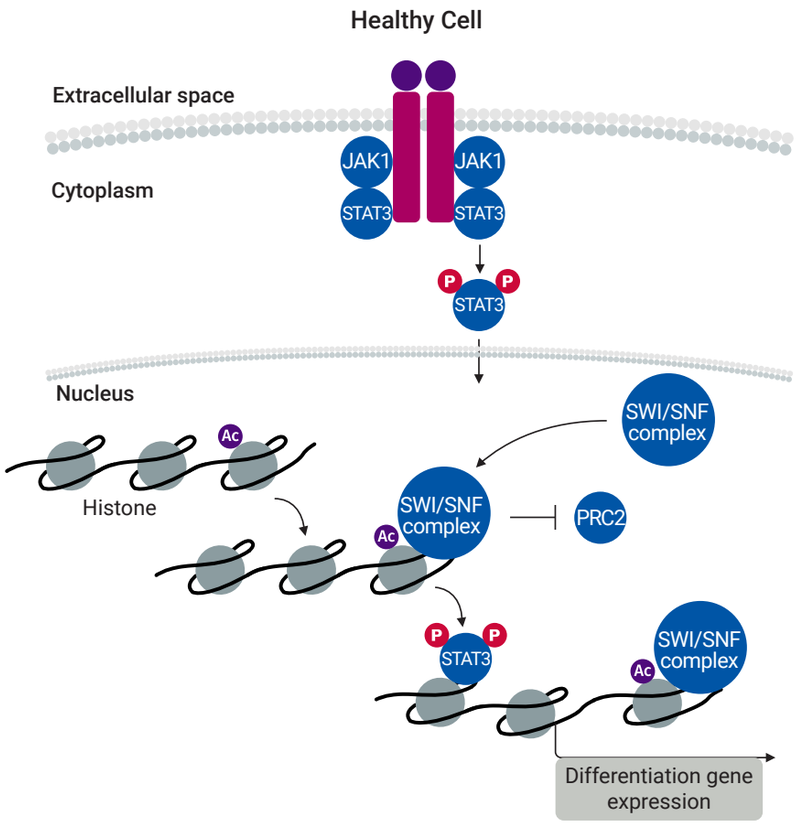

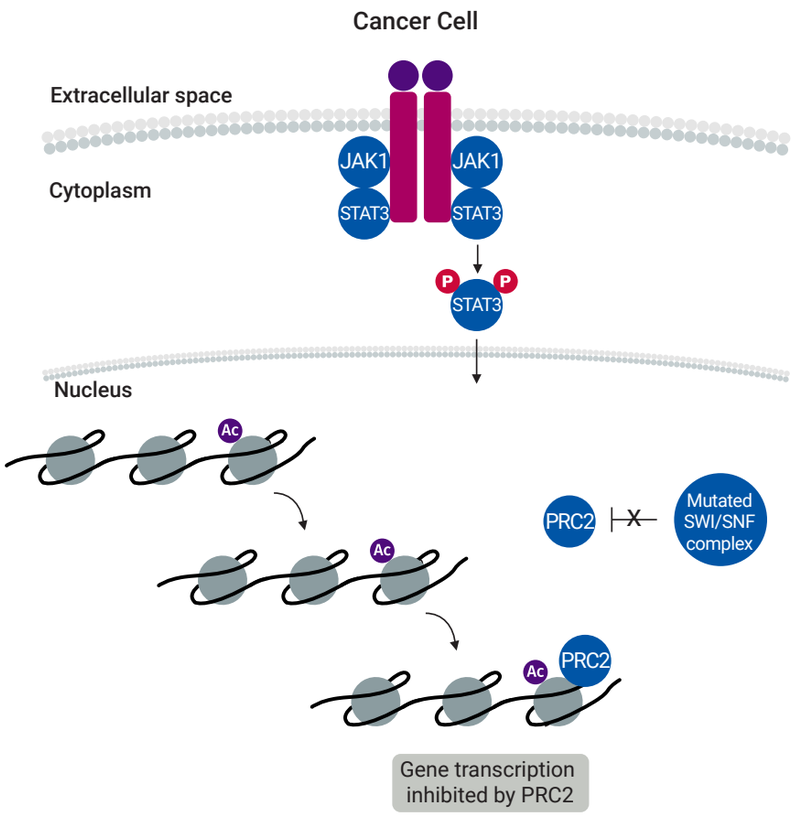

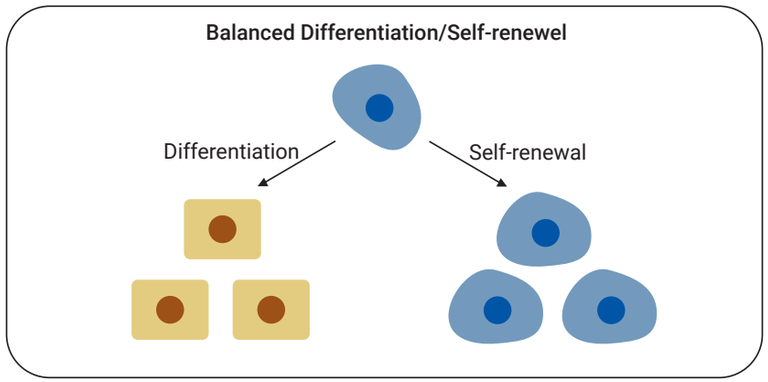

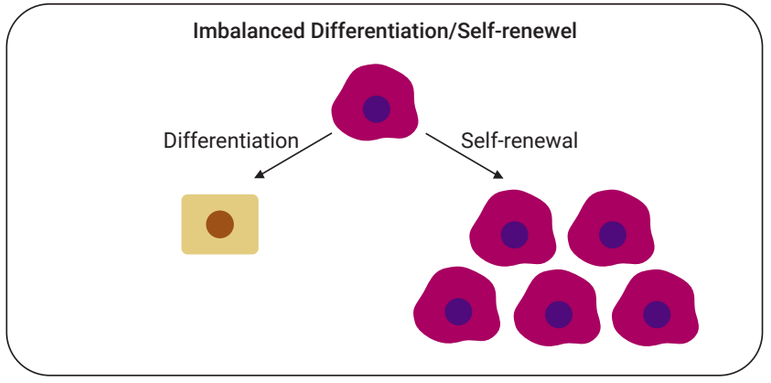

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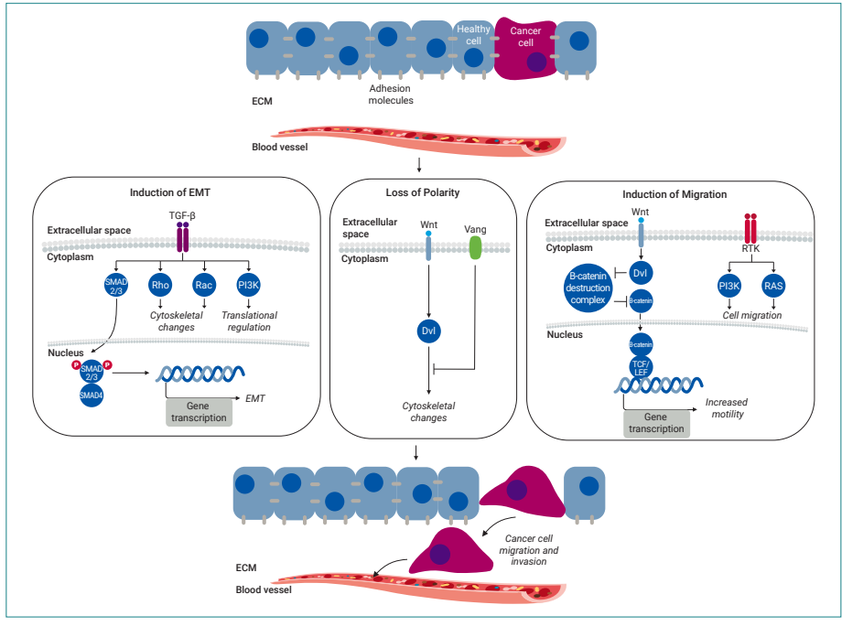
TUMOR INVASION & METASTASIS

Introduction

While treating cancer in early stages is the ideal course of therapy and the reason why preventative care is such a focus of modern medicine, there are some cancers that progress aggressively and do not present symptoms until advanced stages. Once a tumor is established, it moves to invade and metastasize into nearby tissues. As with the early stages of tumor growth, metastasis requires an assortment of mutations and imbalances. Epithelial cells transition to the mesenchymal phenotype (EMT), which allows for higher mobility and cancer cell invasiveness. Overall, loss of cell polarity is commonly observed in cancer and facilitates invasion and metastasis. These physical changes enable the cancer cells to readily travel through blood vessels and target tissues and organs. Paired with the physiological process of angiogenesis, the tumor is established and able to grow – even in a hypoxic and nutrient deficient environment. Within this section we have presented key pathways that drive critical cellular changes that are exhibited during cancer progression. These processes all represent targets of drug discovery efforts to slow cancer spread, control patient symptoms, and prolong life.



