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Review

Mini Review: Molecular Interpretation of the IGF/IGF-1R Axis in Cancer Treatment and Stem Cells-Based Therapy in Regenerative Medicine

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Abstract: In addition to the fundamental role of insulin-like growth factor (IGF)/IGF-1 receptor (IGF-1R) signaling dysregulation in cancer initiation and proliferation, the IGF/IGF-1R signaling also plays an important role in the maintenance of stem cell characteristics and enhancement of stem cell-based therapeutic efficacy. This review focused on the role of IGF/IGF-1R signaling in preclinical IGF-targeted therapies, including IGF-1R monoclonal antibodies, IGF-1R tyrosine kinase inhibitors, and neutralizing antibodies of IGFs in multiple tumors and endocrine disorders. On the other hand, the function of IGF/IGF-1R signaling in stem cell self-renewal, pluripotency and therapeutic efficacy in regenerative medicine was outlined. Finally, the review summarized ongoing studies on IGF/IGF-1R signaling blockade in multiple cancers and highlighted the IGF-1R signaling modifications in stem cells as a potential strategy to improve stem cell-based therapeutics in regenerative medicine.

Keywords: IGF; IGF-1R; monoclonal antibodies; cancer; stem cells; stem cell therapy; regenerative medicine

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1. Introduction

Insulin-like growth factors (IGFs) play pivotal autocrine, paracrine and endocrine roles in the promotion of cell proliferation, differentiation and survival [1,2]. IGFs are members of a ligand family that includes insulin, IGF-1 as well as IGF-2, and they exert their action by binding to specific glycoprotein membrane receptors, namely, type 1 and type 2 IGF receptors (IGF-1R and IGF-2R), insulin receptors A and B (INSR-A and INSR-B) and hybrid receptors (IGF-1R/INSR-A and IGF-1R/INSR-B) [3,4]. Moreover, there is a noticeable homology among the IGF receptors, implying structural similarity and the possibility of signaling crosstalk [3]. Notably, IGFs binding to IGF receptors is regulated by soluble IGF binding proteins (IGFBPs), a family of six homologous molecules with high binding affinity for IGF-1 and IGF-2; IGFBP-3 is the most important of the homologous molecules, which binds to 80% of the IGF-1 [5]. IGF-1R has a tetrameric structure that is comprised of two alpha (α) subunits and two transmembrane beta (β) subunits linked by disulfide bonds [6]. The α subunits are the extracellular domain that directly binds to IGF, and each transmembrane β subunit contains an intracellular tyrosine kinase domain [7]. After engaging, the binding of IGFs induces a conformational change that activates the

tyrosine kinase domain of the β subunit, leading to the autophosphorylation of specific tyrosine residues, which appears to be a critical step in receptor activation [8].

The IGF/IGF-1R signaling has been reported to play an important role in cancer development (Figure 1). Previous studies have reported that the activation of IGF/IGF-1R signaling is essential for cancer initiation and progression through several distinct pathways, including phosphorylation of mitogen-activated protein kinase (MAPK), which subsequently increases cell proliferation, the activation of phosphatidylinositol 3′ kinase (PI3K), which decreases apoptosis, and the regulation of mammalian target of rapamycin (mTOR) expression, which results in translational adaptation [9,10]. However, the activation of signaling pathways is also enhanced by other receptor tyrosine kinases (RTKs). For example, epidermal growth factor receptor (EGFR) enhances MAPK expression, promoting tumor cell proliferation and metastasis; fibroblast growth factor receptor (FGFR) increases PI3K/AKT expression, enhancing tumor angiogenesis; and hepatocyte growth factor receptor (HGFR or MET) enhances phosphorylated extracellular-signal-regulated kinase (ERK) expression, resulting in tumor survival and growth [11–14]. Notably, IGF-1R signaling has also been demonstrated to regulate the cancer stemness in various cancer stem cell (CSC) models, involving colorectal [15], breast [16], liver [17] and lung cancers [18]. IGF-1R signaling is also implicated in cancer development due to its stemness-related properties [16,19] and the resistance of radiation therapy and chemotherapy [20]. Furthermore, several studies showed that the elimination of cancer stemness by inhibiting IGF-1R signaling could be a considered way of targeting IGF/IGF-1R in cancer therapy [19,21]. However, several clinical trials of IGF/IGF-1R-targeting have experienced difficulty, leading to being terminated [22]. Hence, specific biomarkers for selecting suitable patients and the precise targeting of IGF-1R in CSCs are required. For example, the precise targeting of IGF-1R is feasible through the bioengineering of patient-derived chimeric antigen receptor (CAR)-T cells in sarcomas [23].

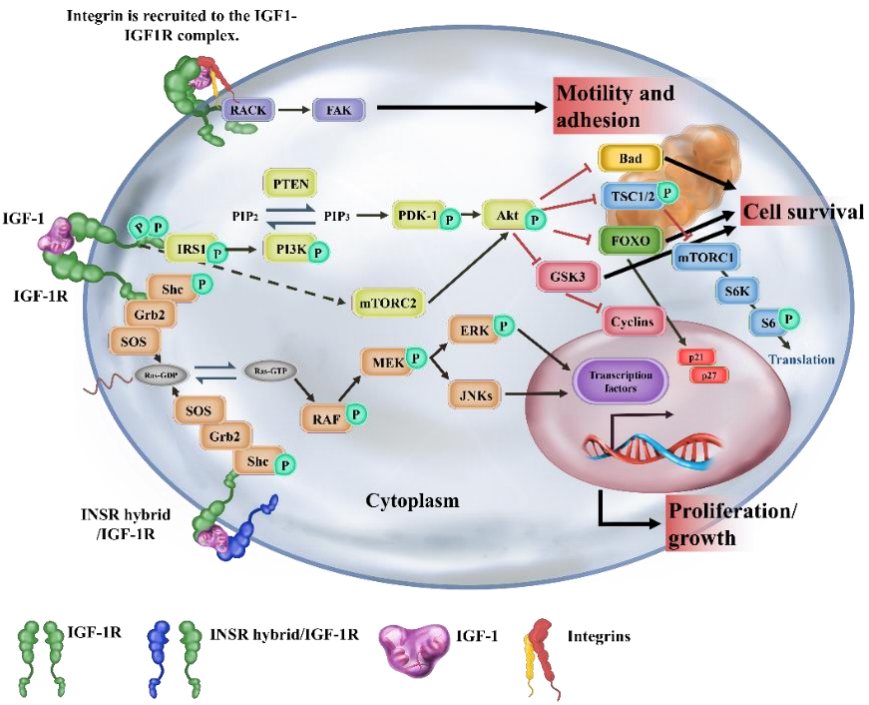

Figure 1. Downstream signaling of insulin-like growth factor-1 receptor (IGF-1R). Ligand binding to IGF-1R or IGF-1R/INSR hybrid receptors leads to the phosphorylation of tyrosines that create binding sites for docking proteins including IRS and Shc. Recruitment of IRS and Shc activates signaling via the PI3K/Akt and Ras/Raf/MAPK pathways, which regulate cellular proliferation, survival, migration, and metabolism. In addition to these pathways, interactions between IGF-1R and

integrins, via scaffolding with RACK1 and FAK proteins, regulate cellular adhesion and motility. Black arrows indicate activation. Red arrows indicate inhibition. The symbol of P represents the site of phosphorylation. Akt, protein kinase B; ERK, extracellular-signal-regulated kinase; IRS, INSR substrate; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/Erk kinase; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin homolog; Shc, Src homology and collagen domain protein.

On the other hand, regenerative medicine is a major focus to determine novel therapies as well as to explore the biology and the pathogenesis of disease [24]. Recent advances in the isolation and development of stem cell have prompted scientists to identify and culture specific cell types for regeneration in various disorders including Parkinson [25], Alzheimer [26], or diseases of the heart [27], muscles [28], lung [29] and liver tissue [30]. Therefore, stem cells are considered efficient tools to treat tissue injuries in regenerative medicine. Several studies have indicated that growth factors including basic fibroblast growth factor (bFGF) and IGFs maintain the stemness and pluripotency of stem cells. Notably, the IGF/IGF-1R signaling has been reported to regulate the self-renewal and stemness of human embryonic stem cells (hESCs) [31,32] as well as the multipotent differentiation and repair capability of mesenchymal stem cells (MSCs). In hESCs differentiation, the overexpression of both IGF-1 and IGF-2 and IGF-1R phosphorylation lead to the differentiation of ESCs into hepatocytes [33,34]. In addition, the overexpression of IGF-1 in human bone marrow mesenchymal stem cells (BMSCs) has been reported to induce CXCL12/CXCR4 signaling in vitro. After transplantation in a rat model of permanent coronary artery occlusion, IGF-1 overexpression in BMSCs accelerated cell mobilization and retention in the injured area through the paracrine action of CXCL12/CXCR4 signaling to improve cardiomyocyte repair [35]. In this review, we discuss the clinical relevance of therapeutic strategies that target the IGF/IGF-1R axis in multiple malignant tumors and the applicability of IGF/IGF-1R axis strategies to improve stem cell-based therapies for human diseases.

2. Therapeutic Strategies Targeting IGF/IGF-1R Axis in Cancer

Recently, a number of different strategies targeting IGF/IGF-1R signaling have been developed for clinical evaluation, including anti-IGF-1R monoclonal antibodies (mAbs), small-molecule tyrosine kinase inhibitors (TKIs), and IGF-1 and 2 neutralizing antibodies (Figure 2). The following sections summarize the physical properties of each class of agents and their clinical evaluation status.

