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Tumor Cytobiology of IGF-1R in Breast Tumor Activation and Propagation; And the Role of Celecoxib in its Inhibition

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Abstract:

The Insulin-like Growth Factor 1 Receptor (IGF-1R) stands as a central orchestrator in cellular signaling, governing pivotal processes encompassing growth, proliferation, and differentiation. Its aberrant activation is intricately intertwined with the pathogenesis and progression of breast cancer, a heterogeneous disease presenting formidable clinical challenges. Amidst the burgeoning landscape of therapeutic interventions, Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID), has emerged as a promising candidate for targeting the dysregulated IGF-1R pathway. This review delineates the intricate molecular mechanisms underlying Celecoxib's modulation of the IGF-1R pathway, elucidating its pharmacokinetic properties and therapeutic implications in breast cancer management. Celecoxib exerts inhibitory effects on IGF-1R through multifaceted molecular interactions, impeding receptor activation and downstream signaling cascades pivotal for tumor proliferation and metastasis. Furthermore, it regulates IGF-1R expression at both transcriptional and translational levels, exerting nuanced control over cellular responses. Moreover, Celecoxib's therapeutic impact transcends mere IGF-1R inhibition, as it potentiates pro-apoptotic pathways and disrupts tumor-permissive microenvironments. A nuanced understanding of Celecoxib's pharmacokinetic profile is imperative, considering its sustained and targeted inhibition of IGF-1R signaling, and its potential synergistic effects in combinatorial therapeutic regimens for breast cancer. This comprehensive elucidation underscores the paramount importance of deciphering Celecoxib's intricate molecular interplay with the IGF-1R pathway, heralding novel avenues for precision medicine and tailored therapeutic interventions in the management of breast cancer.

Keywords: Breast Cancer Subtypes, Celecoxib, Insulin-like Growth Factor 1 Receptor (IGF-1R) Inhibition, Metastasis, Angiogenesis.

1. Introduction

The Insulin-like Growth Factor 1 Receptor (IGF-1R) represents a pivotal molecular entity deeply embedded within the intricate web of cellular signaling pathways governing growth, proliferation, and differentiation. Structurally, IGF-1R is a transmembrane receptor tyrosine kinase,

characterized by a heterotetrameric composition comprising two extracellular α-subunits and two transmembrane β-subunits. Its synthesis predominantly occurs within the endoplasmic reticulum, where nascent receptor subunits undergo post-translational modifications, including glycosylation and disulfide bond formation, crucial for receptor maturation and trafficking to the cell surface [1]. Functionally, IGF-1R orchestrates a myriad of cellular responses upon binding to its cognate ligands, including insulin-like growth factors (IGF-1 and IGF-2). Ligand binding induces conformational changes in the receptor, leading to autophosphorylation of tyrosine residues within the intracellular β-subunit, thereby activating downstream signaling cascades pivotal for cellular growth and survival [2]. Notably, IGF-1R activation engages multiple signaling pathways, including the phosphatidylinositol-3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways, culminating in the modulation of gene expression profiles governing cell cycle progression, apoptosis evasion, and metastatic potential [3].

Breast cancer, a heterogeneous disease characterized by the uncontrolled growth and proliferation of cells within the mammary gland, remains a significant public health concern worldwide. Central to the intricate pathophysiology of breast cancer is the dysregulation of various signaling pathways governing cellular homeostasis, among which the Insulin-like Growth Factor 1 Receptor (IGF-1R) pathway plays a pivotal role [4]. In normal breast tissue, IGF-1R orchestrates essential cellular processes, including cell growth, differentiation, and apoptosis, thereby contributing to mammary gland development and maintenance. Within this physiological context, IGF-1R expression is tightly regulated, ensuring proper cellular responses to external stimuli and hormonal cues [5].

However, aberrant expression and activation of IGF-1R have been consistently implicated in the pathogenesis and progression of breast tumors, including fibroadenomas and breast carcinomas. Elevated levels of IGF-1R have been detected in breast tumor tissues, correlating with increased tumor aggressiveness, metastatic potential, and resistance to conventional therapies [6]. Notably, dysregulated IGF-1R signaling fosters tumor cell proliferation, survival, and invasion through intricate crosstalk with other signaling pathways, such as the PI3K/Akt and MAPK cascades. In the context of breast cancer, the dysregulation of IGF-1R contributes to the evasion of apoptotic checkpoints, facilitating tumor cell survival and progression [7]. Moreover, IGF-1R activation promotes angiogenesis, facilitating the establishment of a tumor-supportive microenvironment conducive to metastatic dissemination. Importantly, the aberrant expression of IGF-1R in breast cancer subtypes, including luminal, HER2-positive, and triple-negative breast cancers, underscores its potential as a prognostic biomarker and therapeutic target [8].

Fibroadenomas, benign tumors of the breast characterized by the proliferation of both epithelial and stromal components, present a unique challenge in breast cancer management due to their diverse cellular composition and heterogeneous nature. The intricate cytobiological mechanisms underlying the activation and progression of fibroadenomas involve a multifaceted interplay of various signaling pathways, among which the Insulin-like Growth Factor 1 Receptor (IGF-1R) pathway emerges as a central player [9]. IGF-1R, a transmembrane receptor tyrosine kinase, governs critical cellular processes, including proliferation, survival, and differentiation. In the context of fibroadenomas, dysregulated IGF-1R signaling contributes to the aberrant proliferation of both epithelial and stromal components, leading to tumor formation and growth. Upon ligand binding, IGF-1R undergoes autophosphorylation, initiating a cascade of intracellular events culminating in the activation of downstream effectors pivotal for cellular proliferation and survival [10].

One key mechanism by which IGF-1R promotes fibroadenoma progression is through the activation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway. Activation of Akt phosphorylates downstream targets involved in cell cycle

regulation and apoptosis evasion, thereby fostering tumor cell proliferation and survival. Additionally, IGF-1R-mediated activation of the mitogen-activated protein kinase (MAPK) pathway promotes cell proliferation and migration, further driving fibroadenoma growth and progression [11]. Furthermore, the dysregulation of IGF-1R signaling within the tumor microenvironment contributes to the establishment of a pro-tumorigenic milieu conducive to tumor growth and metastasis. IGF-1R activation stimulates the production of growth factors and cytokines, promoting angiogenesis and facilitating tumor cell invasion and metastatic dissemination [12].