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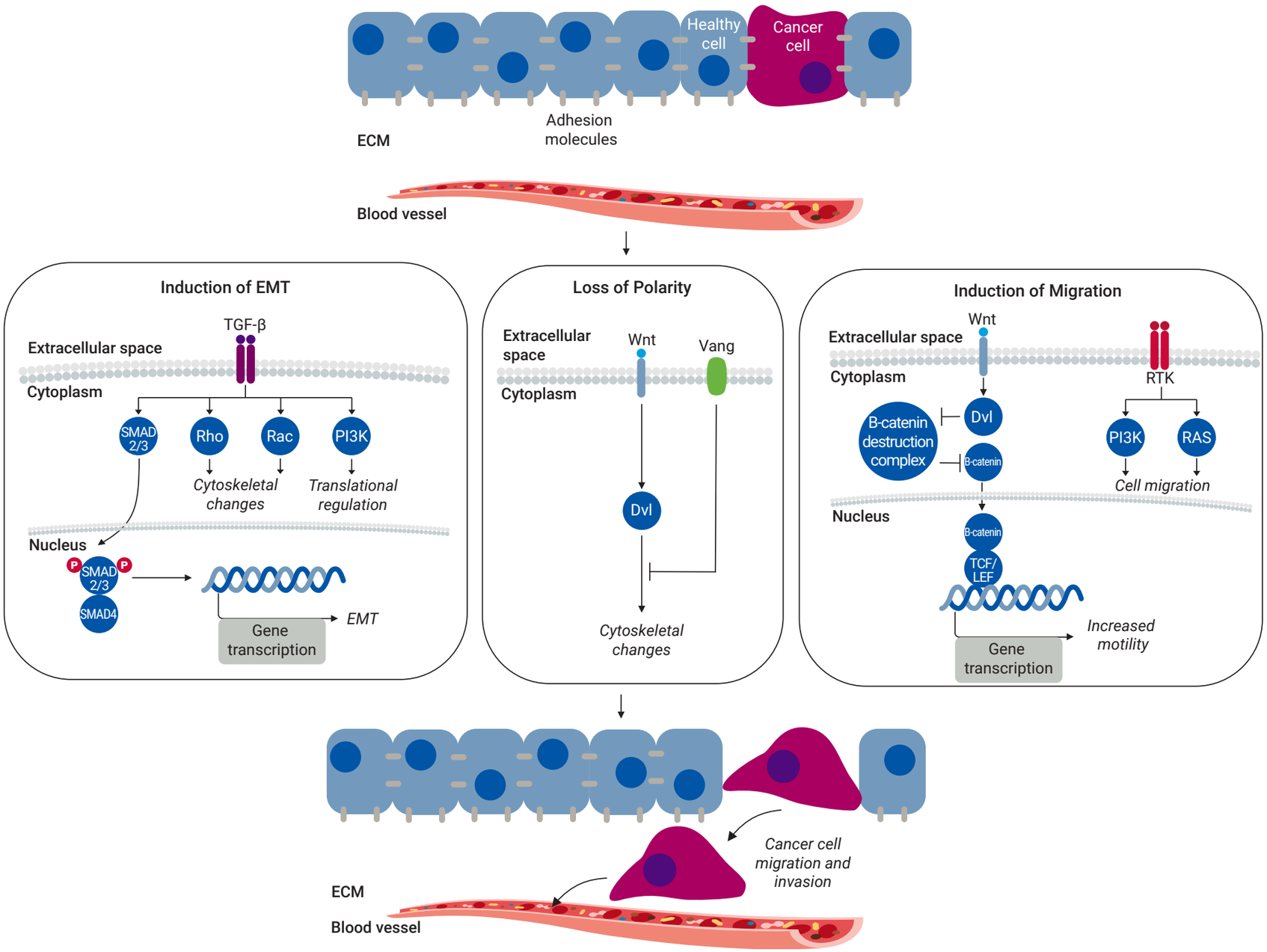

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TUMOR INVASION & METASTASIS

Epithelial-mesenchymal transition (EMT)

In epithelial cells, apical-basal polarity and contact with adjacent cells occurs through adherens, tight junctions, and desmosomes. In contrast, mesenchymal cells do not have apical-basal polarity or a basal lamina separating them from the adjacent tissue and are separated from other cells by the extracellular matrix. During epithelial-mesenchymal transitions (EMT) that occur during biological processes and cancer progression, epithelial cells obtain mesenchymal features. In this process, epithelial cells lose adherent junction and downregulate cytokeratins and E-cadherin, epithelial specific markers. They also gain a fibroblastoid invasive phenotype by increasing mesenchymal markers like fibronectin, N-cadherin, and vimentin.[1] Thus, EMT results in changes in epithelial cell polarity from apical-basal to anteroposterior, transitions from epithelial to mesenchymal phenotype, and allows for higher mobility and cancer cell invasiveness.[2]

EMT is regulated by highly conserved molecular steps. Cancer cells that undergo EMT secrete cytokines such as TGF-β, which is the primary inducer of EMT. TGF-β binds the serine/threonine kinase receptors TGF-β receptor type I (TβRI) and type II (TβRII). Upon activation of these receptors, SMAD and non-SMAD signaling pathways are activated. Specifically, activated TβRI phosphorylates SMAD2/3 that is associated with SMAD4. This complex is transported to the nucleus, where it regulates the transcription of EMT-related genes. The key transcription factors activated by TGF-β are SNAIL, ZEB, and TWIST. SNAIL is an inducer of EMT, while TWIST and ZEB keep the invasive mesenchymal phenotype. TGF-β may induce EMT through non-SMAD pathways through activation of the PI3K-AKT signaling pathway that leads to translational regulation of EMT factors. TGF-β can also initiate the Rac/Rho pathway and initiate cytoskeletal changes.[2]

Overall, activation of EMT transcription factors leads to reducing specific genes that encode for proteins involved in forming adherens and tight junctions, desmosomes, and maintaining the apical-basal cell polarity. These junctions support the epithelial phenotype and control various signaling pathways through associated proteins. Thus, dysregulation of cell-cell junctions affects molecular pathways and can further activate EMT and cancer invasion. The mesenchymal phenotype also promotes cell migration, which increases cancer motility and invasion into neighboring tissues.[2] One of the first steps of metastasis is invasion of cells into the extracellular matrix. Thus, cells obtaining the ability to migrate and invade is the hallmark of EMT and describes the role of EMT in metastasis.[1]

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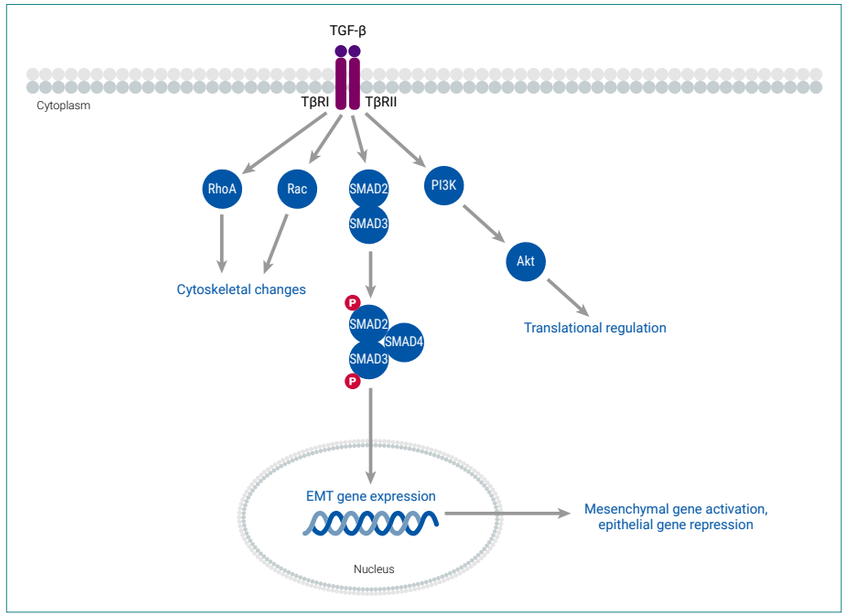

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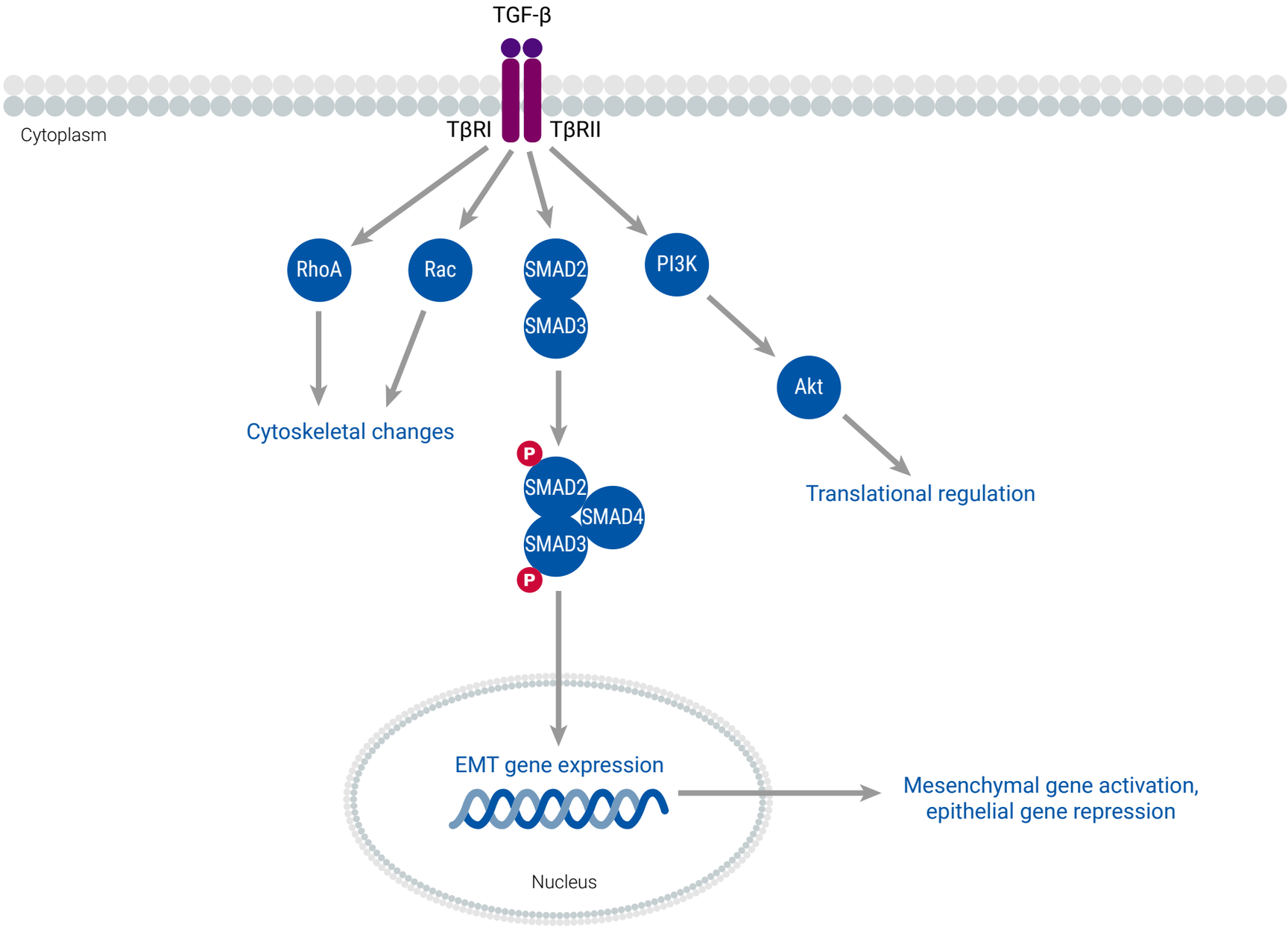