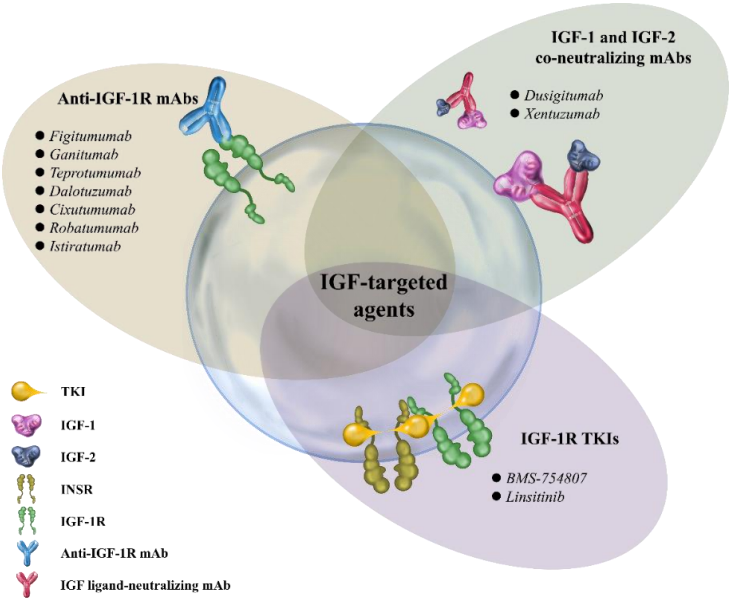

Figure 2. Examples of IGF-targeted agents. Anti-IGF-1R mAbs block ligand–receptor interactions and induce receptor internalization and degradation. Tyrosine kinase inhibitors bind to the receptor

tyrosine kinase domain and block the downstream signaling of IGF-1R and INSR. IGF ligand-neutralizing mAbs bind to both IGF ligands (IGF-1 and IGF-2), thereby blocking the activation of IGF-1R and INSR-A. IGF-1R, insulin-like growth factor-1 receptor; mAbs, monoclonal antibodies; TKI, tyrosine kinase inhibitors; INSR, insulin receptor.

2.1. Anti-IGF-1R mAbs

Several studies have declared that IGF-1R is necessary for cellular oncogenes and is important in modulating the cell survival, motility, adhesion, and metastasis in multiple tumors and endocrine disorders [36,37]. For example, IGF-1R was frequently overexpressed in breast tumors, and its overexpression was important in the malignant transformation of mammary cells [38]. Moreover, the overexpression of IGF-1R provides breast tumors with an inherent resistance to radiotherapy and worsens the prognosis of patients [39]. These findings suggest that IGF-1R is a potential target for therapeutic interventions. The initial strategy involves the use of anti-IGF-1R mAbs to block ligand–receptor interactions and cause IGF-1R internalization and subsequent degradation [40,41]. Several therapeutic mAbs directed against IGF-1R have been developed, and encouraging preclinical outcomes have been observed with figitumumab (IgG2a, phase III) [42–44], ganitumab (IgG1, phase III) [45–47], dalotuzumab (IgG1, phase III) [48,49], teprotumumab (IgG1, phase II) [50,51], cixutumumab (IgG1, phase II) [52,53], robatumumab (IgG1, phase II) [54,55], and BIIB022 (IgG4, phase I) [56] in many malignant tumors. Moreover, istiratumab is a bispecific mAb that inhibits both IGF-1R and ErbB3 (IgG1 with two scFvs, phase II) [57] to kill malignant tumors. In addition, even though some IGF-1R mAbs for INSR exert negligible affinity, these IGF-1R mAbs still bind to their hybrid receptors, causing signal down-regulation. Some preclinical trials have reported Kirsten rat sarcoma virus (KRAS)-mutant tumors with high levels of free circulating IGF-1 in patients, and several reports have suggested that KRAS mutation has varying significance on the effect of IGF-1R inhibition, depending on the tumor type and/or molecular context. For instance, dalotuzumab has been used to treat KRAS wild-type colorectal cancer, with no evidence of anti-tumor activity [43]. However, this report indicated that the KRAS mutation enhanced IGF overexpression and resulted in PI3K activation, which were suppressed by targeting IGF-1R using figitumumab in non-small cell lung cancer cells (NSCLCs) [58]. Conversely, ganitumab was reported to be ineffective in sensitizing patients with KRAS-mutant colorectal cancer to folinic acid, fluorouracil and irinotecan (FOLFIRI) chemotherapy [59]. However, several clinical studies showed that the development of IGF-1R mAbs (figitumumab and ganitumab) was terminated, even though they exhibited preclinical activity against IGF-1R in some tumors, such as myeloma, prostate cancer, colorectal cancer and pancreatic cancer [22]. It is notable that the two mAbs, ganitumab and teprotumumab, which are used as monotherapeutic agents or in combination therapies are in ongoing clinical trials. For example, a combination chemotherapy with ganitumab in patients with Ewing sarcoma is currently in a randomized phase III trial (NCT02306161). Additionally, teprotumumab was evaluated in patients with moderate-to-severe thyroid-associated ophthalmopathy (TAO) in active stages, with a response in 69% of patients receiving the teprotumumab agent compared to a response in 20% of patients receiving a placebo agent in a randomized Phase II trial (NCT01868997) [60]. Subsequently, positive outcomes of the Phase III OPTIC trial of teprotumumab (NCT03298867) were reported in April 2019 [61]. Notably, teprotumumab was approved by the United States Food and Drug Administration (FDA) for use in TAO (2020) [62].

2.2. IGF-1R TKIs

An alternative approach to suppress IGF-1R signaling involves the treatment with small molecule IGF-1R TKIs that block IGF-1R kinase activity. As mentioned previously, approximately 85% of sequence homology was observed between the IGF-1R and INSR-A/B kinase domains, including the ATP-binding site [63]. Some studies indicated that

ATP competitive antagonist of IGF-1R also inhibited the kinase activity of INSR [64,65]; therefore, linsitinib and BMS-754807 were frequently described as dual IGF-1R/INSR inhibitors [64,65]. For instance, linsitinib was reported to exert a superior anti-tumor activity of IGF-1R TKI and significantly blocked the compensatory INSR-A signaling. However, owing to the influence of linsitinib on metabolic insulin signaling through INSR-B, side effects including insulin resistance and hyperglycemia ensue [40,66]. Several studies have indicated the high expression of IGF signaling in many tumors and the sensitivity of tumors to IGF-1R inhibition. For example, the overexpression of IGF-1 in breast cancer cells in vitro was associated with poor prognosis of clinical cancers and correlated with the sensitivity to BMS-754807 in patients with triple-negative breast cancer in vivo [67,68]. Moreover, BMS-754807 has been known to have off-target effects in inhibiting the activation of tropomyosin-receptor-kinase A and B (TrkA and TrkB) and aurora kinases in pancreatic cancer [65], which influenced their therapeutic efficacy. However, some TKIs have exhibited promising preclinical activity in vitro; a few TKIs, including NVP-AEW541 [69], AZ12253801 [70] and BMS-536924 [71], have undergone clinical evaluation, and the results obtained have resulted in their termination. In addition, some TKIs belong to non-ATP competitive antagonists, which only inhibit IGF-1R; the INSR signaling is not affected, and these TKIs also suppress additional related genes. For instance, picropodophyllin (AXL1717) exhibits noticeable anti-tumor activity in multiple tumors through IGF-1R inhibition, leading to tumor regression [72,73], and AXL1717 also interferes with microtubule dynamics, which arrests G2/M phase [74]. Notably, the safety and efficacy of AXL1717 was demonstrated in a phase I clinical trial on patients with NSCLCs [75]. The other non-ATP competitive antagonist, nordihydroguai- aretic acid (masoprocol), was reported to inhibit cell proliferation of prostate tumor both in vitro and in vivo, but the clinical trial of nordihydroguaiaretic acid was terminated (NCT00678015) due to its hepatotoxicity and nephrotoxicity adverse effects [76].

2.3. IGF-Neutralizing Antibodies

This therapeutic approach involves neutralizing antibodies that directly target IGF-1 and IGF-2, thereby inhibiting survival signals through IGF-1R, INSR-A, and IGF-1R/INSR-A without interfering with INSR-B signaling and insulin action [77,78]. Therefore, these agents exhibit higher anti-tumor efficacy in multiple tumors and have a lower potential to cause hyperglycemia compared to IGF-1R TKIs [79–81]. Two IGF-neutralizing antibodies, including dusigitumab, a human IgG2λ monoclonal antibody with a high binding affinity for IGF-1 and IGF-2, inhibiting IGF-1R phosphorylation and INSR-A signaling, respectively, have been used in clinical trials [77]. Notably, dusigitumab suppresses the activation of IGF-1R and INSR-A, without binding to insulin, and thus retains insulin/INSR signaling [77]. Moreover, the phase I/II clinical trial of dusigitumab (NCT01446159) evaluated its anti-tumor efficacy and safety in combination with aromatase inhibitor in patients with metastatic breast cancer (hormone receptor (HR)-positive, and epidermal growth factor receptor 2-negative) [78]. The other antibody is xentuzumab, a IgG1 monoclonal antibody modified by humanization that binds to IGF-1 and IGF-2 with high affinity and blocks the IGF-1R and INSR-A functions [79]. Several studies showed that xentuzumab, in combination with other RTK inhibitors, was used in early clinical trials, including in EGFR-mutant NSCLC with afatinib (NCT02191891), in metastatic prostate cancer with enzalutamide (NCT02204072) and in HR-positive metastatic breast cancer with everolimus and exemestane (NCT02123823). Therefore, these combination agents demonstrated anti-tumor efficacy and a favorable safety profile, and they may serve as new promising therapeutic strategies in cancer therapy.

3. Activation of IGF/IGF-1R Signaling Improves Stem Cell-Based Therapeutic Strategies in Regenerative Medicine

Regenerative medicine is a new promising strategy to improve the treatment of tissue injury caused by trauma, disease, or aging. Owing to their self-renewal ability and pluripo-

tency, stem cells are considered as efficient tools in preventing and treating diseases as well as tissue injuries. Moreover, several studies indicated that some factors and signaling pathways, such as bFGF [82], transforming growth factor β1 (TGF-β1) [83], leukemia inhibitory factor (LIF) [84], bone morphogenetic proteins (BMPs) [85], Wnt/β-catenin signaling [86], SMAD signaling [85], and MAPK signaling [87], maintain the stemness and pluripotency of stem cells. Notably, several studies suggest that IGF/IGF-1R axis activation is a possible regulator of the self-renewal and pluripotent capacities of stem cells through autocrine, paracrine, and receptor crosstalk. The following sections focus on IGF/IGF-1R signaling modification as a promising strategy to improve stem cell-based therapies for human diseases, including heart failure, neurodegenerative and neurological diseases, as well as bone disorders (Table 1).