Central to the pathophysiology of breast cancer is the dysregulation of multiple signaling pathways governing cellular proliferation, survival, and metastasis, with the Insulin-like Growth Factor 1 Receptor (IGF-1R) pathway emerging as a critical player across diverse breast cancer subtypes. In the luminal subtype of breast cancer, characterized by the expression of hormone receptors (estrogen receptor [ER] and/or progesterone receptor [PR]), dysregulated IGF-1R signaling contributes to hormone-independent tumor growth and resistance to endocrine therapies. Upon ligand binding, IGF-1R activates downstream effectors such as the PI3K/Akt pathway, promoting cell cycle progression and survival even in the absence of hormonal stimulation [13].

Similarly, in HER2-positive breast cancer, amplification and overexpression of the human epidermal growth factor receptor 2 (HER2) gene drive constitutive activation of IGF-1R signaling, leading to enhanced tumor cell proliferation and survival. The cross-talk between HER2 and IGF-1R pathways potentiates downstream signaling cascades, including the MAPK pathway, further fueling tumor growth and metastasis. In triple-negative breast cancer (TNBC), characterized by the absence of ER, PR, and HER2 expression, dysregulated IGF-1R signaling plays a pivotal role in promoting aggressive tumor behavior and therapeutic resistance [14]. Activation of IGF-1R triggers diverse signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, facilitating tumor cell proliferation, invasion, and immune evasion. Moreover, within the tumor microenvironment, dysregulated IGF-1R signaling contributes to the establishment of a protumorigenic milieu characterized by angiogenesis, inflammation, and immune suppression. IGF-1R activation promotes the secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF), fostering tumor angiogenesis and facilitating nutrient supply to support tumor growth and metastasis [15].

2. Methods

This review article comprehensively examines the tumor cytobiology of Insulin-like Growth Factor 1 Receptor (IGF-1R) in breast tumor activation and propagation, with a specific focus on the inhibitory role of Celecoxib. A systematic literature search was conducted using electronic databases, including PubMed, MEDLINE, and Google Scholar, to identify relevant studies published in peer-reviewed journals. Search terms included "IGF-1R," "breast cancer," "Celecoxib," "tumor activation," and "tumor propagation." Studies were screened based on their relevance to the topic of interest, with a particular emphasis on molecular mechanisms, cellular pathways, and clinical implications. Data extraction was performed to retrieve key findings related to the involvement of IGF-1R in breast tumor activation and propagation, as well as the mechanisms underlying Celecoxib's inhibition of IGF-1R signaling. Information regarding the molecular interactions between Celecoxib and IGF-1R, as well as downstream signaling pathways affected by Celecoxib treatment, was compiled and analyzed. Additionally, studies investigating the pharmacokinetics of Celecoxib, including its absorption, metabolism, and excretion, were reviewed to provide insights into its therapeutic potential and clinical utility.

3. Unraveling the Intricate Cytobiological Pathways Regulated by Insulin-like Growth Factor 1 Receptor (IGF-1R) in Breast Cancer Metastasis

The Insulin-like Growth Factor 1 Receptor (IGF-1R) plays a pivotal role in the invasion and metastasis of breast cancer cells by orchestrating a complex array of molecular mechanisms that promote cellular motility, invasiveness, and survival. Understanding the detailed cytobiological pathways regulated by IGF-1R is crucial for elucidating its contribution to breast cancer metastasis and identifying potential therapeutic targets to intervene in this process [16].