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TUMOR INVASION & METASTASIS

Cell polarity

Cell polarity is essential for maintaining cellular homeostasis and organizing intracellular pathways. Cell migration and invasion involve changes in cell shape, which requires the loss of apical-basal polarity and organizing front-rear polarity. The process is tightly controlled in normal cells, since excess cell migration can result in serious pathological consequences.[1] Cellular architecture is organized along the apical-basal axis that is associated with epithelial signaling and the planar axis orthogonal to the apical-basal axis that organizes cell polarity.[2] Loss of cell polarity is commonly observed in cancer and facilitates invasion and metastasis.[1]

Three complexes establish and preserve apical-basal polarity: the Par, Scribble, and Crumbs complexes. The Par complex is located at the apical side within tight junctions and promotes formation and maintenance of these areas. It consists of Par3, Par6, and aPKC (apical protein kinase C). Par3 and Par6 mediate protein-protein interactions and associate with tight junction proteins and aPKC. The Rho GTPases Rac1 and Cdc42 associate with the Par complex and activate aPKC. This then phosphorylates Crumbs, Lgl, and GSK3β (glycogen synthase kinase-3β). The Crumbs complex also localizes to the apical side and consists of Pals1 and PATJ. PATJ promotes tight junction formation. The Scribble complex localizes basolaterally and comprises Scribble, Dlg, and Lgl. aPKC regulates signaling events for establishing apical-basal, front-rear polarity, and cell invasion.[1]

Planar cell polarity (PCP) proteins generate polarity orthogonal to the apical-basal axis and coordinate cell division and cilia function. Planar cell polarity proteins include Van Gogh (Vang), Frizzled (Fz), Dishevelled (Dvl), and the signaling ligand Wnt, which localize to the cytoplasm. Regulation of these components leads to cell migration and invasion that occurs through the asymmetrical localization of the PCP proteins and migration of cells orthogonal to apicobasal polarity.[1] Increasing evidence shows that the Wnt/PCP signaling pathway promotes the proliferative and migratory properties of tumor cells. Wnt/PCP signaling is adapted to promote cancer cell migration, since it results in the mutual antagonism between Fzd/Dvl and Vang/Pk complexes, leading to cytoskeletal rearrangements. The expression of core PCP components is elevated in some cancers.[2]

Destabilization of junctional complexes and loss of epithelial polarity is commonly associated with cancer. Invasive cancer cells use the epithelial-mesenchymal transition to develop from the mesenchymal mode. During this process, the polarity complexes are deconstructed and loss of the epithelial cell-cell junctions and apical-basal polarity occurs, which establishes a front-rear polarity. Proto-oncogenes such as Ras and PI3K/AKT activate the epithelial-mesenchymal transition, which increases the invasive and metastatic potential of cancer cells.[1,3]

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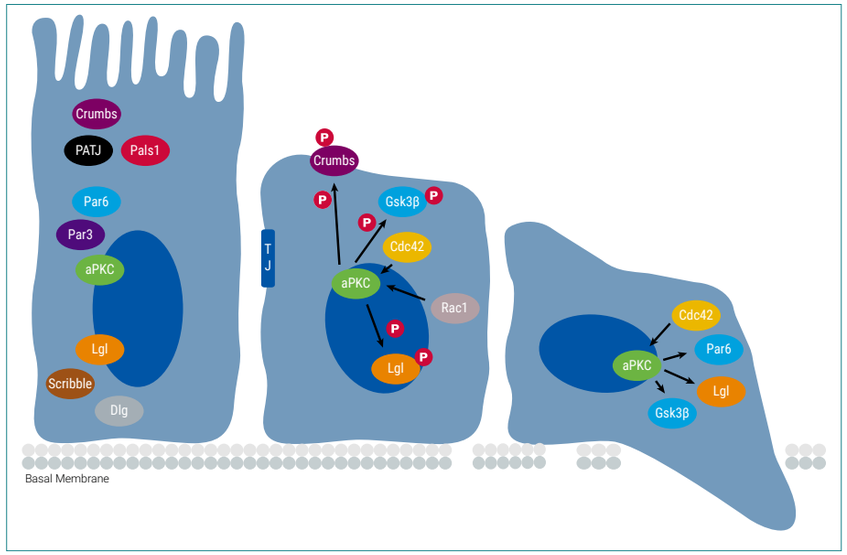

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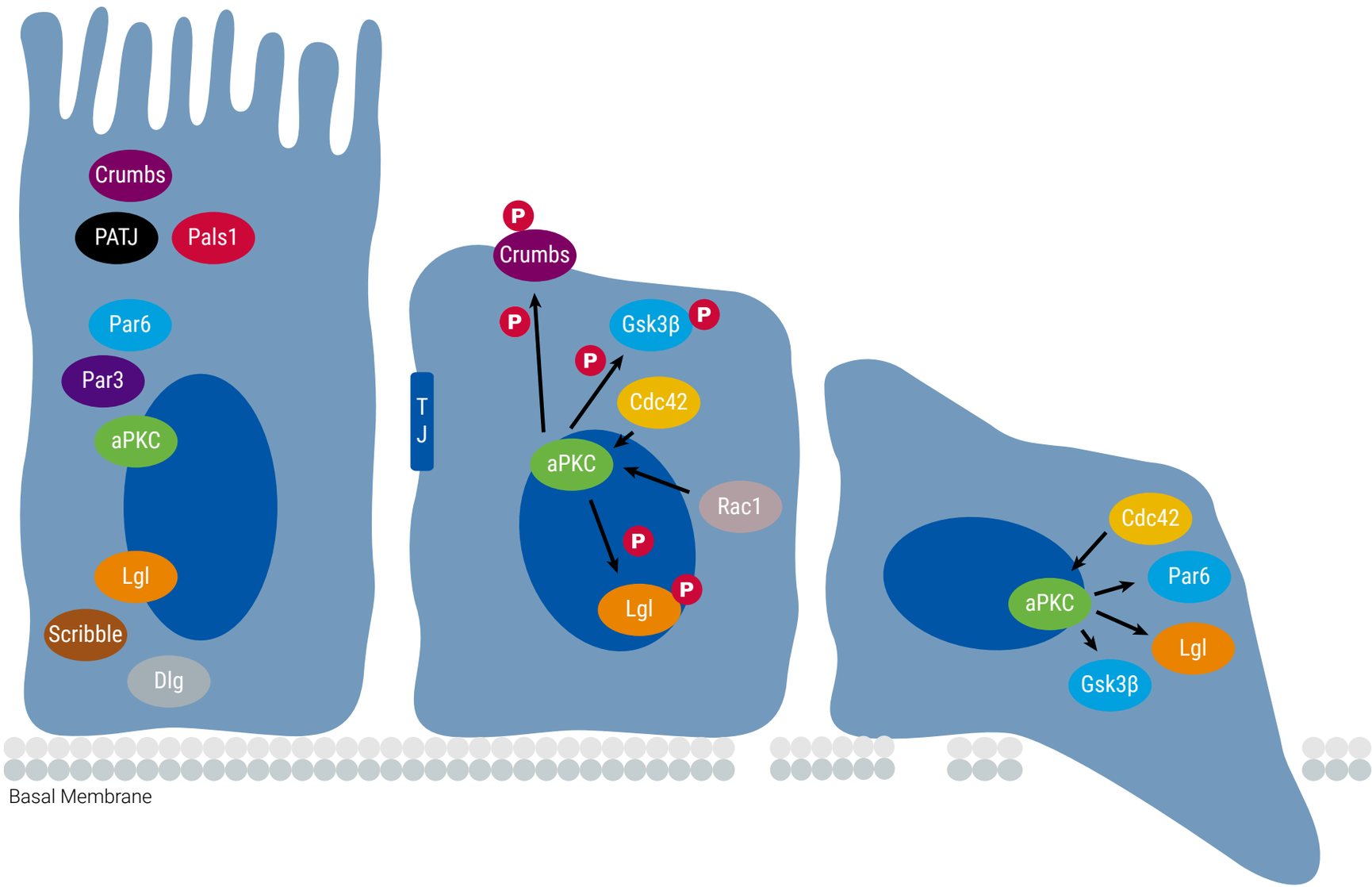