Table 1. Therapy efficacy in stem cells and MSCs that overexpress IGF-1R in regenerative medicine.

Overexpression of IGF/IGF-1R in Stem Cells	Function	Pathway	Disease	Ref.
hESCs	Promoting self-renewal and survival	Self-renewal through HRG/ERBB2, and anti-apoptosis through PI3K/AKT	-	[31,88]
UMSCs	Adipogenic differentiation	bFGF induces IGF and FGF receptor	-	[89]
BMSCs	Osteogenic differentiation	Hedgehog pathway	-	[90]
PMSCs	Increasing cell proliferation and maintaining multipotency	Induce OCT4 expression	-	[91,92]
BMSCs	Promoting cell survival and neural progenitor cell recruitment	-	Ischemic stroke	[93]
DPSCs	Promoting neuroplasticity	Crosstalk between IGF-1/IGF-1R and CXCL12/CXCR4 pathway	Ischemic stroke	[94]
hNSCs	Promoting neuroprotection	-	Amyotrophic lateral sclerosis (ALS)	[95]
CSCs	Promoting cardiomyocyte survival and myocardial regeneration	FOXO3/p27/p51 pathway	Myocardial infarction	[96,97]

hESCs, human embryonic stem cells; UMSCs, umbilical cord-derived MSCs; BMSCs, bone marrow-derived MSCs; PMSCs, placental mesenchymal stem cells; DPSCs, dental pulp-derived MSCs; hNSCs, human neural stem cells; CSCs, cardiac stem cells.

3.1. Human Embryonic Stem Cells (hESCs)

Human ESCs are derived from the inner cell mass and contribute to multiple types of cells in the body [98]. Although many factors have been reported to maintain hESC populations, including bFGF [82,99], TGF-β1 [83,100], activin A [101], neurotrophins [102], Wnt/β-catenin signaling [86] and sphingosine-1-phosphate (S1P) [103], knowledge on the receptor activation required for the self-renewal of hESCs is limited. Notably, this study displayed the activation of IGF-1R signaling upon the co-culture of hESCs in the conditional medium of mouse embryonic fibroblast [31]. Furthermore, IGF-1R was overexpressed along with specific markers such as OCT4, SSEA4, and SSEA3. In addition, suppressing IGF-1R activation using IGF-1R mABs and knocking down IGF-1R expression by siRNA not only limits cell expansion but also promotes cell differentiation [31]. Moreover, the activation of IGF/IGF-1R signaling in hESCs promotes self-renewal by HRG/ERBB2 signaling and enhances cell survival through the PI3K/AKT pathway [31]. In addition, another study indicated that the activation of IGF-2/IGF-1R signaling is also essential for self-renewal, and high levels of IGF-2 maintain hESC proliferation and promote cell survival via a bFGF-dependent pathway [32]. Furthermore, IGF-1R signaling was implicated in the regulation of the pluripotency of hESCs. For example, this study indicated that IGF-1R signaling induced the proliferative ability of cardiomyocytes that differentiated from hESCs. Likewise, blocking IGF-1R activation using a IGF-1R mAbs decreased cardiomyocyte proliferation, while the addition of recombinant protein of IGF-1 or IGF-2 induced cardiomyocyte pro-

liferation through the PI3K/AKT pathway [88]. However, this study demonstrated that microRNA-223 directly targeted IGF-1R and inhibited the AKT signaling, leading to hESCs differentiation [104]. The study also indicated that suppressing the activation of IGF-1R and its downstream signaling pathway induced hepatocyte differentiation from hESCs [34]. Therefore, these studies demonstrate that IGF-1R signaling is required for the maintenance of the stemness of hESCs, but the role of IGF-1R signaling in the differentiation of hESC needs to be elucidated.

3.2. Human Neural Stem Cells (hNSCs)

Human NSCs are derived from regions such as the subgranular zone (SGZ) in the hippocampal dentate gyrus and subventricular zone (SVZ) adjacent to the lateral ventricles. The hNSCs function as an additional tool for the development of regenerative therapy, and several clinical trials have indicated hNSCs as a promising target to treat neurological disorders, including amyotrophic lateral sclerosis (ALS) [105,106]. ALS is a lethal neurodegenerative disease that causes the rapid loss of motor neurons and muscular paralysis [107]. The report indicated that the overexpression of IGF-1 on hNSCs cultures enhances neural differentiation and promotes neuronal development by neurite outgrowth [95]. Furthermore, IGF-1-overexpressing hNSCs exhibit augmented neuroprotective effects against excitotoxicity, suggesting the potential of stem cell-based therapy in ALS [95]. In addition, another study indicated that hNSCs transplantation with IGF-1 transduction demonstrably improved injury-induced spatial learning deficits and decreased the activation of astroglial and microglial accumulation while enhancing the mobilization of oligodendrocyte precursor cells [108].

3.3. Cardiac Stem Cells (CSCs)

Although the reports on cardiac stem cells have been controversial in recent years, the IGF/IGF-1R axis has been reported to play a role in activating cardiac repair by governing CSCs survival, proliferation, migration and differentiation [109]. The IGF-1/IGF-1R activation is a basic cardioprotective mechanism associated with survival that improves ischemic cardiac function [96]. Moreover, a study indicated that c-kit+ expression in human CSCs promoted IGF-1 secretion, thereby enhancing IGF-1R signaling and ultimately improving cardiomyocyte survival [110]. IGF-1 overexpression in a subset of CD90+ CSCs was shown to activate IGF-1R signaling, promote stem cell survival, and protect surrounding cardiomyocytes from apoptosis after myocardial infarction. In intramyocardial transplantation, IGF-1-overexpressing MSCs are transplanted into the injured area, leading to preserved CSCs in the injured region; this enhances myocardial regeneration without differentiating into cardiac myocytes, smooth muscle, or endothelial cells [111]. Moreover, a study demonstrated that the mechanism of IGF-1 signaling activation promotes c-kit+ murine CSCs proliferation through the down-regulation of FOXO3/p27/p57 signaling [97]. Furthermore, the overexpression of IGF-1 promotes c-kit+/CD45- CSCs survival in obese mice, leading to significant improvements in cardiomyopathy caused by Western diet-induced obesity [112].

3.4. Mesenchymal Stem Cells (MSCs)

MSCs are multipotent adult stem cells with a great potential to differentiate into adipocytes, osteocytes, chondrocytes, neurons, and glial cells [113–115] and to maintain the self-renewal capability [116]. Several studies have demonstrated that IGF-1R signaling regulates MSC differentiation and maintains multipotency. For example, the addition of IGF-1 in adipocyte induction culture medium promotes adipogenesis in BMSCs by stimulating peroxisome proliferator-activated receptor-γ (PPAR-γ) expression and lipid accumulation [117]. A report also indicated that IGFs positively regulate the activation of AKT signaling, induce PPAR-γ expression and contribute to the maintenance of adipogenic differentiation in an AKT-1- and AKT-2-depleted animal model [118]. Moreover, the addition of bFGF enhances the autocrine IGF-1 and IGF-2 induction and induces IGF-1R

activation, resulting in the adipogenesis and osteogenesis of UMSCs [89]. In addition to adipogenesis, IGF-1R signaling reportedly participates in osteogenic differentiation [90]. This study demonstrated that the autocrine IGFs/IGF-1R loop in BMSCs was activated and up-regulated through hedgehog signaling, which is required for osteoblast differentiation in skeletal development. Moreover, IGF-1R and its downstream AKT/mTOR signaling stabilize Gli2 protein and enhance the hedgehog-mediated effect on osteogenic differentiation [90]. Signaling via both IGF-1 and Runx2, which are osteogenic transcription factors, was up-regulated by serum response factor (SRF) to control bone remodeling. In mice with SRF-deleted osteoblasts, the transactivity of IGF-1 and Runx2 was restored through SRF overexpression, promoting osteoblastogenesis [119]. In addition, a few studies indicated that adding IGF-1 to hPMSCs under low-oxygen condition increased OCT4 expression, leading to cell proliferation and maintenance of the multipotency of hPMSCs through the activation of IGF-1R signaling [91,92]. In an animal model of acute myocardial infarction, the transplantation of adipose-derived MSCs (ADSCs) that overexpressed both IGF-1 and HGF to the injured area promoted neovascularization and suppressed inflammation. Although this report showed that both IGF-1 and HGF were overexpressed in ADSCs, significant cardiac regeneration was not observed [120]. Furthermore, several studies also demonstrated that IGF-1R activation in MSCs induces crosstalk and influences neighboring cells as well as their surrounding microenvironment, which could aid in tissue regeneration in human diseases. Stroke causes nervous system damage via ischemic and hypoxic changes to the injured brain, inducing muscle weakness and paralysis. Therefore, MSCs are considered as a promising therapeutic tool to treat stroke. For example, this study demonstrated that the intravenous injection of BMSCs in the brains of rats with stroke-induced middle cerebral artery occlusion increased IGF-1 expression and enhanced the activation of IGF-1/IGF-1R signaling, which corresponds to enhanced cell survival and neural progenitor cell recruitment to the injured area, leading to improved neurological functions [93]. Furthermore, the study reported that the transplantation of IGF-1R-overexpressing hDPSCs that crosstalk with CXCL12/CXCR4 signaling exhibited greater anti-apoptotic and anti-inflammatory effects as well as neural differentiation capacity in a cerebral ischemic animal model [94]. In addition, MSCs are consider to be a potential target in treating muscular injury and myocardial infarction. For example, IGF-1 addition to MSCs in vitro displayed the potential target for reducing scar formation, enhancing angiogenesis, promoting the reconstitution of muscle structure, and improving muscle function [121]. Furthermore, the in vivo transplantation of IGF-1-primed BMSCs represses cardiac dysfunction, increases the survival ability of engrafted BMSCs in the injured heart, leads to decreased cardiomyocytes cell apoptosis, and suppresses the expression of several inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 [122]. In addition, IGF-2 is an essential factor of the stem cell niche and has been reported to modulate the proliferation and differentiation of ADSCs. The study showed that the IGF-2/IGF-1R axis significantly induced the cell proliferation of ADSCs and increased the expression of stemness markers, such as Nanog, Oct4 and Sox2. Notably, IGF-2 had been reported to have a pivotal role in the differentiation of ADSCs to adipocytes and osteoblasts [123].