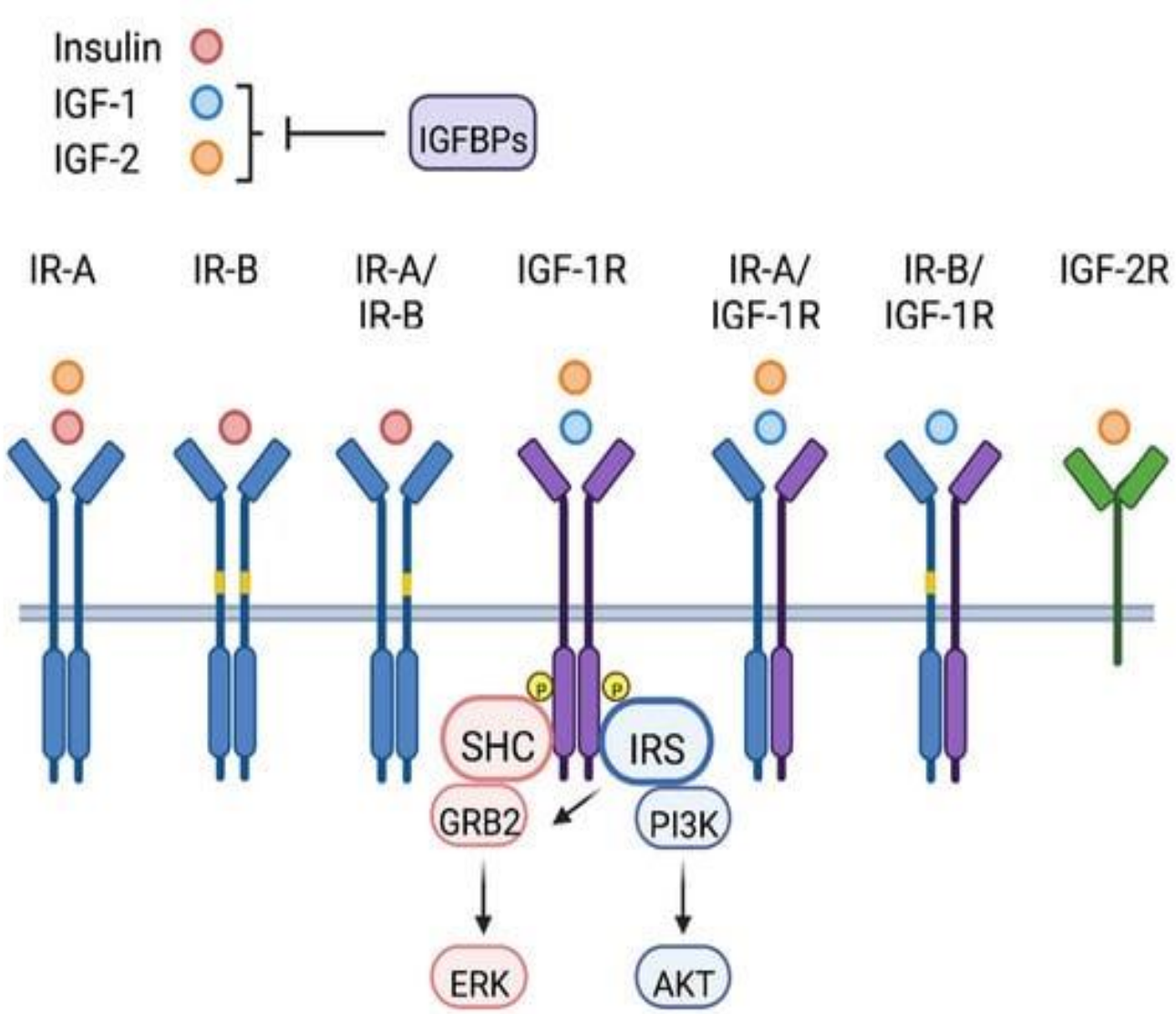

Figure 1. The insulin and insulin-like growth factor signaling pathway consists of insulin, IGF-1, and IGF-2 ligands, along with their corresponding receptors (insulin receptor, IGF-1 receptor, and IGF-2 receptor), and IGF binding proteins (IGFB Ps). The receptors can form homodimers or heterodimers, activating downstream signaling pathways involving SHC and insulin receptor substrate (IRS) proteins. Additionally, the IGF-2 receptor acts as a decoy receptor to block IGF-2 signaling. In normal conditions, insulin primarily binds to insulin receptors, IGF-1 binds to IGF-1 receptors and hybrid receptors, and IGF-2 binds to IR-A, IGF-1R, and IR-A/IGF-1R hybrid receptors. IGFBPs regulate the availability of IGF-1 and IGF-2 [17].

3.1. Enhanced Cellular Motility

IGF-1R activation stimulates the reorganization of the cytoskeleton and the formation of dynamic protrusions such as lamellipodia and filopodia, facilitating cell motility and migration. This process is mediated by the activation of downstream effectors such as the Rho family of small GTPases, which regulate actin dynamics and cytoskeletal rearrangements necessary for cell movement [18].

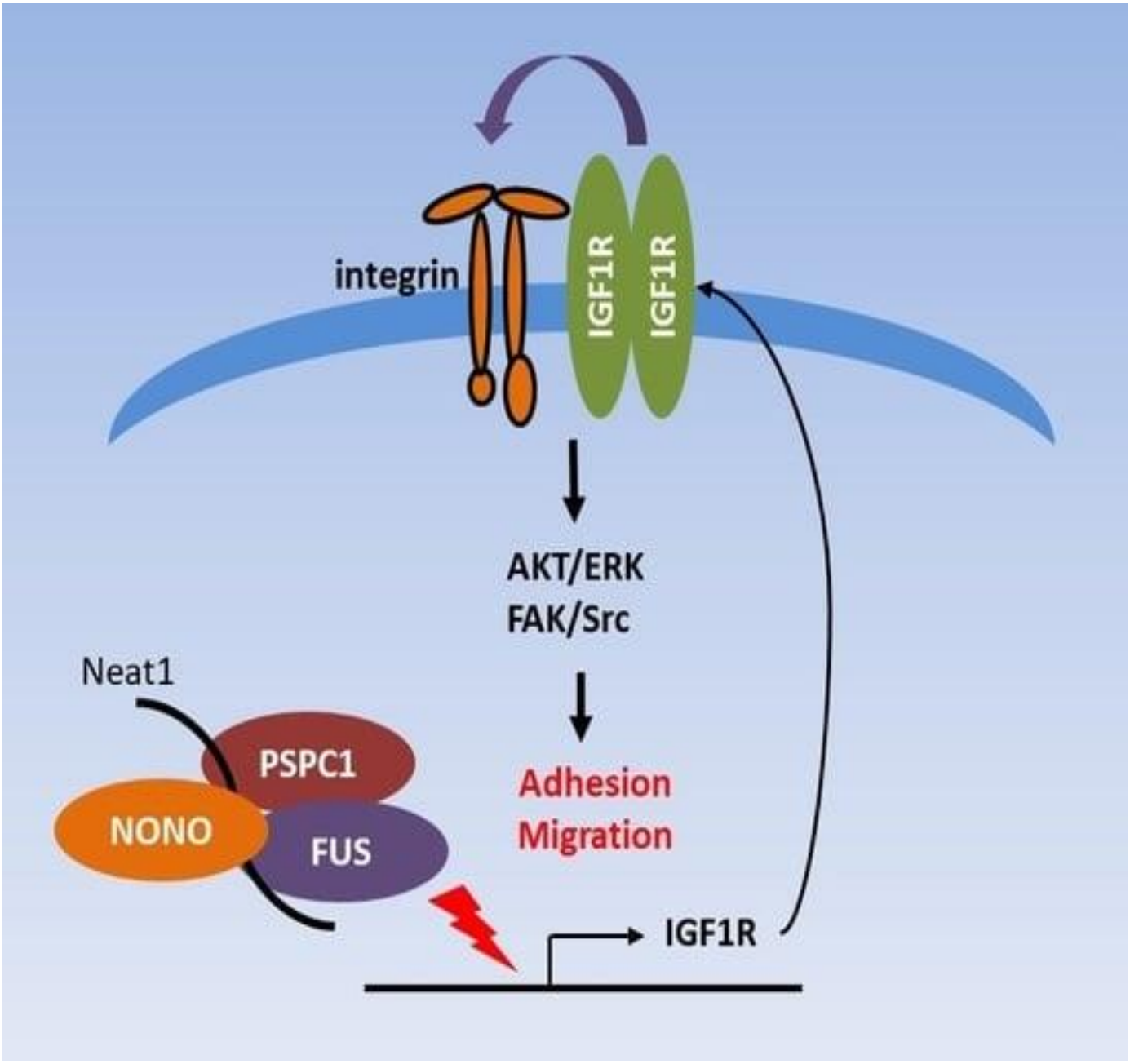

Figure 2. Activation of IGF1R leads to the activation of canonical downstream signaling pathways, such as PI3K/AKT and MAPK/ERK, crucial for tumor cell growth, survival, migration, epithelial-mesenchymal transition (EMT), and drug resistance. Moreover, IGF1R interacts with integrin cell surface receptors to activate non-canonical signaling pathways involving FAK and Src kinases, promoting focal contact maturation and cytoskeleton remodeling, thereby enhancing cellular motility, invasion, and metastasis. PSPC1, a protein, enhances cell adhesion and motility by increasing IGF1R expression, thereby stimulating downstream focal adhesion and integrin signaling pathways, including integrin/FAK/Src and AKT axes. The interaction between PSPC1 and IGF1R, along with their associated lncRNA Neat1, contributes to potentiated cell motility. These findings offer insights into the molecular mechanisms underlying the oncogenic PSPC1/IGF1R axis and suggest its potential as a therapeutic target and biomarker for innovative theranostic approaches in cancer treatment [18].