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TUMOR INVASION & METASTASIS

Cell migration

Increased cell migration is a factor in cancer development and metastasis. Genetic and epigenetic changes and dysregulation in cell migration signaling pathways cause carcinogenesis.[1] Metastasis development from a primary tumor site is a multistep event and includes epithelial-mesenchymal transition (EMT), tumor neoangiogenesis, and spread of malignancy. Spread of malignancy occurs from malignant cell transport through blood vessels, targeting tissues and organs.[2]

Developmental pathways such as Wnt and receptor tyrosine kinase (RTK) control cell migration and are commonly overactivated in solid tumors and metastasis. Wnt signaling molecules bind to the frizzled family of receptors and is either canonical (β-catenin dependent) or non-canonical (β-catenin independent). The canonical pathway is activated upon binding to a ligand. Wnt triggers a signaling cascade that results in cell migratory gene activation. Wnt binding to frizzled-7 leads to recruitment of Dishevelled (Dvl) proteins, which promotes β-catenin destruction complex disaggregation. The complex is composed of the tumor suppressor adenomatous polyposis coli (APC), the serine/threonine protein kinase glycogen synthase kinase 3 (GSK3), Axin, and casein kinase (CKI). The disaggregation of the β-catenin destruction complex inactivates it and results in β-catenin accumulation in the cytoplasm. β-catenin then migrates to the nucleus and interacts with the TCF/LEF-1 family of transcription factors. These transcription factors activate genes encoding for proteins involved in EMT and motility (Snail).[2,3]

RTKs are cell surface receptors that mediate signaling pathways involved in cell migration and are often mutated in a variety of cancers. Mutations that affect RTKs result in increased cell migration. RTKs are auto-phosphorylated upon ligand binding, which activates Ras and induces Raf. Raf phosphorylates MEK, which phosphorylates ERK. Raf also activates the MAP3 kinase signaling cascade that activates MKK, MEK, and ERK. RTK auto-phosphorylation also activates the PI3K pathway, which activates Akt and induces mTOR.[4]

During metastasis, which occurs in late stage cancer, tumors may undergo EMT by which polarized epithelial cells transform into migratory mesenchymal cells with invasive properties. Activation of Wnt signaling stabilizes transcriptional factors that are responsible for EMT. In addition, pharmacological inhibition of the PI3K-Akt signaling pathway in cells with hyperactivated Wnt signaling leads to β-catenin accumulation in the nucleus, resulting in increased metastasis. Further, exosomes are vehicles for transporting active Wnt ligands or incorporating β-catenin and may be a mechanism in which tumors prime their metastatic niche.[5]

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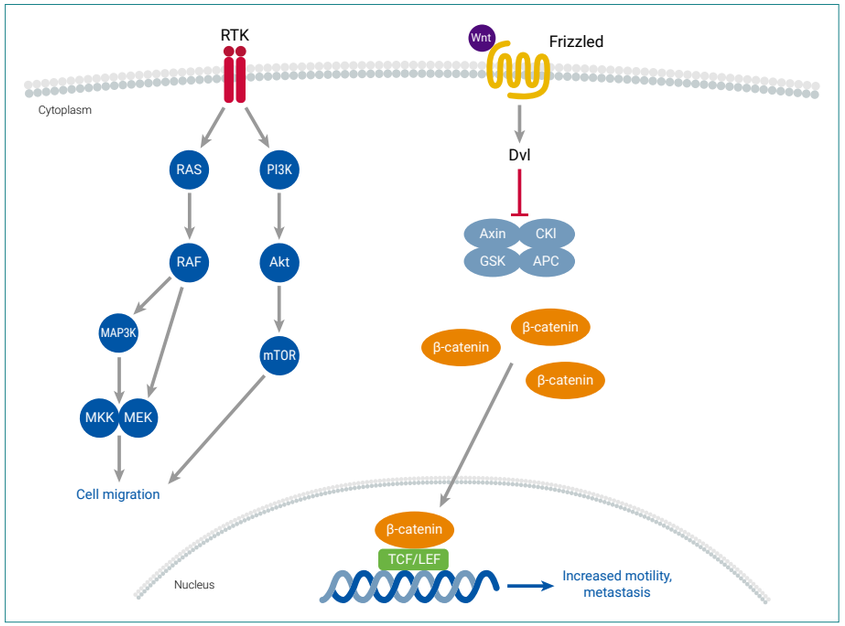

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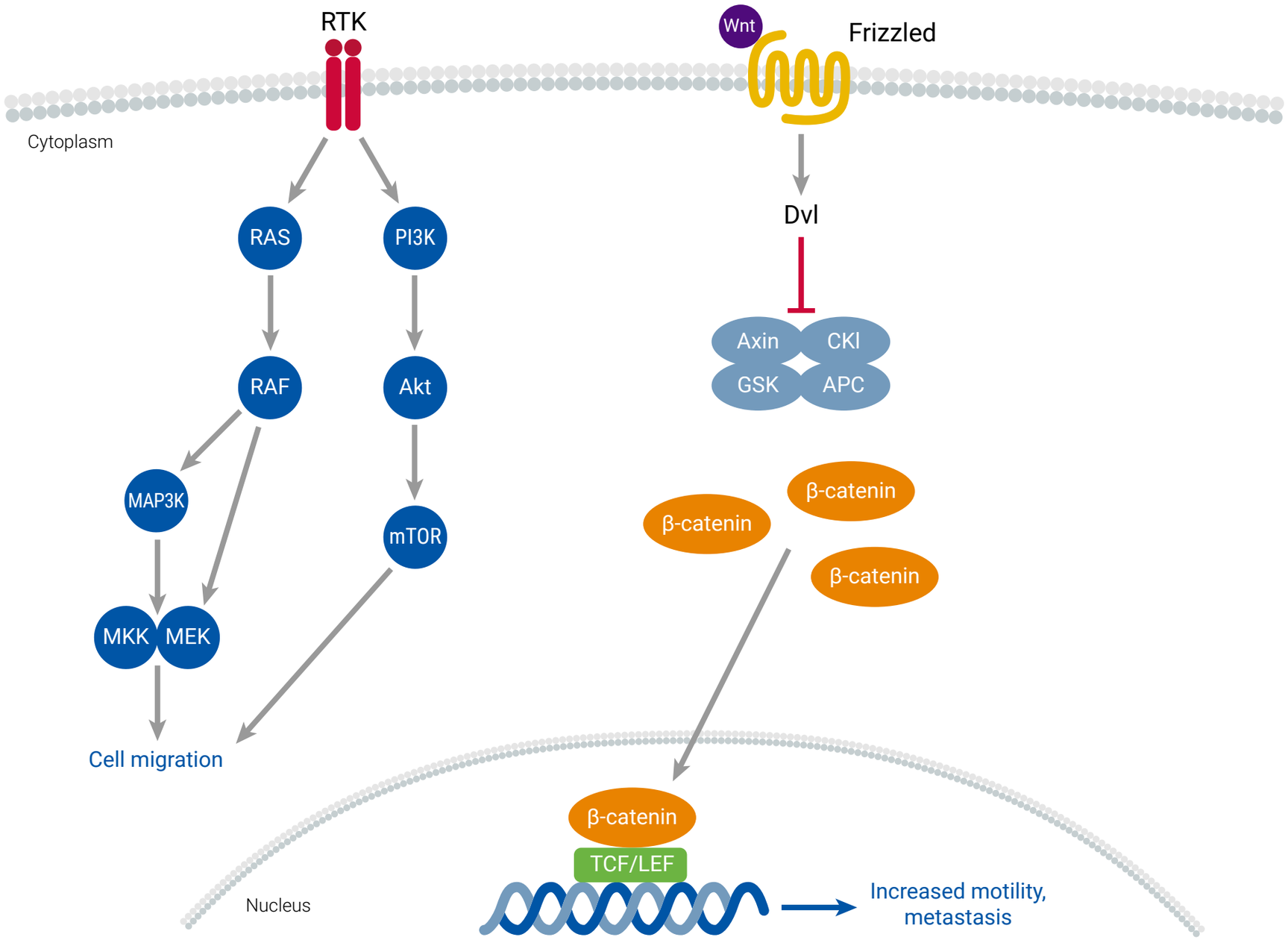

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TUMOR INVASION & METASTASIS

Angiogenesis

Angiogenesis is a physiological process that involves the proliferation, migration, and morphogenesis of endothelial cells from existing vessels into new blood vessels. It is a hallmark of cancer and linked to metastasis. There are several differences between normal angiogenesis and tumor angiogenesis. One difference involves the source of the endothelial cell mitogen or chemoattractant. Indeed, tumor cells require invasion of the epithelial basement membrane to access the blood vessels since they originate in non-vascularized epithelium. In addition, tumor angiogenesis is continuous as long as the tumor is in place, whereas normal angiogenesis continues for a limited amount of time.[1]

Angiogenesis is triggered by extracellular signals like hypoxia or growth factors. Tumor cells become hypoxic as they expand away from the blood supply.[1] Angiogenesis allows tumor cells to continue growing, even in a hypoxic and nutrient deficient environment. The primary driver of this activity is hypoxia-inducible factor (HIF).[2] HIFs are continuously expressed and degraded under normoxia. Hypoxia is a common characteristic in many types of solid tumors. Elevated HIF levels are correlated with tumor metastasis, angiogenesis, poor patient progression as well as tumor resistance to therapy. Hypoxia, via HIF, upregulates angiogenic growth factors like vascular endothelial growth factors (VEGF). VEGF and HIF are important signaling proteins that attract the endothelial cell to the tumor mass and stimulate new blood vessels or induce growth of pre-existing blood vessels.[1] VEGF and other growth factor stimulation through HIF activates PI3K through AKT, which can also indirectly activate MAPK. PI3K/AKT activation leads to upregulated VEGF and HIF transcription.[3] Thus, the PI3K/AKT and MAPK signaling pathways regulate angiogenesis by increasing HIF and VEGF expression in response to growth factors.[3,4]