4. Conclusions

Studies on the role of IGFs in cancer have been conducted mainly on solid tumors including colon [124], prostate [124,125] and breast cancers [126]. For instance, high levels of IGF-1R in patients with colon cancer, as compared to healthy control, could indicate poor prognosis [127]. Therefore, a deeper understanding of cancer biology has led to the development of anti-tumor drugs targeting the specific oncogenic substrate IGF-1R. Since the IGFs/IGF-1R signaling is often dyseregulated in cancer development, it has been considered an attractive pharmacological target for solid tumors. This review summarizes the contribution of IGFs/IGF-1R signaling in the treatment of cancer and stem cells and also highlights the relevance of IGFs/IGF-1R signaling in potential strategies for cancer or stem cell-based therapies, respectively. In cancer, the dysregulation of IGFs/IGF-1R signaling

can induce several hallmark genes of cancer and contribute to malignant transformation, tumor progression and resistance to a number of anti-tumor therapies such as radiation therapy and chemotherapy. Hence, the suppression of IGF-1R signaling is considered to be a promising strategy to inhibit tumor growth and improve survival in multiple cancers. Currently, several strategies have been developed to inhibit IGFs/IGF-1R signaling in cancer therapy. For example, teprotumumab, introduced in 2020, was the first licensed anti-IGF-1R agent for TAO treatment [62]. However, most anti-tumor IGF-1R mAbs or TKIs have not yet displayed significant benefits in patients randomly recruited to phase II/III clinical trials, which is probably due to the paucity of reliable predictive biomarkers of IGF-1R inhibition. Therefore, studies that target IGFs/IGF-1R in multiple tumors with suitable molecular contexts, including IGF-1R suppression, are being conducted to efficiently treat triple-negative breast cancers rather than HR-positive metastatic breast cancers [128–130] as well as treat KRAS-mutant NSCLCs rather than wild-type lung cancers [58]. Moreover, because the activation of IGFs/IGF-1R signaling results in the bypass pathway, the combination of IGF-1R mAbs/TKIs and other RTKs as anti-tumor agents is considered to a more effective strategy in cancer therapy.

On the other hand, IGFs are among the earliest growth factors to be found in a developing embryo and putatively act as autocrine and paracrine factors on several developing cells such as stem cells. This review emphasizes that IGF-1/IGF-1R signaling is an important functional pathway to identify stem cells and MSCs with superior self-renewal capacities as well as to determine the pluripotency of these cells. Furthermore, regulating IGF-1/IGF-1R signaling is a promising strategy to maintain stemness and improve the efficacy of stem cell-based therapies in several disease conditions. Moreover, IGF-1R signaling is also implicated in cancer development due to its stemness-related properties and resistance of radiation therapy and chemotherapy. Therefore, the activation of IGF-1R signaling in stem cell-based therapies wherein the stem cells differentiate into tissue-specific cell types in vitro deserves attention. Additionally, it is also imperative to research the use of the in vivo transplantation of genetically modified IGF-1R stem cells or MSCs to minimize the adverse consequences of tissue regeneration therapy and improve the therapeutic efficacy of regeneration in human diseases.

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References

1. Kasprzak, A.; Kwasniewski, W.; Adamek, A.; Gozdzicka-Jozefiak, A. Insulin-like growth factor (IGF) axis in cancerogenesis. *Mutat. Res. Rev. Mutat. Res.* **2017**, *772*, 78–104. [CrossRef] [PubMed]
2. LeRoith, D.; Roberts, C.T., Jr. The insulin-like growth factor system and cancer. *Cancer Lett.* **2003**, *195*, 127–137. [CrossRef]
3. De Meyts, P.; Whittaker, J. Structural biology of insulin and IGF1 receptors: Implications for drug design. *Nat. Rev. Drug Discov.* **2002**, *1*, 769–783. [CrossRef] [PubMed]
4. Kim, S.Y.; Toretsky, J.A.; Scher, D.; Helman, L.J. The role of IGF-1R in pediatric malignancies. *Oncologist* **2009**, *14*, 83–91. [CrossRef]
5. Baxter, R.C. IGF binding proteins in cancer: Mechanistic and clinical insights. *Nat. Rev. Cancer* **2014**, *14*, 329–341. [CrossRef]
6. Adams, T.E.; Epa, V.C.; Garrett, T.P.; Ward, C.W. Structure and function of the type 1 insulin-like growth factor receptor. *Cell Mol. Life Sci.* **2000**, *57*, 1050–1093. [CrossRef]
7. Xu, Y.; Kong, G.K.; Menting, J.G.; Margetts, M.B.; Delaine, C.A.; Jenkin, L.M.; Kiselyov, V.V.; De Meyts, P.; Forbes, B.E.; Lawrence, M.C. How ligand binds to the type 1 insulin-like growth factor receptor. *Nat. Commun.* **2018**, *9*, 821. [CrossRef]
8. Kavran, J.M.; McCabe, J.M.; Byrne, P.O.; Connacher, M.K.; Wang, Z.; Ramek, A.; Sarabipour, S.; Shan, Y.; Shaw, D.E.; Hristova, K.; et al. How IGF-1 activates its receptor. *Elife* **2014**, *3*, 3772. [CrossRef]