3.2. Extracellular Matrix Degradation

IGF-1R signaling promotes the secretion of matrix metalloproteinases (MMPs) and other proteases that degrade the extracellular matrix (ECM), facilitating tumor cell invasion through basement membranes and surrounding stromal tissues. MMPs degrade ECM components such as collagen and fibronectin, creating pathways for tumor cell migration and invasion [19].

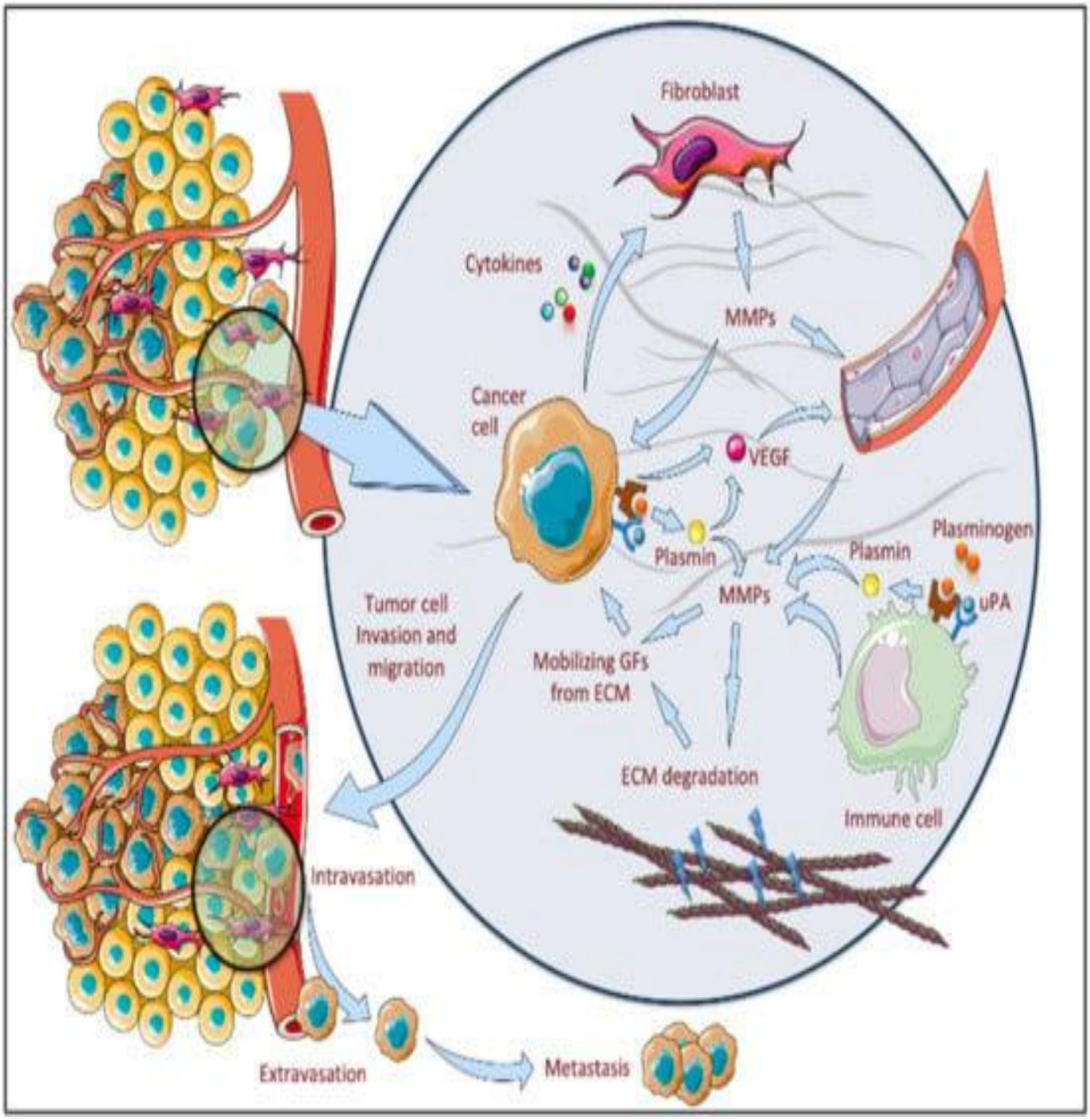

Figure 3. In the complex landscape of the tumor microenvironment, matrix metalloproteinases (MMPs) play a pivotal role. They are not only secreted by fibroblasts, immune cells, and tumor cells but also interact with other components of the microenvironment. Plasminogen, upon binding to its receptors, undergoes conversion to plasmin facilitated by urokinase plasminogen activator (uPA). Plasmin, in turn, can activate multiple MMPs and specific growth factors. Together, these molecules orchestrate a conducive microenvironment conducive to extracellular matrix (ECM) degradation, facilitating tumor cell invasion and migration [20].

3.3. Epithelial-Mesenchymal Transition (EMT)

Activation of IGF-1R signaling induces the epithelial-mesenchymal transition (EMT), a process characterized by the loss of epithelial traits and acquisition of mesenchymal characteristics, including increased motility and invasiveness. IGF-1R-mediated EMT is driven by the downregulation of epithelial markers (e.g., E-cadherin) and upregulation of mesenchymal markers (e.g., N-cadherin, vimentin), enabling tumor cells to adopt a more invasive phenotype [21].