The tumor microenvironment, which is composed of tumor cells, vascular endothelial cells, and stromal cells, also regulates tumor angiogenesis. The PI3K/AKT pathway can control the tumor microenvironment by regulating endothelial migration, proliferation, and survival. Cancer cell and vascular endothelial cell interaction in the tumor microenvironment affects angiogenesis. In cancer cells, growth factors activate the PI3K/AKT/mTOR/HIF axis and induce VEGF. This increases angiogenic response and activates endothelial cells. Thus, tumor growth, metastasis, and angiogenesis involve the PI3K signaling pathway.[3,5]

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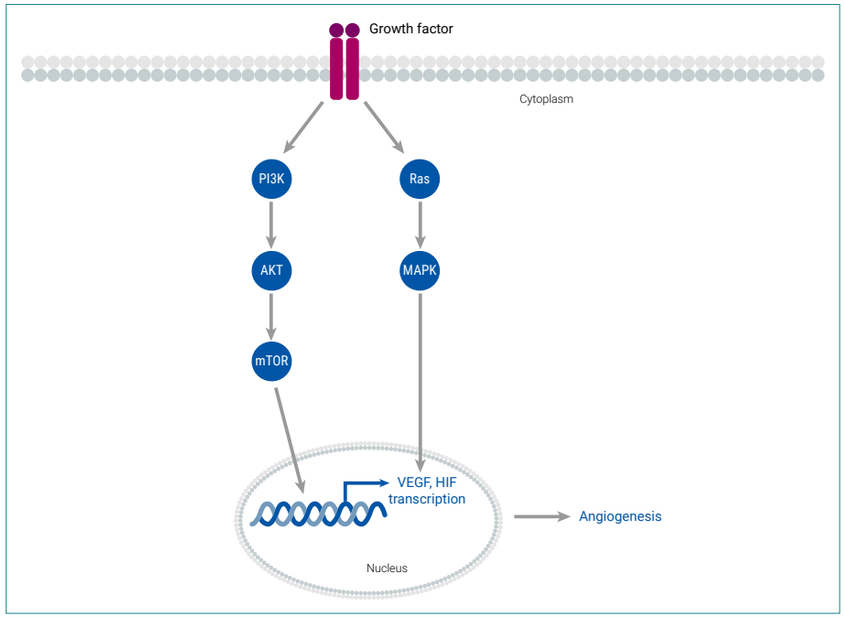

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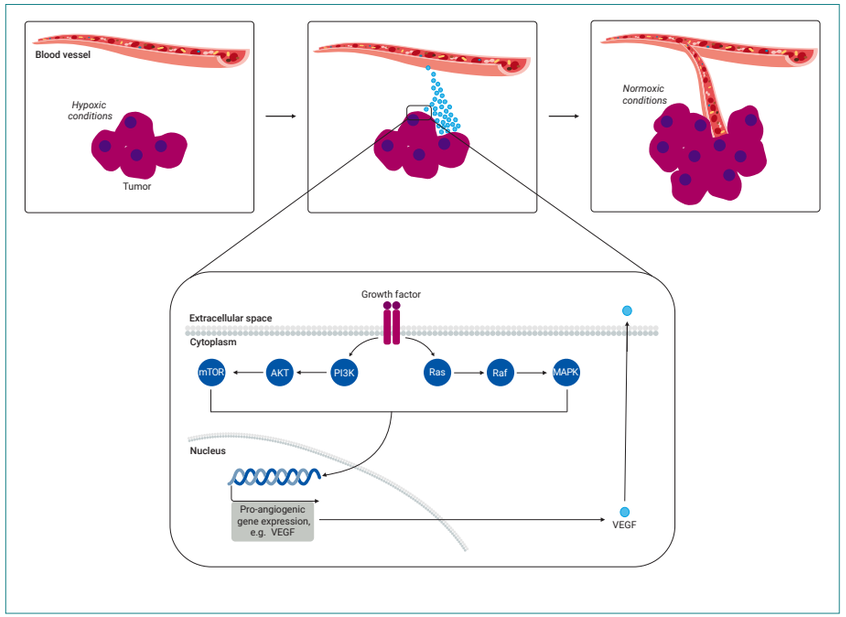

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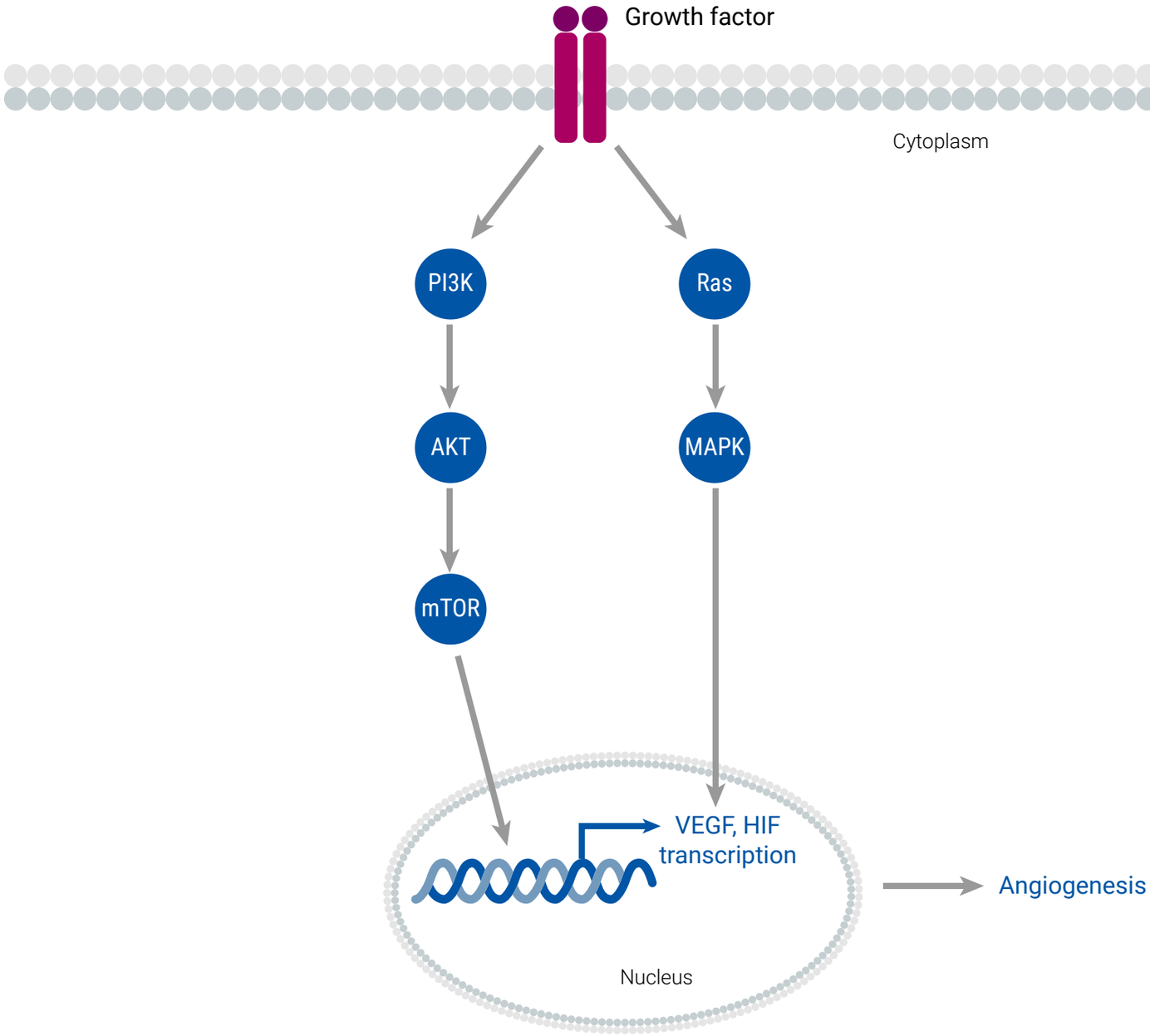