9. Dearth, R.K.; Cui, X.; Kim, H.J.; Hadsell, D.L.; Lee, A.V. Oncogenic transformation by the signaling adaptor proteins insulin receptor substrate (IRS)-1 and IRS-2. *Cell Cycle* **2007**, *6*, 705–713. [CrossRef]
10. Limesand, K.H.; Chibly, A.M.; Fribley, A. Impact of targeting insulin-like growth factor signaling in head and neck cancers. *Growth Horm. IGF Res.* **2013**, *23*, 135–140. [CrossRef]
11. Liu, C.; Zhang, Z.; Tang, H.; Jiang, Z.; You, L.; Liao, Y. Crosstalk between IGF-1R and other tumor promoting pathways. *Curr. Pharm. Des.* **2014**, *20*, 2912–2921. [CrossRef]
12. Tang, R.; Chen, J.; Tang, M.; Liao, Z.; Zhou, L.; Jiang, J.; Hu, Y.; Liao, Q.; Xiong, W.; Tang, Y.; et al. LncRNA SLCO4A1-AS1 predicts poor prognosis and promotes proliferation and metastasis via the EGFR/MAPK pathway in colorectal cancer. *Int. J. Biol. Sci.* **2019**, *15*, 2885–2896. [CrossRef]
13. Brader, S.; Eccles, S.A. Phosphoinositide 3-kinase signalling pathways in tumor progression, invasion and angiogenesis. *Tumori* **2004**, *90*, 2–8. [CrossRef]
14. Owusu, B.Y.; Galemmo, R.; Janetka, J.; Klampfer, L. Hepatocyte Growth Factor, a Key Tumor-Promoting Factor in the Tumor Microenvironment. *Cancers* **2017**, *9*, 35. [CrossRef]
15. Dallas, N.A.; Xia, L.; Fan, F.; Gray, M.J.; Gaur, P.; van Buren, G., 2nd; Samuel, S.; Kim, M.P.; Lim, S.J.; Ellis, L.M. Chemoresistant colorectal cancer cells, the cancer stem cell phenotype, and increased sensitivity to insulin-like growth factor-I receptor inhibition. *Cancer Res.* **2009**, *69*, 1951–1957. [CrossRef]
16. Chang, W.W.; Lin, R.J.; Yu, J.; Chang, W.Y.; Fu, C.H.; Lai, A.; Yu, J.C.; Yu, A.L. The expression and significance of insulin-like growth factor-1 receptor and its pathway on breast cancer stem/progenitors. *Breast Cancer Res.* **2013**, *15*, R39. [CrossRef]
17. Chang, T.S.; Chen, C.L.; Wu, Y.C.; Liu, J.J.; Kuo, Y.C.; Lee, K.F.; Lin, S.Y.; Lin, S.E.; Tung, S.Y.; Kuo, L.M.; et al. Inflammation Promotes Expression of Stemness-Related Properties in HBV-Related Hepatocellular Carcinoma. *PLoS ONE* **2016**, *11*, e0149897. [CrossRef]
18. Xu, C.; Xie, D.; Yu, S.C.; Yang, X.J.; He, L.R.; Yang, J.; Ping, Y.F.; Wang, B.; Yang, L.; Xu, S.L.; et al. beta-Catenin/POU5F1/SOX2 transcription factor complex mediates IGF-I receptor signaling and predicts poor prognosis in lung adenocarcinoma. *Cancer Res.* **2013**, *73*, 3181–3189. [CrossRef]
19. Hart, L.S.; Dolloff, N.G.; Dicker, D.T.; Koumenis, C.; Christensen, J.G.; Grimberg, A.; El-Deiry, W.S. Human colon cancer stem cells are enriched by insulin-like growth factor-1 and are sensitive to figitumumab. *Cell Cycle* **2011**, *10*, 2331–2338. [CrossRef]
20. Ojo, D.; Wei, F.; Liu, Y.; Wang, E.; Zhang, H.; Lin, X.; Wong, N.; Bane, A.; Tang, D. Factors Promoting Tamoxifen Resistance in Breast Cancer via Stimulating Breast Cancer Stem Cell Expansion. *Curr. Med. Chem.* **2015**, *22*, 2360–2374. [CrossRef]
21. Urtasun, N.; Vidal-Pla, A.; Perez-Torras, S.; Mazo, A. Human pancreatic cancer stem cells are sensitive to dual inhibition of IGF-IR and ErbB receptors. *BMC Cancer* **2015**, *15*, 223. [CrossRef]
22. Osher, E.; Macaulay, V.M. Therapeutic Targeting of the IGF Axis. *Cells* **2019**, *8*, 895. [CrossRef]
23. Huang, X.; Park, H.; Greene, J.; Pao, J.; Mulvey, E.; Zhou, S.X.; Albert, C.M.; Moy, F.; Sachdev, D.; Yee, D.; et al. IGF1R- and ROR1-Specific CAR T Cells as a Potential Therapy for High Risk Sarcomas. *PLoS ONE* **2015**, *10*, e0133152. [CrossRef]
24. Suman, S.; Domingues, A.; Ratajczak, J.; Ratajczak, M.Z. Potential Clinical Applications of Stem Cells in Regenerative Medicine. *Adv. Exp. Med. Biol.* **2019**, *1201*, 1–22. [CrossRef]
25. Xi, J.; Zhang, S.C. Stem cells in development of therapeutics for Parkinson's disease: A perspective. *J. Cell Biochem.* **2008**, *105*, 1153–1160. [CrossRef]
26. Magga, J.; Savchenko, E.; Malm, T.; Rolova, T.; Pollari, E.; Valonen, P.; Lehtonen, S.; Jantunen, E.; Aarnio, J.; Lehenkari, P.; et al. Production of monocytic cells from bone marrow stem cells: Therapeutic usage in Alzheimer's disease. *J. Cell Mol. Med.* **2012**, *16*, 1060–1073. [CrossRef]
27. Perin, E.C.; Silva, G.V.; Zheng, Y.; Gahremanpour, A.; Canales, J.; Patel, D.; Fernandes, M.R.; Keller, L.H.; Quan, X.; Coulter, S.A.; et al. Randomized, double-blind pilot study of transendocardial injection of autologous aldehyde dehydrogenase-bright stem cells in patients with ischemic heart failure. *Am. Heart J.* **2012**, *163*, 415–421.e1. [CrossRef]
28. Cerletti, M.; Jurga, S.; Witczak, C.A.; Hirshman, M.F.; Shadrach, J.L.; Goodyear, L.J.; Wagers, A.J. Highly efficient, functional engraftment of skeletal muscle stem cells in dystrophic muscles. *Cell* **2008**, *134*, 37–47. [CrossRef]
29. Weiss, D.J.; Bertoncello, I.; Borok, Z.; Kim, C.; Panoskaltsis-Mortari, A.; Reynolds, S.; Rojas, M.; Stripp, B.; Warburton, D.; Prockop, D.J. Stem cells and cell therapies in lung biology and lung diseases. *Proc. Am. Thorac Soc.* **2011**, *8*, 223–272. [CrossRef]
30. Rashid, S.T.; Corbineau, S.; Hannan, N.; Marciniak, S.J.; Miranda, E.; Alexander, G.; Huang-Doran, I.; Griffin, J.; Ahrlund-Richter, L.; Skepper, J.; et al. Modeling inherited metabolic disorders of the liver using human induced pluripotent stem cells. *J. Clin. Invest.* **2010**, *120*, 3127–3136. [CrossRef]
31. Wang, L.; Schulz, T.C.; Sherrer, E.S.; Dauphin, D.S.; Shin, S.; Nelson, A.M.; Ware, C.B.; Zhan, M.; Song, C.Z.; Chen, X.; et al. Self-renewal of human embryonic stem cells requires insulin-like growth factor-1 receptor and ERBB2 receptor signaling. *Blood* **2007**, *110*, 4111–4119. [CrossRef] [PubMed]
32. Bendall, S.C.; Stewart, M.H.; Menendez, P.; George, D.; Vijayaragavan, K.; Werbowetski-Ogilvie, T.; Ramos-Mejia, V.; Rouleau, A.; Yang, J.; Bosse, M.; et al. IGF and FGF cooperatively establish the regulatory stem cell niche of pluripotent human cells in vitro. *Nature* **2007**, *448*, 1015–1021. [CrossRef] [PubMed]
33. Magner, N.L.; Jung, Y.; Wu, J.; Nolta, J.A.; Zern, M.A.; Zhou, P. Insulin and IGFs enhance hepatocyte differentiation from human embryonic stem cells via the PI3K/AKT pathway. *Stem Cells* **2013**, *31*, 2095–2103. [CrossRef] [PubMed]

34. Waraky, A.; Aleem, E.; Larsson, O. Downregulation of IGF-1 receptor occurs after hepatic linage commitment during hepatocyte differentiation from human embryonic stem cells. *Biochem. Biophys. Res. Commun.* **2016**, *478*, 1575–1581. [CrossRef] [PubMed]
35. Haider, H.; Jiang, S.; Idris, N.M.; Ashraf, M. IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1alpha/CXCR4 signaling to promote myocardial repair. *Circ. Res.* **2008**, *103*, 1300–1308. [CrossRef]
36. Smith, T.J.; Janssen, J. Insulin-like Growth Factor-I Receptor and Thyroid-Associated Ophthalmopathy. *Endocr. Rev.* **2019**, *40*, 236–267. [CrossRef]
37. Loughran, G.; Huigsloot, M.; Kiely, P.A.; Smith, L.M.; Floyd, S.; Ayllon, V.; O'Connor, R. Gene expression profiles in cells transformed by overexpression of the IGF-I receptor. *Oncogene* **2005**, *24*, 6185–6193. [CrossRef]
38. Jones, R.A.; Campbell, C.I.; Wood, G.A.; Petrik, J.J.; Moorehead, R.A. Reversibility and recurrence of IGF-IR-induced mammary tumors. *Oncogene* **2009**, *28*, 2152–2162. [CrossRef]
39. Taunk, N.K.; Goyal, S.; Moran, M.S.; Yang, Q.; Parikh, R.; Haffty, B.G. Prognostic significance of IGF-1R expression in patients treated with breast-conserving surgery and radiation therapy. *Radiother. Oncol.* **2010**, *96*, 204–208. [CrossRef]
40. King, H.; Aleksic, T.; Haluska, P.; Macaulay, V.M. Can we unlock the potential of IGF-1R inhibition in cancer therapy? *Cancer Treat. Rev.* **2014**, *40*, 1096–1105. [CrossRef]
41. Sachdev, D.; Li, S.L.; Hartell, J.S.; Fujita-Yamaguchi, Y.; Miller, J.S.; Yee, D. A chimeric humanized single-chain antibody against the type I insulin-like growth factor (IGF) receptor renders breast cancer cells refractory to the mitogenic effects of IGF-I. *Cancer Res.* **2003**, *63*, 627–635.
42. Pavlicek, A.; Lira, M.E.; Lee, N.V.; Ching, K.A.; Ye, J.; Cao, J.; Garza, S.J.; Hook, K.E.; Ozeck, M.; Shi, S.T.; et al. Molecular predictors of sensitivity to the insulin-like growth factor 1 receptor inhibitor Figitumumab (CP-751,871). *Mol. Cancer Ther.* **2013**, *12*, 2929–2939. [CrossRef]
43. de Bono, J.S.; Piulats, J.M.; Pandha, H.S.; Petrylak, D.P.; Saad, F.; Aparicio, L.M.; Sandhu, S.K.; Fong, P.; Gillessen, S.; Hudes, G.R.; et al. Phase II randomized study of figitumumab plus docetaxel and docetaxel alone with crossover for metastatic castration-resistant prostate cancer. *Clin. Cancer Res.* **2014**, *20*, 1925–1934. [CrossRef]
44. Calvo, E.; Soria, J.C.; Ma, W.W.; Wang, T.; Bahleda, R.; Tolcher, A.W.; Gernhardt, D.; O'Connell, J.; Millham, R.; Giri, N.; et al. A Phase I Clinical Trial and Independent Patient-Derived Xenograft Study of Combined Targeted Treatment with Dacomitinib and Figitumumab in Advanced Solid Tumors. *Clin. Cancer Res.* **2017**, *23*, 1177–1185. [CrossRef]
45. Beltran, P.J.; Chung, Y.A.; Moody, G.; Mitchell, P.; Cajulis, E.; Vonderfecht, S.; Kendall, R.; Radinsky, R.; Calzone, F.J. Efficacy of ganitumab (AMG 479), alone and in combination with rapamycin, in Ewing's and osteogenic sarcoma models. *J. Pharmacol. Exp. Ther.* **2011**, *337*, 644–654. [CrossRef]
46. Glisson, B.; Besse, B.; Dols, M.C.; Dubey, S.; Schupp, M.; Jain, R.; Jiang, Y.; Menon, H.; Nackaerts, K.; Orlov, S.; et al. A Randomized, Placebo-Controlled, Phase 1b/2 Study of Rilotumumab or Ganitumab in Combination With Platinum-Based Chemotherapy as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer. *Clin. Lung Cancer* **2017**, *18*, 615–625.e8. [CrossRef]
47. Beltran, P.J.; Mitchell, P.; Chung, Y.A.; Cajulis, E.; Lu, J.; Belmontes, B.; Ho, J.; Tsai, M.M.; Zhu, M.; Vonderfecht, S.; et al. AMG 479, a fully human anti-insulin-like growth factor receptor type I monoclonal antibody, inhibits the growth and survival of pancreatic carcinoma cells. *Mol. Cancer Ther.* **2009**, *8*, 1095–1105. [CrossRef]
48. Brana, I.; Berger, R.; Golan, T.; Haluska, P.; Edenfield, J.; Fiorica, J.; Stephenson, J.; Martin, L.P.; Westin, S.; Hanjani, P.; et al. A parallel-arm phase I trial of the humanised anti-IGF-1R antibody dalotuzumab in combination with the AKT inhibitor MK-2206, the mTOR inhibitor ridaforolimus, or the NOTCH inhibitor MK-0752, in patients with advanced solid tumours. *Br. J. Cancer* **2014**, *111*, 1932–1944. [CrossRef]
49. Sclafani, F.; Kim, T.Y.; Cunningham, D.; Kim, T.W.; Tabernero, J.; Schmoll, H.J.; Roh, J.K.; Kim, S.Y.; Park, Y.S.; Guren, T.K.; et al. A Randomized Phase II/III Study of Dalotuzumab in Combination With Cetuximab and Irinotecan in Chemorefractory, KRAS Wild-Type, Metastatic Colorectal Cancer. *J. Natl. Cancer Inst.* **2015**, *107*, djv258. [CrossRef]
50. Ramalingam, S.S.; Spigel, D.R.; Chen, D.; Steins, M.B.; Engelman, J.A.; Schneider, C.P.; Novello, S.; Eberhardt, W.E.; Crino, L.; Habben, K.; et al. Randomized phase II study of erlotinib in combination with placebo or R1507, a monoclonal antibody to insulin-like growth factor-1 receptor, for advanced-stage non-small-cell lung cancer. *J. Clin. Oncol.* **2011**, *29*, 4574–4580. [CrossRef]
51. Pappo, A.S.; Vassal, G.; Crowley, J.J.; Bolejack, V.; Hogendoorn, P.C.; Chugh, R.; Ladanyi, M.; Grippo, J.F.; Dall, G.; Staddon, A.P.; et al. A phase 2 trial of R1507, a monoclonal antibody to the insulin-like growth factor-1 receptor (IGF-1R), in patients with recurrent or refractory rhabdomyosarcoma, osteosarcoma, synovial sarcoma, and other soft tissue sarcomas: Results of a Sarcoma Alliance for Research through Collaboration study. *Cancer* **2014**, *120*, 2448–2456. [CrossRef]
52. Malempati, S.; Weigel, B.; Ingle, A.M.; Ahern, C.H.; Carroll, J.M.; Roberts, C.T.; Reid, J.M.; Schmechel, S.; Voss, S.D.; Cho, S.Y.; et al. Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: A report from the Children's Oncology Group. *J. Clin. Oncol.* **2012**, *30*, 256–262. [CrossRef]
53. Attias-Geva, Z.; Bentov, I.; Ludwig, D.L.; Fishman, A.; Bruchim, I.; Werner, H. Insulin-like growth factor-I receptor (IGF-IR) targeting with monoclonal antibody cixutumumab (IMC-A12) inhibits IGF-I action in endometrial cancer cells. *Eur. J. Cancer* **2011**, *47*, 1717–1726. [CrossRef]
54. Wang, Y.; Hailey, J.; Williams, D.; Wang, Y.; Lipari, P.; Malkowski, M.; Wang, X.; Xie, L.; Li, G.; Saha, D.; et al. Inhibition of insulin-like growth factor-I receptor (IGF-IR) signaling and tumor cell growth by a fully human neutralizing anti-IGF-IR antibody. *Mol. Cancer Ther.* **2005**, *4*, 1214–1221. [CrossRef]