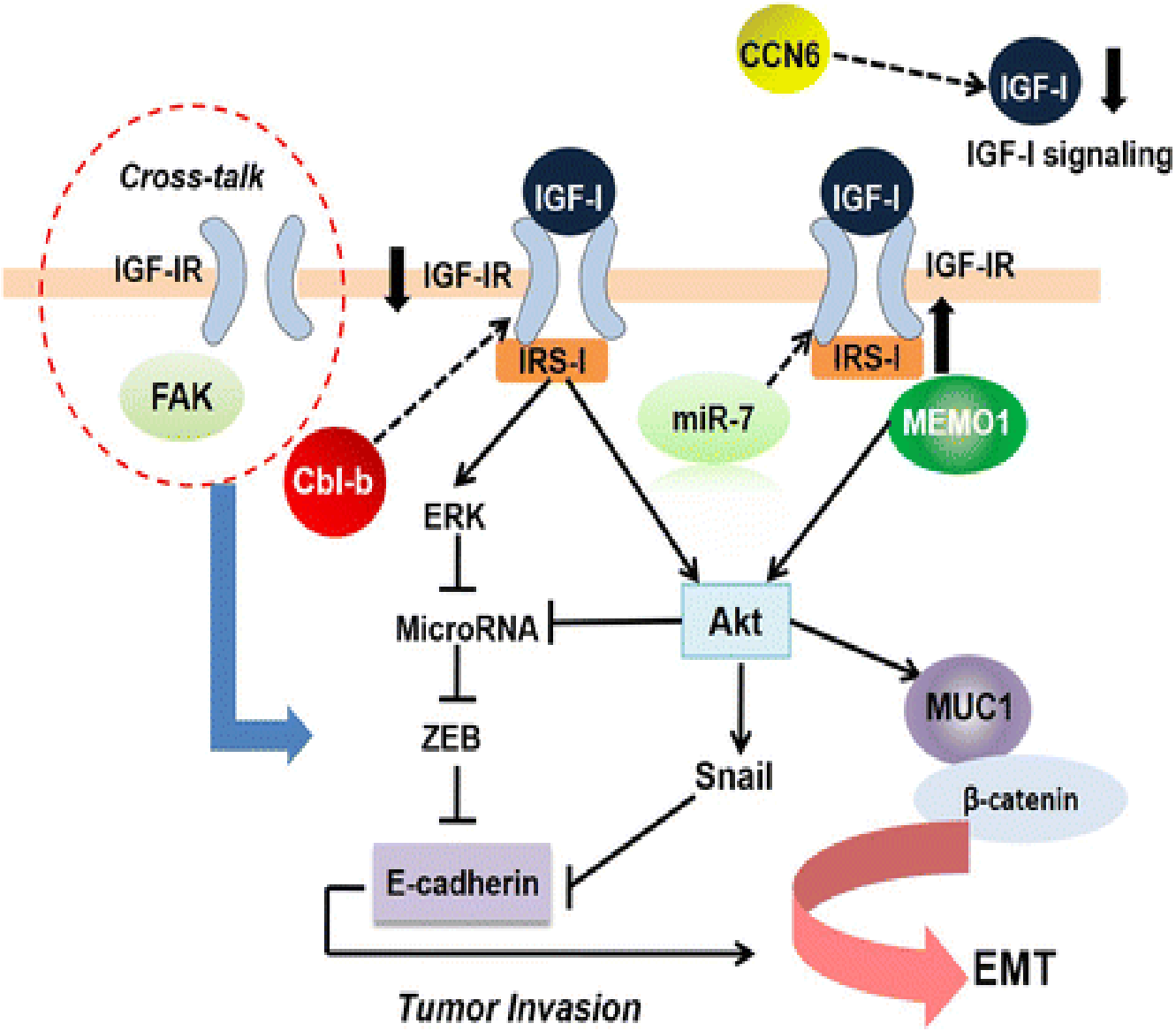

Figure 4. Several critical factors contribute to the insulin-like growth factor receptor (IGF-IR)-mediated epithelial-mesenchymal transition (EMT) process. As a transmembrane tyrosine kinase receptor, IGF-IR activation initiates downstream signaling cascades, including the phosphorylation of insulin receptor substrate 1 (IRS-1), subsequently activating the PI3K/Akt and ERK/MAPK pathways. Specifically, IGF-I-induced EMT involves an Akt-GSK-3β-ZEB2 axis and an Akt/ERK-miR-200c-ZEB2 axis. Additionally, ubiquitin ligase Cbl-b regulates IGF-IR degradation, thus inhibiting the Akt/ERK-miR-200c-ZEB2 axis in IGF-I-induced EMT. CCN6 protein contributes to maintaining normal breast homeostasis by decreasing extracellular IGF-I levels and repressing IGF-IR signaling. MEMO1 triggers EMT via activation of the IGF-IR/IRS-1 pathway, while MUC1 serves as a critical downstream effector mediating IGF-I-induced EMT in breast cancer cells. MicroRNA-7 counteracts EMT progression by targeting IGF-IR in gastric cancer. Furthermore, IGF-IR interacts with focal adhesion kinase (FAK) in triple-negative breast cancer (TNBC), enhancing ZEB-1 and Snail expression, thereby promoting EMT, cell migration, and invasion [22].

3.4. **Angiogenesis**

IGF-1R signaling promotes angiogenesis, the process of new blood vessel formation, by stimulating the secretion of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Enhanced angiogenesis facilitates the recruitment of blood vessels to support tumor growth and metastasis, providing nutrients and oxygen to fuel the expanding tumor mass [23].