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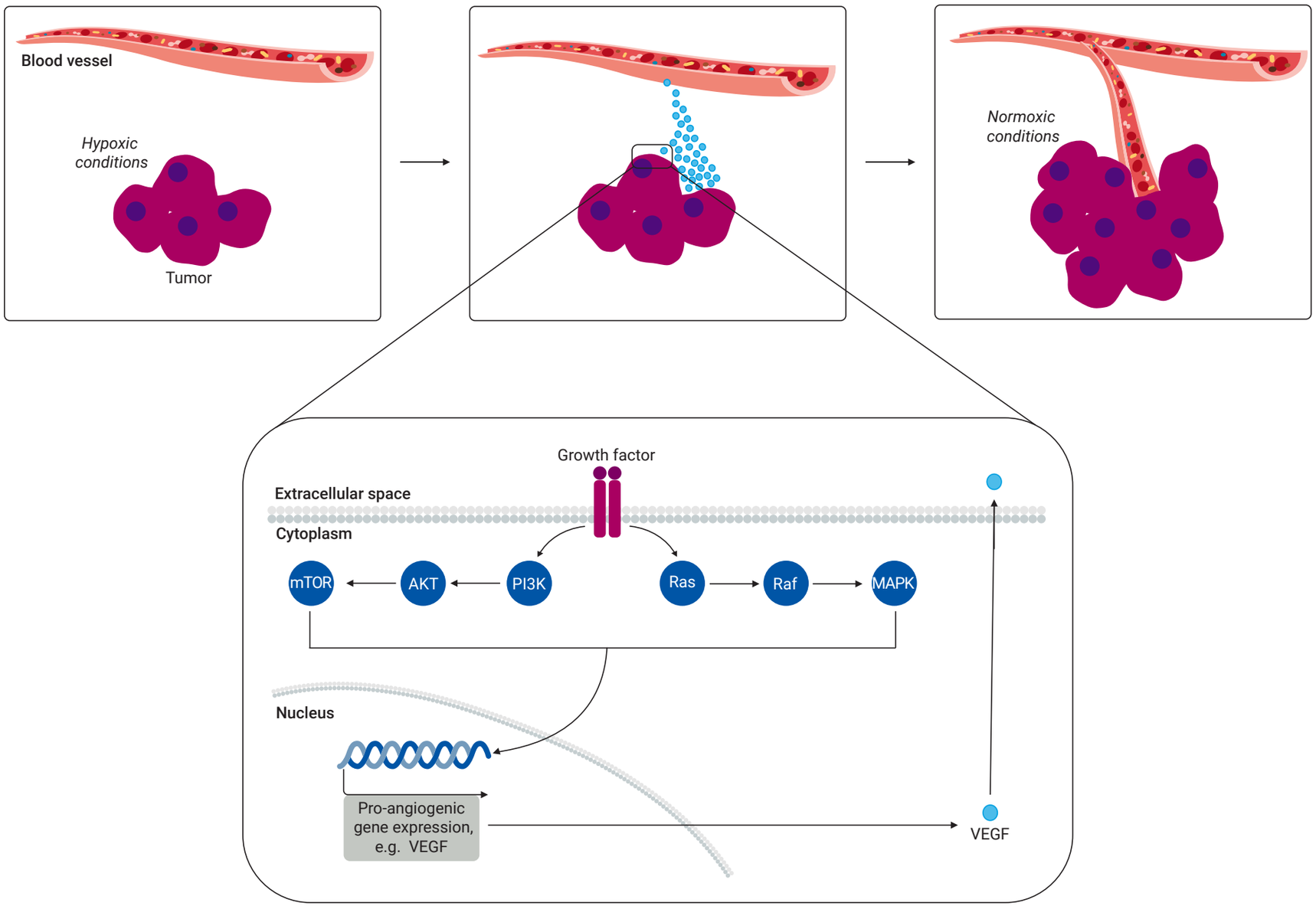

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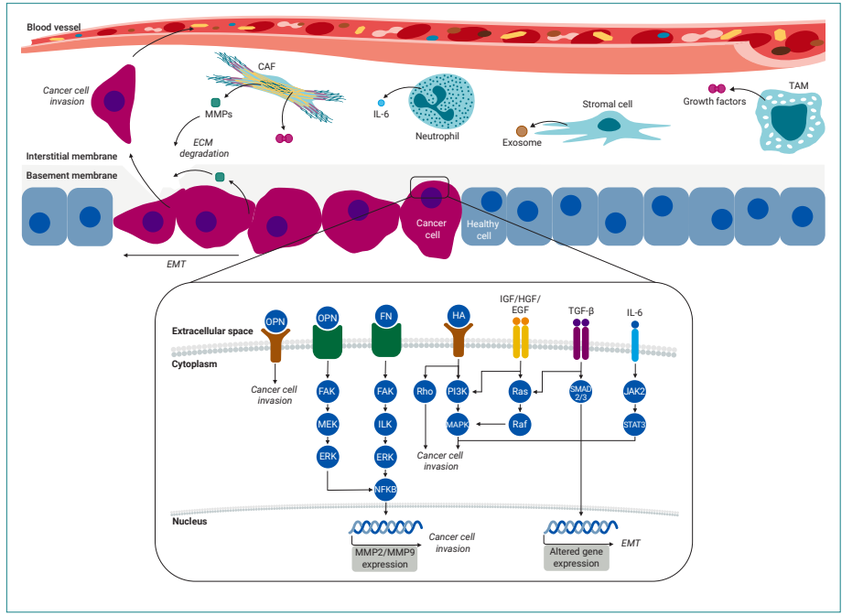
COMPLEXITY OF THE TUMOR STROMA

Introduction

Examining the conditions in which a tumor is growing reveals a complex ecosystem, tailored to facilitate cancer cell survival and evolving in response to therapeutic intervention. The extracellular matrix (ECM) is a dynamic structural component of the microenvironment which can modify cellular behavior and differentiation. The ECM is involved in the larger picture of the tumor microenvironment (TME) and includes the basement membrane (BM), endothelial cells, adipose cells, tumor-infiltrating immune cells, cancer-associated fibroblasts (CAFs), immune cells, and signaling molecules that regulate tumor progression and expansion. The TME influences accessibility of therapies to reach the tumor and fosters an environment that facilitates and promotes both drug resistance and tumor persistence. Deconvolution of the complexity of the tumor stroma is a critical focus of drug discovery efforts in order to provide improved and personalized treatment options for patients, leading to better outcomes.



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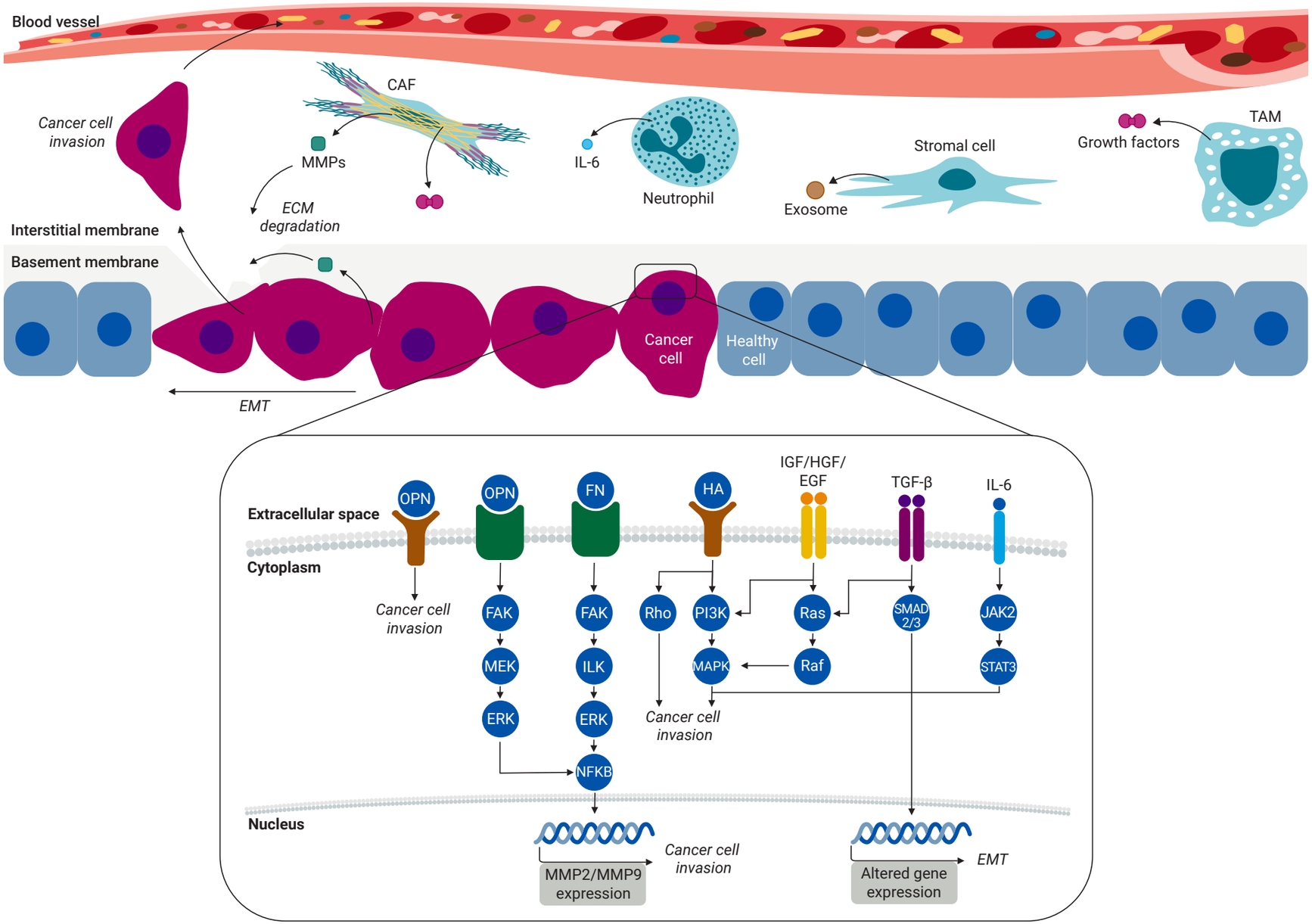

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COMPLEXITY OF THE TUMOR STROMA

Extracellular matrix (ECM)

The extracellular matrix (ECM) is a highly dynamic structural component of the tumor microenvironment. It is made up of a network of biochemically distinct components that include fibrous proteins, glycoproteins, proteoglycans, and polysaccharides that work together to provide structural support for cells. The ECM is constantly being remodeled where components are deposited, degraded, or modified.[1] Cellular behavior and differentiation are controlled by the ECM and when the dynamics are dysregulated, cancer development may occur.[2]