55. Anderson, P.M.; Bielack, S.S.; Gorlick, R.G.; Skubitz, K.; Daw, N.C.; Herzog, C.E.; Monge, O.R.; Lassaletta, A.; Boldrini, E.; Papai, Z.; et al. A phase II study of clinical activity of SCH 717454 (robatumumab) in patients with relapsed osteosarcoma and Ewing sarcoma. *Pediatr. Blood Cancer* **2016**, *63*, 1761–1770. [CrossRef]
56. von Mehren, M.; Britten, C.D.; Pieslor, P.; Saville, W.; Vassos, A.; Harris, S.; Galluppi, G.R.; Darif, M.; Wainberg, Z.A.; Cohen, R.B.; et al. A phase 1, open-label, dose-escalation study of BIIB022 (anti-IGF-1R monoclonal antibody) in subjects with relapsed or refractory solid tumors. *Invest. New Drugs* **2014**, *32*, 518–525. [CrossRef]
57. Fitzgerald, J.B.; Johnson, B.W.; Baum, J.; Adams, S.; Iadevaia, S.; Tang, J.; Rimkunas, V.; Xu, L.; Kohli, N.; Rennard, R.; et al. MM-141, an IGF-IR- and ErbB3-directed bispecific antibody, overcomes network adaptations that limit activity of IGF-IR inhibitors. *Mol. Cancer Ther.* **2014**, *13*, 410–425. [CrossRef]
58. Molina-Arcas, M.; Hancock, D.C.; Sheridan, C.; Kumar, M.S.; Downward, J. Coordinate direct input of both KRAS and IGF1 receptor to activation of PI3 kinase in KRAS-mutant lung cancer. *Cancer Discov.* **2013**, *3*, 548–563. [CrossRef]
59. Cohn, A.L.; Tabernero, J.; Maurel, J.; Nowara, E.; Sastre, J.; Chuah, B.Y.S.; Kopp, M.V.; Sakaeva, D.D.; Mitchell, E.P.; Dubey, S.; et al. A randomized, placebo-controlled phase 2 study of ganitumab or conatumumab in combination with FOLFIRI for second-line treatment of mutant KRAS metastatic colorectal cancer. *Ann. Oncol.* **2013**, *24*, 1777–1785. [CrossRef]
60. Smith, T.J.; Kahaly, G.J.; Ezra, D.G.; Fleming, J.C.; Dailey, R.A.; Tang, R.A.; Harris, G.J.; Antonelli, A.; Salvi, M.; Goldberg, R.A.; et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N. Engl. J. Med.* **2017**, *376*, 1748–1761. [CrossRef]
61. Slentz, D.H.; Nelson, C.C.; Smith, T.J. Teprotumumab: A novel therapeutic monoclonal antibody for thyroid-associated ophthalmopathy. *Expert Opin. Investig. Drugs* **2020**, *29*, 645–649. [CrossRef] [PubMed]
62. Markham, A. Teprotumumab: First Approval. *Drugs* **2020**, *80*, 509–512. [CrossRef]
63. Favelyukis, S.; Till, J.H.; Hubbard, S.R.; Miller, W.T. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase. *Nat. Struct. Biol.* **2001**, *8*, 1058–1063. [CrossRef] [PubMed]
64. Mulvihill, M.J.; Cooke, A.; Rosenfeld-Franklin, M.; Buck, E.; Foreman, K.; Landfair, D.; O'Connor, M.; Pirritt, C.; Sun, Y.; Yao, Y.; et al. Discovery of OSI-906: A selective and orally efficacious dual inhibitor of the IGF-1 receptor and insulin receptor. *Future Med. Chem.* **2009**, *1*, 1153–1171. [CrossRef]
65. Carboni, J.M.; Wittman, M.; Yang, Z.; Lee, F.; Greer, A.; Hurlburt, W.; Hillerman, S.; Cao, C.; Cantor, G.H.; Dell-John, J.; et al. BMS-754807, a small molecule inhibitor of insulin-like growth factor-1R/IR. *Mol. Cancer Ther.* **2009**, *8*, 3341–3349. [CrossRef] [PubMed]
66. Buck, E.; Gokhale, P.C.; Koujak, S.; Brown, E.; Eyzaguirre, A.; Tao, N.; Rosenfeld-Franklin, M.; Lerner, L.; Chiu, M.I.; Wild, R.; et al. Compensatory insulin receptor (IR) activation on inhibition of insulin-like growth factor-1 receptor (IGF-1R): Rationale for cotargeting IGF-1R and IR in cancer. *Mol. Cancer Ther.* **2010**, *9*, 2652–2664. [CrossRef]
67. Creighton, C.J.; Casa, A.; Lazard, Z.; Huang, S.; Tsimelzon, A.; Hilsenbeck, S.G.; Osborne, C.K.; Lee, A.V. Insulin-like growth factor-I activates gene transcription programs strongly associated with poor breast cancer prognosis. *J. Clin. Oncol.* **2008**, *26*, 4078–4085. [CrossRef] [PubMed]
68. Litzenburger, B.C.; Creighton, C.J.; Tsimelzon, A.; Chan, B.T.; Hilsenbeck, S.G.; Wang, T.; Carboni, J.M.; Gottardis, M.M.; Huang, F.; Chang, J.C.; et al. High IGF-IR activity in triple-negative breast cancer cell lines and tumorgrafts correlates with sensitivity to anti-IGF-IR therapy. *Clin. Cancer Res.* **2011**, *17*, 2314–2327. [CrossRef] [PubMed]
69. Piao, W.; Wang, Y.; Adachi, Y.; Yamamoto, H.; Li, R.; Imsumran, A.; Li, H.; Maehata, T.; Ii, M.; Arimura, Y.; et al. Insulin-like growth factor-I receptor blockade by a specific tyrosine kinase inhibitor for human gastrointestinal carcinomas. *Mol. Cancer Ther.* **2008**, *7*, 1483–1493. [CrossRef]
70. Chitnis, M.M.; Lodhia, K.A.; Aleksic, T.; Gao, S.; Protheroe, A.S.; Macaulay, V.M. IGF-1R inhibition enhances radiosensitivity and delays double-strand break repair by both non-homologous end-joining and homologous recombination. *Oncogene* **2014**, *33*, 5262–5273. [CrossRef]
71. Litzenburger, B.C.; Kim, H.J.; Kuiatse, I.; Carboni, J.M.; Attar, R.M.; Gottardis, M.M.; Fairchild, C.R.; Lee, A.V. BMS-536924 reverses IGF-IR-induced transformation of mammary epithelial cells and causes growth inhibition and polarization of MCF7 cells. *Clin. Cancer Res.* **2009**, *15*, 226–237. [CrossRef]
72. Vasilcanu, R.; Vasilcanu, D.; Rosengren, L.; Natalishvili, N.; Sehat, B.; Yin, S.; Girnita, A.; Axelson, M.; Girnita, L.; Larsson, O. Picropodophyllin induces downregulation of the insulin-like growth factor 1 receptor: Potential mechanistic involvement of Mdm2 and beta-arrestin1. *Oncogene* **2008**, *27*, 1629–1638. [CrossRef]
73. Girnita, A.; Girnita, L.; del Prete, F.; Bartolazzi, A.; Larsson, O.; Axelson, M. Cyclolignans as inhibitors of the insulin-like growth factor-1 receptor and malignant cell growth. *Cancer Res.* **2004**, *64*, 236–242. [CrossRef]
74. Waraky, A.; Akopyan, K.; Parrow, V.; Stromberg, T.; Axelson, M.; Abrahmsen, L.; Lindqvist, A.; Larsson, O.; Aleem, E. Picropodophyllin causes mitotic arrest and catastrophe by depolymerizing microtubules via insulin-like growth factor-1 receptor-independent mechanism. *Oncotarget* **2014**, *5*, 8379–8392. [CrossRef]
75. Ekman, S.; Harmenberg, J.; Frodin, J.E.; Bergstrom, S.; Wassberg, C.; Eksborg, S.; Larsson, O.; Axelson, M.; Jerling, M.; Abrahmsen, L.; et al. A novel oral insulin-like growth factor-1 receptor pathway modulator and its implications for patients with non-small cell lung carcinoma: A phase I clinical trial. *Acta Oncol.* **2016**, *55*, 140–148. [CrossRef]
76. Friedlander, T.W.; Weinberg, V.K.; Huang, Y.; Mi, J.T.; Formaker, C.G.; Small, E.J.; Harzstark, A.L.; Lin, A.M.; Fong, L.; Ryan, C.J. A phase II study of insulin-like growth factor receptor inhibition with nordihydroguaiaretic acid in men with non-metastatic hormone-sensitive prostate cancer. *Oncol. Rep.* **2012**, *27*, 3–9. [CrossRef]