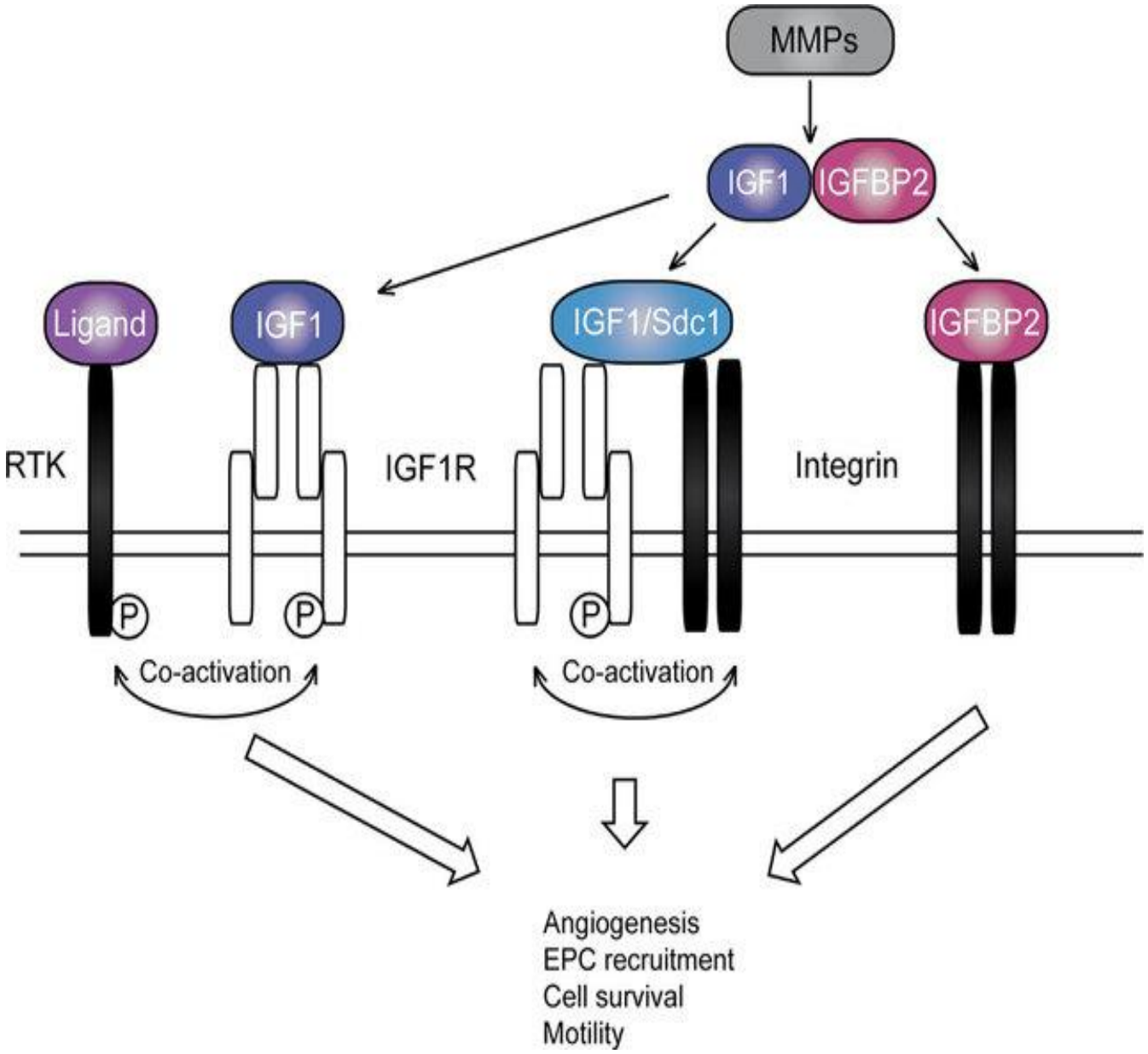

Figure 5. The interplay between insulin-like growth factors (IGF) and angiogenic signaling involves intricate mechanisms. IGF receptors (IGFRs), such as IGF1R, can collaborate with other receptor tyrosine kinases (RTKs), leading to heightened pro-angiogenic signaling. Both IGF1 and syndecan-1 (Sdc1) can induce clustering of IGFRs and integrins, synergistically activating these membrane proteins and amplifying the pro-angiogenic response. Additionally, integrins can be directly stimulated by IGF binding protein 2 (IGFBP2). Matrix metalloproteinases (MMPs) play a role in disrupting the interaction between IGFs and IGFBP2, thereby increasing the bioavailability of both proteins and sustaining angiogenic actions. This interplay contributes to the regulation of endothelial progenitor cell (EPC) function and angiogenesis [24].

3.5. **Immune Evasion**

IGF-1R signaling contributes to immune evasion by suppressing anti-tumor immune responses and promoting immune tolerance within the tumor microenvironment. Activation of IGF-1R inhibits the function of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, impairing their ability to recognize and eliminate tumor cells. Additionally, IGF-1R signaling promotes the recruitment of immunosuppressive cell populations such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further dampening anti-tumor immunity [25].