Cells create and rearrange ECM components depending on specific tissue needs. The major components are collagen, proteoglycans, laminin, and fibronectin, which make up both the basement membrane and interstitial matrix. Collagen is the basis of ECM architecture and is involved in wound repair and organ development. It is found in tendons, cartilage, skin, and the cornea. Fibrillar collagens are made up of several subtypes of collagen depending on the tissue location, and ECM proteins mediate their formation. Proteoglycans are the functional modifiers of the ECM and are characterized as proteins that have glycosaminoglycans covalently bonded to them. They vary in size and have integral functions in the ECM, like space-filling and lubrication, binding to growth factors and other ECM proteins, serving as a molecular bridge between the cell surface and ECM, and directing organ size and shape. Laminin connects the cell to the ECM through binding of integrins. They are involved in adhesion, differentiation, migration, phenotype maintenance, and apoptotic resistance. Fibronectin is the mechanosensitive connection between the cell and the ECM.[2]

Normal ECM dynamics maintain a healthy microenvironment by keeping tumor-prone cells, fibroblasts, eosinophils, macrophages, and stromal cells contained. The ECM molecules influence biochemical and biophysical processes in the cell and besides providing structural support, determine cell functions and phenotypes. To maintain tissue homeostasis and balance the deposition and degradation of ECM components, cells sense ECM properties through contact with focal adhesion complexes. This regulates the expression of ECM components and enzymes based on signals of the ECM. Any imbalance in the deposition and degradation of the ECM can lead to cancer. The ECM also influences cell migration, since cells migrate from regions with lower ECM concentration to higher ECM concentration.[2]

Changes to ECM components can dysregulate adhesion and migration, since the different properties of the ECM are connected. Changes in the ECM can also influence stromal cell behavior and aid in tumor-associated angiogenesis and inflammation, leading to a tumorigenic microenvironment. Abnormal ECM dynamics compromise the basement membrane and promote epithelial-mesenchymal transition, allowing for invasion by cancer cells. Activated fibroblasts or cancer-associated fibroblasts (CAFs) from pathological conditions promote upregulation of LOX activities, which stabilize collagen assembly and build the ECM. Thickening of collagen fibers allow for cancer cells to migrate rapidly to areas enriched in collagen. Immune cells are recruited to the site of invading cancer cells and promote cancer progression. The dysregulated ECM promotes tumor-associated angiogenesis, which allows for tumor cell invasion and metastasis to distant sites where cancer cells leave circulation and invade local tissues.[3]

Numerous molecular networks and extracellular molecules regulate cancer cell invasion and metastatic processes. These include ECM molecules, ECM receptors, and growth factors. ECM molecules are hyaluronan (HA), fibronectin (FN), and Small Integrin-Binding Ligand N-linked Glycoprotein (SIBLING). HA makes up the glycosaminoglycan present in the ECM and promotes cell invasion through binding to the ECM receptor CD44 and activating the PI3K/AKT and Rho signaling pathways.

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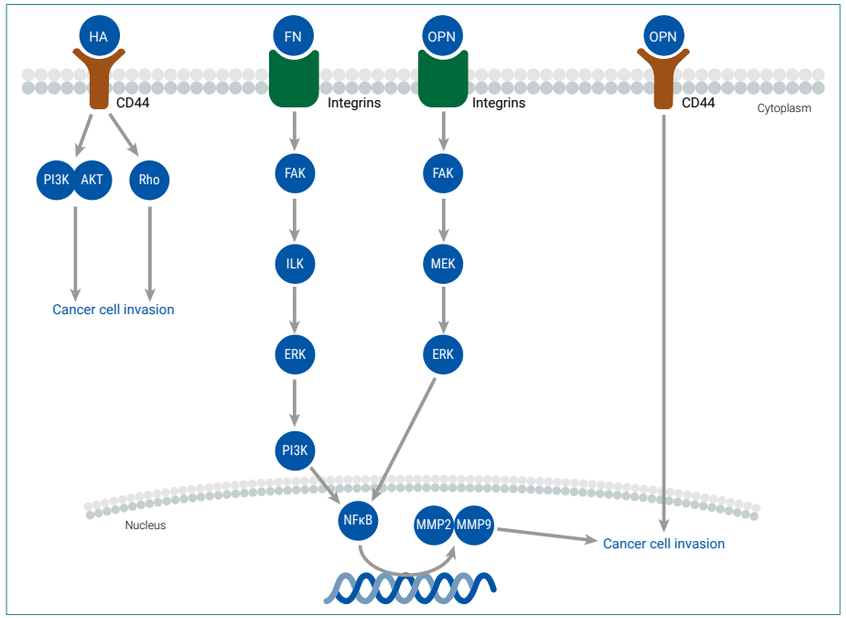
FN is a glycoprotein that is a cell-matrix and cell-cell adhesion mediator. Overexpression of FN is reported in some cancers and involved in cell invasion and metastasis through binding to integrins and upregulating the growth factor matrix metalloproteinases (MMPs) MMP-2 and MMP-9 via the FAK/ILK/ERK/Pi3K/NF-kB pathways. The SIBLING protein osteopontin (OPN) is a non-structural ECM protein and identified as a biomarker of tumor metastasis. OPN binds to integrins and CD44 to promote cancer cell invasion. MMP-9 over-expression is induced through the FAK/MEK/ERK/NF-kB pathway when OPN binds to integrin.[4]



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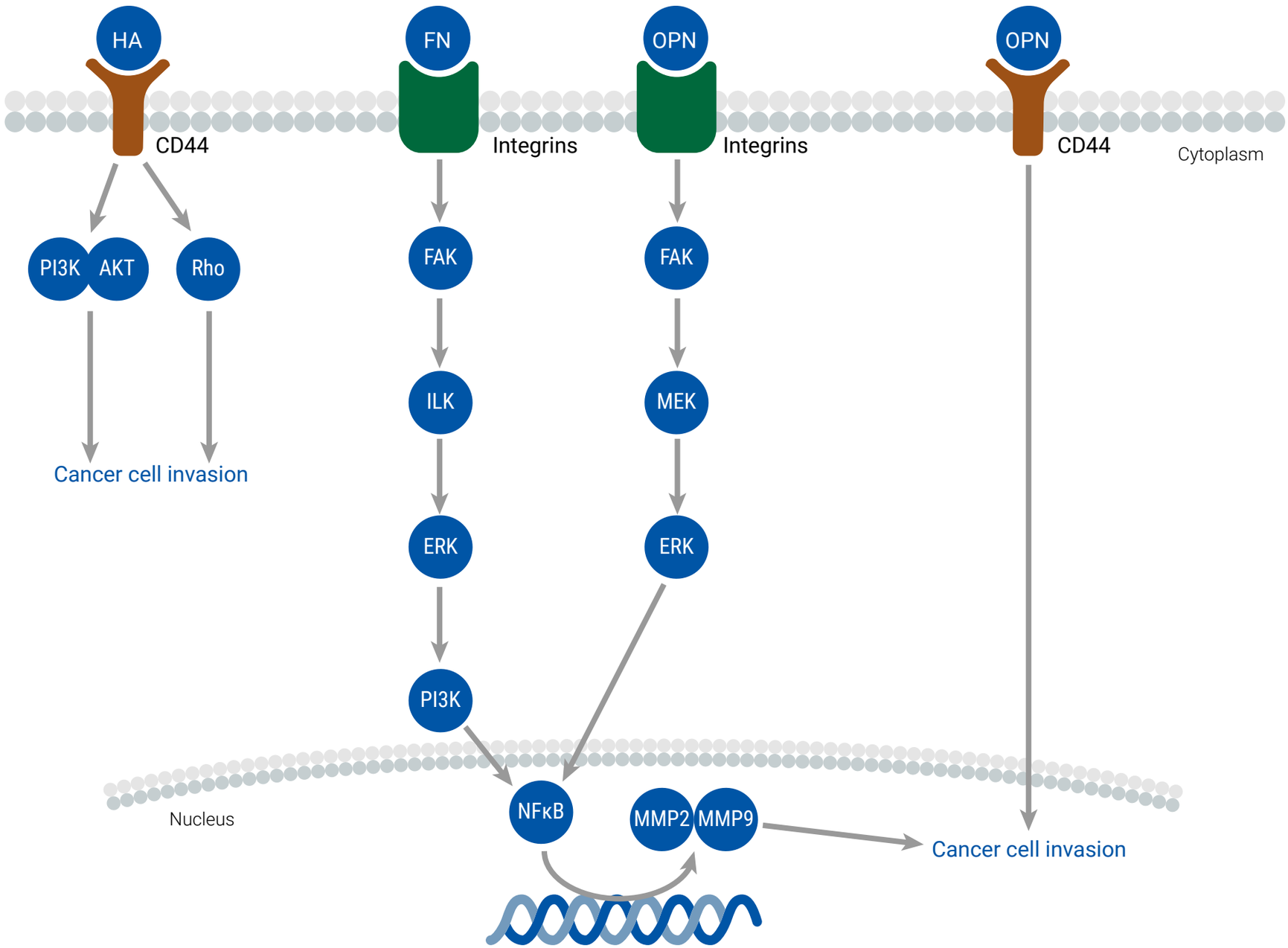

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COMPLEXITY OF THE TUMOR STROMA

Tumor microenvironment

The tumor microenvironment (TME) is a complex and evolving entity that regulates essential tumor survival and promotion functions.[1,2] Early in tumor growth, cancer cells and the various TME components develop a relationship. This relationship supports cancer cell survival, local invasion, and metastasis. Tumor development and progression creates a hypoxic and acidic environment, so the TME creates a program to promote angiogenesis that restores oxygen and nutrient supply, while removing metabolic waste.[2] The TME comprises the extracellular matrix (ECM) and basement membrane (BM), endothelial cells, adipose cells, tumor-infiltrating immune cells, cancer-associated fibroblasts (CAFs), immune cells, and signaling molecules that regulate tumor progression.[1]