77. Gao, J.; Chesebrough, J.W.; Cartlidge, S.A.; Ricketts, S.A.; Incognito, L.; Veldman-Jones, M.; Blakey, D.C.; Tabrizi, M.; Jallal, B.; Trail, P.A.; et al. Dual IGF-I/II-neutralizing antibody MEDI-573 potently inhibits IGF signaling and tumor growth. *Cancer Res.* **2011**, *71*, 1029–1040. [CrossRef]
78. Haluska, P.; Menefee, M.; Plimack, E.R.; Rosenberg, J.; Northfelt, D.; LaVallee, T.; Shi, L.; Yu, X.Q.; Burke, P.; Huang, J.; et al. Phase I dose-escalation study of MEDI-573, a bispecific, antiligand monoclonal antibody against IGFI and IGFII, in patients with advanced solid tumors. *Clin. Cancer Res.* **2014**, *20*, 4747–4757. [CrossRef]
79. Friedbichler, K.; Hofmann, M.H.; Kroez, M.; Ostermann, E.; Lamche, H.R.; Koessl, C.; Borges, E.; Pollak, M.N.; Adolf, G.; Adam, P.J. Pharmacodynamic and antineoplastic activity of BI 836845, a fully human IGF ligand-neutralizing antibody, and mechanistic rationale for combination with rapamycin. *Mol. Cancer Ther.* **2014**, *13*, 399–409. [CrossRef]
80. Goya, M.; Miyamoto, S.; Nagai, K.; Ohki, Y.; Nakamura, K.; Shitara, K.; Maeda, H.; Sangai, T.; Kodama, K.; Endoh, Y.; et al. Growth inhibition of human prostate cancer cells in human adult bone implanted into nonobese diabetic/severe combined immunodeficient mice by a ligand-specific antibody to human insulin-like growth factors. *Cancer Res.* **2004**, *64*, 6252–6258. [CrossRef]
81. Dransfield, D.T.; Cohen, E.H.; Chang, Q.; Sparrow, L.G.; Bentley, J.D.; Dolezal, O.; Xiao, X.; Peat, T.S.; Newman, J.; Pilling, P.A.; et al. A human monoclonal antibody against insulin-like growth factor-II blocks the growth of human hepatocellular carcinoma cell lines in vitro and in vivo. *Mol. Cancer Ther.* **2010**, *9*, 1809–1819. [CrossRef]
82. Xu, C.; Rosler, E.; Jiang, J.; Lebkowski, J.S.; Gold, J.D.; O'Sullivan, C.; Delavan-Boorsma, K.; Mok, M.; Bronstein, A.; Carpenter, M.K. Basic fibroblast growth factor supports undifferentiated human embryonic stem cell growth without conditioned medium. *Stem Cells* **2005**, *23*, 315–323. [CrossRef]
83. Mullen, A.C.; Wrana, J.L. TGF-beta Family Signaling in Embryonic and Somatic Stem-Cell Renewal and Differentiation. *Cold Spring Harb. Perspect. Biol.* **2017**, *9*, a022186. [CrossRef]
84. Williams, R.L.; Hilton, D.J.; Pease, S.; Willson, T.A.; Stewart, C.L.; Gearing, D.P.; Wagner, E.F.; Metcalf, D.; Nicola, N.A.; Gough, N.M. Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. *Nature* **1988**, *336*, 684–687. [CrossRef] [PubMed]
85. Ying, Q.L.; Nichols, J.; Chambers, I.; Smith, A. BMP induction of Id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with STAT3. *Cell* **2003**, *115*, 281–292. [CrossRef]
86. Dravid, G.; Ye, Z.; Hammond, H.; Chen, G.; Pyle, A.; Donovan, P.; Yu, X.; Cheng, L. Defining the role of Wnt/beta-catenin signaling in the survival, proliferation, and self-renewal of human embryonic stem cells. *Stem Cells* **2005**, *23*, 1489–1501. [CrossRef] [PubMed]
87. Ying, Q.L.; Wray, J.; Nichols, J.; Batlle-Morera, L.; Doble, B.; Woodgett, J.; Cohen, P.; Smith, A. The ground state of embryonic stem cell self-renewal. *Nature* **2008**, *453*, 519–523. [CrossRef] [PubMed]
88. McDevitt, T.C.; Laflamme, M.A.; Murry, C.E. Proliferation of cardiomyocytes derived from human embryonic stem cells is mediated via the IGF/PI 3-kinase/Akt signaling pathway. *J. Mol. Cell Cardiol.* **2005**, *39*, 865–873. [CrossRef]
89. Park, S.B.; Yu, K.R.; Jung, J.W.; Lee, S.R.; Roh, K.H.; Seo, M.S.; Park, J.R.; Kang, S.K.; Lee, Y.S.; Kang, K.S. bFGF enhances the IGFs-mediated pluripotent and differentiation potentials in multipotent stem cells. *Growth Factors* **2009**, *27*, 425–437. [CrossRef]
90. Shi, Y.; Chen, J.; Karner, C.M.; Long, F. Hedgehog signaling activates a positive feedback mechanism involving insulin-like growth factors to induce osteoblast differentiation. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 4678–4683. [CrossRef]
91. Youssef, A.; Han, V.K. Low Oxygen Tension Modulates the Insulin-Like Growth Factor-1 or -2 Signaling via Both Insulin-Like Growth Factor-1 Receptor and Insulin Receptor to Maintain Stem Cell Identity in Placental Mesenchymal Stem Cells. *Endocrinology* **2016**, *157*, 1163–1174. [CrossRef]
92. Youssef, A.; Iosef, C.; Han, V.K. Low-oxygen tension and IGF-I promote proliferation and multipotency of placental mesenchymal stem cells (PMSCs) from different gestations via distinct signaling pathways. *Endocrinology* **2014**, *155*, 1386–1397. [CrossRef]
93. Zhang, J.; Li, Y.; Chen, J.; Yang, M.; Katakowski, M.; Lu, M.; Chopp, M. Expression of insulin-like growth factor 1 and receptor in ischemic rats treated with human marrow stromal cells. *Brain Res.* **2004**, *1030*, 19–27. [CrossRef]
94. Lee, H.T.; Chang, H.T.; Lee, S.; Lin, C.H.; Fan, J.R.; Lin, S.Z.; Hsu, C.Y.; Hsieh, C.H.; Shyu, W.C. Role of IGF1R(+) MSCs in modulating neuroplasticity via CXCR4 cross-interaction. *Sci. Rep.* **2016**, *6*, 32595. [CrossRef]
95. Lunn, J.S.; Sakowski, S.A.; McGinley, L.M.; Pacut, C.; Hazel, T.G.; Johe, K.; Feldman, E.L. Autocrine production of IGF-I increases stem cell-mediated neuroprotection. *Stem Cells* **2015**, *33*, 1480–1489. [CrossRef]
96. Troncoso, R.; Ibarra, C.; Vicencio, J.M.; Jaimovich, E.; Lavandero, S. New insights into IGF-1 signaling in the heart. *Trends Endocrinol. Metab.* **2014**, *25*, 128–137. [CrossRef]
97. Johnson, A.M.; Kartha, C.C. Proliferation of murine c-kit(pos) cardiac stem cells stimulated with IGF-1 is associated with Akt-1 mediated phosphorylation and nuclear export of FoxO3a and its effect on downstream cell cycle regulators. *Growth Factors* **2014**, *32*, 53–62. [CrossRef]
98. Klimanskaya, I.; Kimbrel, E.A.; Lanza, R. Embryonic Stem Cells. In *Principles of Tissue Engineering*; Academic Press: London, UK, 2014; pp. 565–579. [CrossRef]
99. Mossahebi-Mohammadi, M.; Quan, M.; Zhang, J.S.; Li, X. FGF Signaling Pathway: A Key Regulator of Stem Cell Pluripotency. *Front. Cell Dev. Biol.* **2020**, *8*, 79. [CrossRef]
100. Amit, M.; Shariki, C.; Margulets, V.; Itskovitz-Eldor, J. Feeder layer- and serum-free culture of human embryonic stem cells. *Biol. Reprod.* **2004**, *70*, 837–845. [CrossRef]