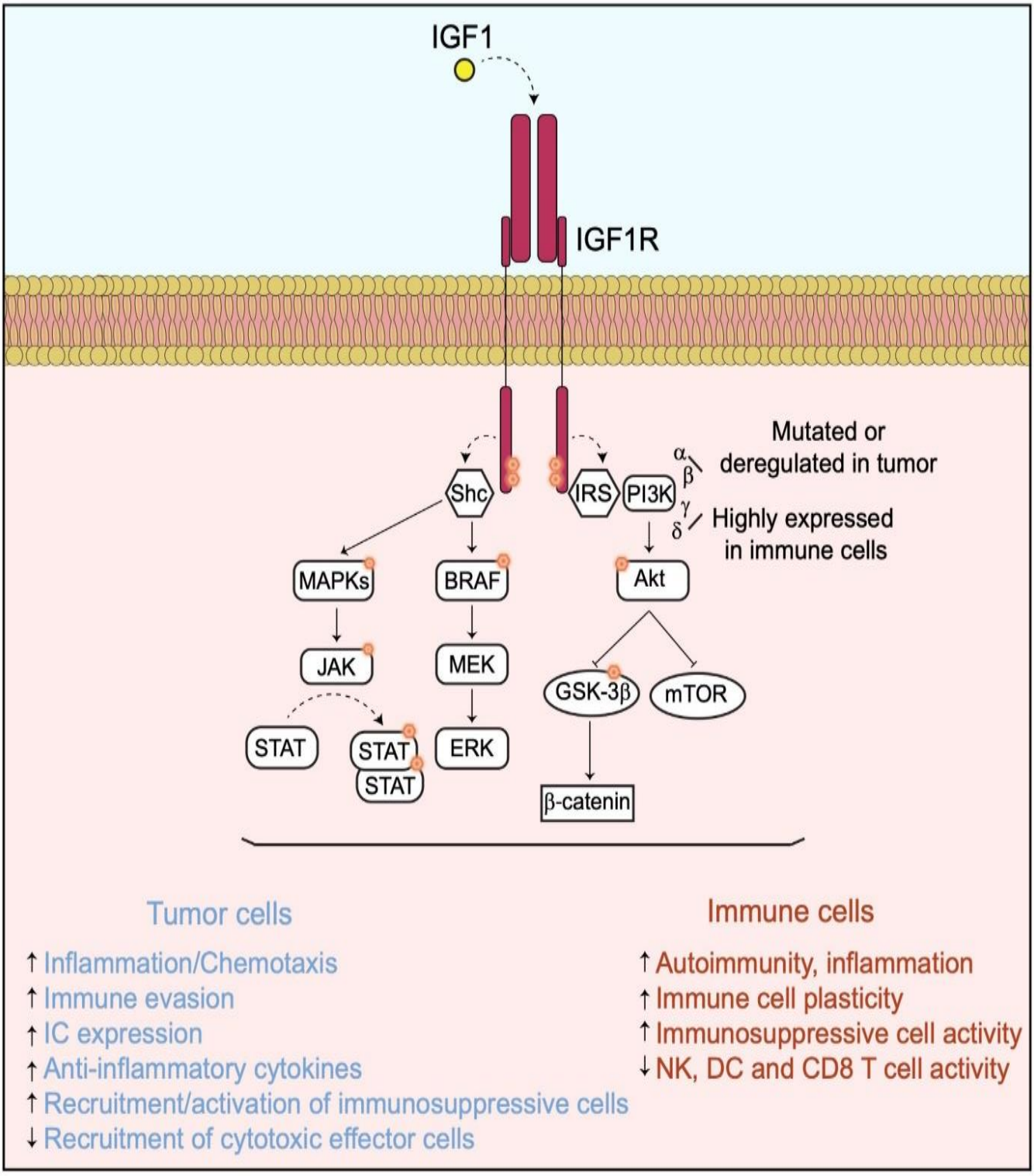

Figure 6. The IGF1/IGF1R axis plays a crucial role in cancer biology by activating downstream signaling pathways associated with cell proliferation, survival, and immunomodulation. Upon binding of IGF1 to IGF1R, various signaling cascades are initiated, facilitating cancer cell growth and resistance to cell death. Additionally, these pathways can influence the tumor microenvironment by modulating immune responses [26].

3.6. **Metastatic Colonization**

IGF-1R signaling promotes the survival and outgrowth of disseminated tumor cells at metastatic sites by enhancing their interaction with the microenvironment and facilitating the establishment of metastatic niches. Activation of IGF-1R promotes the expression of survival factors and anti-apoptotic proteins, enabling disseminated tumor cells to resist anoikis and other pro-apoptotic

signals encountered during transit and colonization [27].

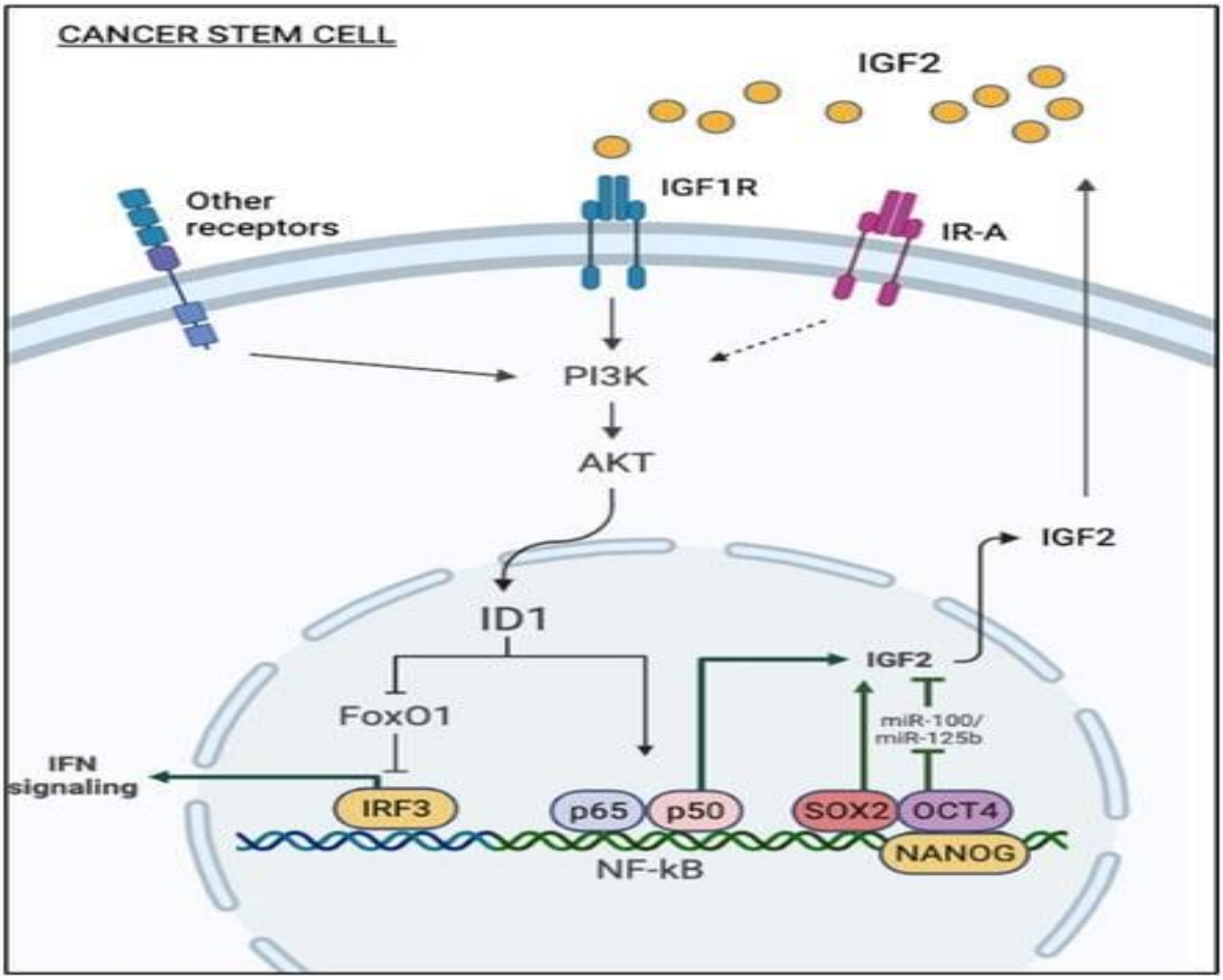

Figure 7. In cancer stem cells, autocrine production of insulin-like growth factor 2 (IGF2) is regulated through several mechanisms. Autocrine IGF2 stimulates the expression of inhibitor of DNA binding 1 (Id1) via the PI3K/AKT pathway. Id1, in turn, relieves the suppression of interferon regulatory factor 3 (IRF3) promoter induced by the transcription factor FOXO, thus derepressing interferon (IFN) signaling. Consequently, Id1 also upregulates IGF2, activating the NF-κB pathway. Additionally, transcription factors associated with cancer cell stemness, such as SOX2, OCT4, and Nanog, can stimulate the autocrine production of IGF2. Loss of expression of microRNAs miR-100 and miR-125b further enhances stem cell features of cancer cells by upregulating the IGF2/Akt/mTOR pathway. These mechanisms collectively contribute to the autocrine production of IGF2 in cancer stem cells, promoting their self-renewal and survival abilities [28].