CAFs facilitate crosstalk between cancer cells and the TME and are developed from tissue resident fibroblasts, adipocytes, endothelial cells, pericytes, stellate cells, and bone marrow-derived mesenchymal stem cells. Injury to tissues causes fibroblasts to form myofibroblasts, which produce transforming growth factor-β (TGF-β). When activated, myofibroblasts play a role in proliferation, contractile properties, secretory phenotypes, and ECM formation. In the TME, cancer cells and other stroma cells secrete growth factors like TGF-β, platelet derived growth factor (PGDF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and fibroblast growth factor 2 (FGF2). These growth factors convert fibroblasts into CAFs, which are similar to myofibroblasts. CAFs also secrete TGF-β, which allows them to control metastasis, since it is required for epithelial-mesenchymal transition (EMT) and angiogenesis. During EMT, epithelial cells lose cell polarity and cell-to-cell adhesions and develop migratory and invasive phenotypes, making it a critical step in metastasis.[2] TGF-β is one of the growth factors that induces EMT through different pathways such as MAPK, PI3K, and SMAD. Because of these pathways, epithelial features are down-regulated and mesenchymal features are up-regulated. HGF, IGF, and EGF promote EMT through the PI3K/Akt and Ras/MAPK pathways.[3] CAFs also secrete MMP-3, which promotes cancer cell invasion through the TME by degrading E-cadherin. MMP-3 releases VEGF to promote angiogenesis. Thus, CAFs promote tumor develop and migration through the TME.[2]

Stromal cells are multipotent stem cells found in various adult tissues, including bone marrow, adipose tissue, liver, and lung. They are also found in some tumors and influence TME function and development because cancer cells often recruit stroma cells from nearby endogenous tissue.[1,2] The tumor reprograms cancer-associated stroma cells and enhances the EMT, which promotes angiogenesis and metastasis. They also aid in metastasis by secreting exosomes that carry proteins, lipids, miRNAs, and mRNA.[1] Thus, stromal cells facilitate angiogenesis, proliferation, invasion, and metastasis in the TME.[2]

Immune cells are another critical component of the TME and can either suppress or promote tumor growth.[2] During every step of cancer development, cancer cells are exposed to immune cells. Exposure to antigens activates adaptive immunity, which evaluates cancer cell threat. Adaptive immune cells are T-cells, B-cells, and natural killer (NK) cells. Tumor progression activates innate immunity and includes macrophages, neutrophils, and dendritic cells. During tumor evolution, cancer cells develop methods to avoid immune attacks and exploit immune cells to enhance their metastatic potential. For example, macrophages can present foreign antigens to T-cells and prime naïve T-cells. Macrophages that are recruited to the tumor site by chemokines produced from cancer cells are called tumor-associated macrophages (TAMs).[1]

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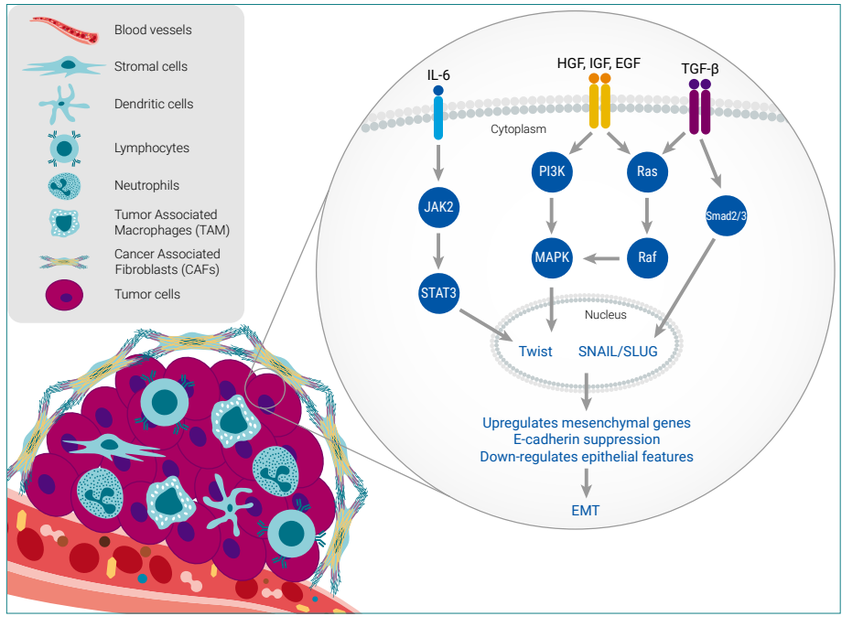
Neutrophils associated with cancer cells can secrete inflammatory factors such as IL-6. Macrophages associated with cancer cells can stimulate the Wnt/β-catenin pathway and evoke mesenchymal markers. IL-6 also evokes EMT through the JAK2/STAT3 pathway and down-regulates epithelial markers and up-regulates mesenchymal markers.[3] TAMs promote EMT through increasing phosphorylation of SMAD2/3, which is mediated by TGF-β. Thus, TAMs promote metastasis through activating EMT, invasion, and angiogenesis.[1]

Overall, interactions between cancer cells and the cellular and structural components of the TME allow cancer cells to invade and metastasize. CAFs secrete growth factors that promote tumor development and migration through the TME. Stromal cells secrete factors that facilitate angiogenesis, proliferation, invasion, and metastasis. Cancer-associated immune cells alter normal immune system capabilities to promote cancer development and avoid immune system attacks. Thus, the TME regulates cancer metastasis by emitting factors that trigger signaling pathways to activate transcription factors for inducing EMT, migration, and invasion.[3]



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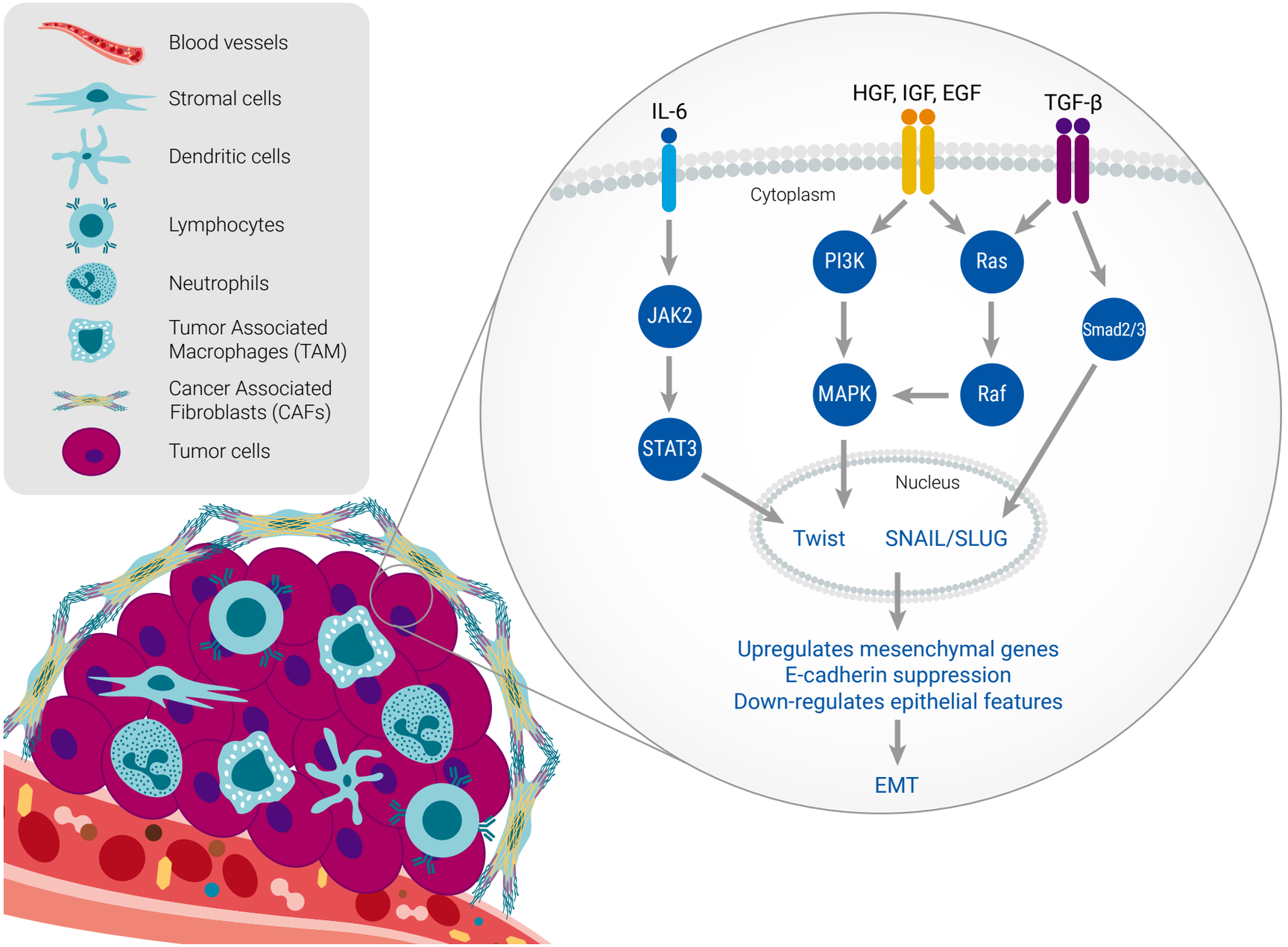

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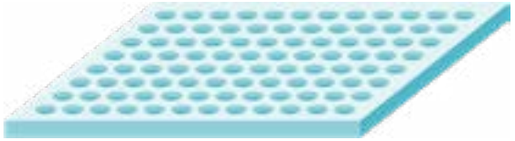

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