4. Unveiling the Intricacies of Celecoxib's Inhibition of Insulin-like Growth Factor 1 Receptor (IGF-1R) Pathway in Breast Cancer: Insights into Cytobiological Mechanisms and Pharmacokinetics

Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID) primarily used for the management of pain and inflammation associated with arthritis, has garnered increasing attention for its potential anticancer properties, particularly in breast cancer. One of the mechanisms underlying its anticancer effects involves the inhibition of the Insulin-like Growth Factor 1 Receptor (IGF-1R) pathway, thereby impeding tumor growth and metastasis [29]. the detailed cytobiological mechanisms of Celecoxib's inhibition of IGF-1R, including its pharmacokinetics:

4.1. Molecular Interaction

Celecoxib inhibits IGF-1R through direct binding to the ATP-binding pocket of the receptor. This interaction prevents ATP from binding to the receptor, thereby hindering receptor autophosphorylation, a crucial step in receptor activation. Structural studies have elucidated the precise binding mode of Celecoxib within the ATP-binding pocket, highlighting key residues involved in the interaction and providing insights into the mechanism of inhibition [30].

4.2. Downregulation of IGF-1R Expression

Celecoxib modulates gene expression profiles, leading to the downregulation of IGF-1R at both the transcriptional and translational levels. This effect is mediated by the inhibition of transcription factors or signaling pathways involved in IGF-1R gene regulation. Celecoxib-induced changes in chromatin structure or epigenetic modifications may also contribute to the suppression of IGF-1R expression, resulting in reduced receptor abundance on the cell surface [31].

4.3. Inhibition of Downstream Signaling Pathways

Celecoxib disrupts downstream signaling cascades activated by IGF-1R, including the PI3K/Akt and MAPK pathways. By inhibiting the phosphorylation of Akt and ERK, key mediators of cell survival and proliferation, Celecoxib attenuates the pro-survival and growth-promoting signals initiated by IGF-1R activation. This leads to the inhibition of cell proliferation and survival, thereby impeding tumor growth and metastasis [32].

4.4. Induction of Apoptosis

Celecoxib promotes apoptosis in breast cancer cells by sensitizing them to apoptotic stimuli and triggering caspase-dependent cell death pathways. Inhibition of IGF-1R signaling by Celecoxib disrupts the balance between pro-survival and pro-apoptotic signals, leading to the activation of apoptotic pathways and subsequent tumor cell death. This apoptotic effect contributes to the anticancer properties of Celecoxib in breast cancer therapy [33].

4.5. Pharmacokinetics

Celecoxib exhibits favorable pharmacokinetic properties, including good oral bioavailability and rapid absorption following oral administration. It undergoes extensive metabolism in the liver, primarily by cytochrome P450 enzymes, to form inactive metabolites that are excreted primarily in the feces. The plasma half-life of Celecoxib ranges from 3 to 11 hours, allowing for sustained inhibition of IGF-1R signaling with regular dosing. These pharmacokinetic characteristics contribute to the efficacy and safety profile of Celecoxib as an anticancer agent targeting IGF-1R [34].

5. Results:

The literature review revealed compelling evidence supporting the critical role of IGF-1R in breast tumor activation and propagation. Aberrant expression and activation of IGF-1R have been consistently implicated in breast cancer pathogenesis, contributing to tumor growth, metastasis, and therapeutic resistance. Molecular interactions between IGF-1R and its ligands, including IGF-1 and IGF-2, trigger downstream signaling cascades, including the PI3K/Akt and MAPK pathways, which promote cell proliferation, survival, and invasion. Furthermore, studies investigating the inhibitory effects of Celecoxib on IGF-1R signaling have demonstrated promising therapeutic potential. Celecoxib exerts its anticancer effects by directly binding to IGF-1R, inhibiting receptor autophosphorylation, and disrupting downstream signaling pathways. Moreover, Celecoxib downregulates IGF-1R expression at both the transcriptional and translational levels, leading to reduced receptor abundance on the cell surface. Additionally, Celecoxib induces apoptosis in breast cancer cells by sensitizing them to apoptotic stimuli and triggering caspase-dependent cell death pathways. Overall, the findings of this review underscore the significance of IGF-1R as a therapeutic target in breast cancer and highlight the potential of Celecoxib as an adjuvant therapy for inhibiting IGF-1R-mediated tumor activation and propagation. Further research is warranted to elucidate the precise molecular mechanisms

underlying Celecoxib's anticancer effects and to optimize its therapeutic efficacy in breast cancer management.

6. Discussion

The elucidation of the tumor cytobiology of Insulin-like Growth Factor 1 Receptor (IGF-1R) in breast cancer activation and propagation, as well as the inhibitory role of Celecoxib, underscores the intricate interplay between molecular pathways and therapeutic interventions in breast cancer management. Our review highlights the pivotal contribution of dysregulated IGF-1R signaling to breast cancer pathogenesis, including tumor growth, metastasis, and therapeutic resistance. By targeting IGF-1R, Celecoxib offers a promising therapeutic strategy for disrupting key signaling cascades involved in breast cancer progression. One of the notable findings of this review is the multifaceted mechanisms through which Celecoxib exerts its inhibitory effects on IGF-1R signaling. Through direct molecular interactions with IGF-1R and downstream effectors, Celecoxib disrupts crucial signaling pathways involved in cell proliferation, survival, and invasion. Furthermore, Celecoxib modulates gene expression profiles, leading to the downregulation of IGF-1R expression and the induction of apoptotic pathways in breast cancer cells. These findings underscore the pleiotropic effects of Celecoxib on IGF-1R-mediated tumorigenesis and highlight its potential as a multifaceted therapeutic agent in breast cancer treatment. Moreover, the pharmacokinetic profile of Celecoxib, characterized by favorable oral bioavailability and sustained plasma levels, enhances its clinical utility as an adjuvant therapy for breast cancer. The ability of Celecoxib to inhibit IGF-1R signaling with regular dosing provides a rationale for its incorporation into existing treatment regimens to improve patient outcomes and survival rates. However, further clinical studies are warranted to evaluate the safety, efficacy, and long-term effects of Celecoxib in breast cancer patients, particularly in combination with standard-of-care therapies.

7. Conclusion

In conclusion, the tumor cytobiology of IGF-1R in breast cancer activation and propagation represents a dynamic and multifaceted process regulated by intricate molecular pathways. Celecoxib, through its inhibitory effects on IGF-1R signaling, offers a promising therapeutic approach for disrupting tumor growth and metastasis in breast cancer. The findings of this review underscore the importance of targeting IGF-1R-mediated pathways in breast cancer management and highlight the potential of Celecoxib as a valuable addition to current treatment strategies.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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