101. Beattie, G.M.; Lopez, A.D.; Bucay, N.; Hinton, A.; Firpo, M.T.; King, C.C.; Hayek, A. Activin A maintains pluripotency of human embryonic stem cells in the absence of feeder layers. *Stem Cells* **2005**, *23*, 489–495. [CrossRef]
102. Pyle, A.D.; Lock, L.F.; Donovan, P.J. Neurotrophins mediate human embryonic stem cell survival. *Nat. Biotechnol.* **2006**, *24*, 344–350. [CrossRef]
103. Pebay, A.; Wong, R.C.; Pitson, S.M.; Wolvetang, E.J.; Peh, G.S.; Filipczyk, A.; Koh, K.L.; Tellis, I.; Nguyen, L.T.; Pera, M.F. Essential roles of sphingosine-1-phosphate and platelet-derived growth factor in the maintenance of human embryonic stem cells. *Stem Cells* **2005**, *23*, 1541–1548. [CrossRef]
104. Yu, Y.H.; Zhang, L.; Wu, D.S.; Zhang, Z.; Huang, F.F.; Zhang, J.; Chen, X.P.; Liang, D.S.; Zeng, H.; Chen, F.P. MiR-223 regulates human embryonic stem cell differentiation by targeting the IGF-1R/Akt signaling pathway. *PLoS ONE* **2013**, *8*, e78769. [CrossRef]
105. Feldman, E.L.; Boulis, N.M.; Hur, J.; Johe, K.; Rutkove, S.B.; Federici, T.; Polak, M.; Bordeau, J.; Sakowski, S.A.; Glass, J.D. Intraspinal neural stem cell transplantation in amyotrophic lateral sclerosis: Phase 1 trial outcomes. *Ann. Neurol.* **2014**, *75*, 363–373. [CrossRef]
106. Glass, J.D.; Hertzberg, V.S.; Boulis, N.M.; Riley, J.; Federici, T.; Polak, M.; Bordeau, J.; Fournier, C.; Johe, K.; Hazel, T.; et al. Transplantation of spinal cord-derived neural stem cells for ALS: Analysis of phase 1 and 2 trials. *Neurology* **2016**, *87*, 392–400. [CrossRef]
107. Zarei, S.; Carr, K.; Reiley, L.; Diaz, K.; Guerra, O.; Altamirano, P.F.; Pagani, W.; Lodin, D.; Orozco, G.; Chinea, A. A comprehensive review of amyotrophic lateral sclerosis. *Surg. Neurol. Int.* **2015**, *6*, 171. [CrossRef]
108. Koutsoudaki, P.N.; Papastefanaki, F.; Stamatakis, A.; Kouroupi, G.; Xingi, E.; Stylianopoulou, F.; Matsas, R. Neural stem/progenitor cells differentiate into oligodendrocytes, reduce inflammation, and ameliorate learning deficits after transplantation in a mouse model of traumatic brain injury. *Glia* **2016**, *64*, 763–779. [CrossRef]
109. Lewis, F.C.; Kumar, S.D.; Ellison-Hughes, G.M. Non-invasive strategies for stimulating endogenous repair and regenerative mechanisms in the damaged heart. *Pharmacol. Res.* **2018**, *127*, 33–40. [CrossRef]
110. Kawaguchi, N.; Smith, A.J.; Waring, C.D.; Hasan, M.K.; Miyamoto, S.; Matsuoka, R.; Ellison, G.M. c-kitpos GATA-4 high rat cardiac stem cells foster adult cardiomyocyte survival through IGF-1 paracrine signalling. *PLoS ONE* **2010**, *5*, e14297. [CrossRef]
111. Jackson, R.; Tilokee, E.L.; Latham, N.; Mount, S.; Rafatian, G.; Strydhorst, J.; Ye, B.; Boodhwani, M.; Chan, V.; Ruel, M.; et al. Paracrine Engineering of Human Cardiac Stem Cells With Insulin-Like Growth Factor 1 Enhances Myocardial Repair. *J. Am. Heart Assoc.* **2015**, *4*, e002104. [CrossRef]
112. Andrade, D.; Oliveira, G.; Menezes, L.; Nascimento, A.L.; Carvalho, S.; Stumbo, A.C.; Thole, A.; Garcia-Souza, E.; Moura, A.; Carvalho, L.; et al. Insulin-like growth factor-1 short-period therapy improves cardiomyopathy stimulating cardiac progenitor cells survival in obese mice. *Nutr. Metab. Cardiovasc. Dis.* **2020**, *30*, 151–161. [CrossRef] [PubMed]
113. Dominici, M.; Le Blanc, K.; Mueller, I.; Slaper-Cortenbach, I.; Marini, F.; Krause, D.; Deans, R.; Keating, A.; Prockop, D.; Horwitz, E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* **2006**, *8*, 315–317. [CrossRef] [PubMed]
114. Hernandez, R.; Jimenez-Luna, C.; Perales-Adan, J.; Perazzoli, G.; Melguizo, C.; Prados, J. Differentiation of Human Mesenchymal Stem Cells towards Neuronal Lineage: Clinical Trials in Nervous System Disorders. *Biomol. Ther.* **2020**, *28*, 34–44. [CrossRef] [PubMed]
115. Zhang, Y.; Dong, N.; Hong, H.; Qi, J.; Zhang, S.; Wang, J. Mesenchymal Stem Cells: Therapeutic Mechanisms for Stroke. *Int. J. Mol. Sci.* **2022**, *23*, 2550. [CrossRef]
116. Jackson, W.M.; Nesti, L.J.; Tuan, R.S. Concise review: Clinical translation of wound healing therapies based on mesenchymal stem cells. *Stem Cells Transl. Med.* **2012**, *1*, 44–50. [CrossRef]
117. Scavo, L.M.; Karas, M.; Murray, M.; Leroith, D. Insulin-like growth factor-I stimulates both cell growth and lipogenesis during differentiation of human mesenchymal stem cells into adipocytes. *J. Clin. Endocrinol. Metab.* **2004**, *89*, 3543–3553. [CrossRef]
118. Peng, X.D.; Xu, P.Z.; Chen, M.L.; Hahn-Windgassen, A.; Skeen, J.; Jacobs, J.; Sundararajan, D.; Chen, W.S.; Crawford, S.E.; Coleman, K.G.; et al. Dwarfism, impaired skin development, skeletal muscle atrophy, delayed bone development, and impeded adipogenesis in mice lacking Akt1 and Akt2. *Genes Dev.* **2003**, *17*, 1352–1365. [CrossRef]
119. Chen, J.; Yuan, K.; Mao, X.; Miano, J.M.; Wu, H.; Chen, Y. Serum response factor regulates bone formation via IGF-1 and Runx2 signals. *J. Bone Miner. Res.* **2012**, *27*, 1659–1668. [CrossRef]
120. Gomez-Mauricio, G.; Moscoso, I.; Martin-Cancho, M.F.; Crisostomo, V.; Prat-Vidal, C.; Baez-Diaz, C.; Sanchez-Margallo, F.M.; Bernad, A. Combined administration of mesenchymal stem cells overexpressing IGF-1 and HGF enhances neovascularization but moderately improves cardiac regeneration in a porcine model. *Stem Cell Res. Ther.* **2016**, *7*, 94. [CrossRef]
121. Pumberger, M.; Qazi, T.H.; Ehrentraut, M.C.; Textor, M.; Kueper, J.; Stoltenburg-Didinger, G.; Winkler, T.; von Roth, P.; Reinke, S.; Borselli, C.; et al. Synthetic niche to modulate regenerative potential of MSCs and enhance skeletal muscle regeneration. *Biomaterials* **2016**, *99*, 95–108. [CrossRef]
122. Guo, J.; Zheng, D.; Li, W.F.; Li, H.R.; Zhang, A.D.; Li, Z.C. Insulin-like growth factor 1 treatment of MSCs attenuates inflammation and cardiac dysfunction following MI. *Inflammation* **2014**, *37*, 2156–2163. [CrossRef]
123. Wang, C.; Li, X.; Dang, H.; Liu, P.; Zhang, B.O.; Xu, F. Insulin-like growth factor 2 regulates the proliferation and differentiation of rat adipose-derived stromal cells via IGF-1R and IR. *Cytotherapy* **2019**, *21*, 619–630. [CrossRef]
124. Tufail, M.; Wu, C. Targeting the IGF-1R in prostate and colorectal cancer: Reasons behind trial failure and future directions. *Ther. Deliv.* **2022**, *13*, 167–186. [CrossRef]

125. Ahearn, T.U.; Peisch, S.; Pettersson, A.; Ebot, E.M.; Zhou, C.K.; Graff, R.E.; Sinnott, J.A.; Fazli, L.; Judson, G.L.; Bismar, T.A.; et al. Expression of IGF/insulin receptor in prostate cancer tissue and progression to lethal disease. *Carcinogenesis* **2018**, *39*, 1431–1437. [CrossRef]
126. Lero, M.W.; Shaw, L.M. Diversity of insulin and IGF signaling in breast cancer: Implications for therapy. *Mol. Cell Endocrinol.* **2021**, *527*, 111213. [CrossRef]
127. Wolpin, B.M.; Meyerhardt, J.A.; Chan, A.T.; Ng, K.; Chan, J.A.; Wu, K.; Pollak, M.N.; Giovannucci, E.L.; Fuchs, C.S. Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. *J. Clin. Oncol.* **2009**, *27*, 176–185. [CrossRef]
128. Robertson, J.F.; Ferrero, J.M.; Bourgeois, H.; Kennecke, H.; de Boer, R.H.; Jacot, W.; McGreivy, J.; Suzuki, S.; Zhu, M.; McCaffery, I.; et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: A randomised, controlled, double-blind, phase 2 trial. *Lancet Oncol.* **2013**, *14*, 228–235. [CrossRef]
129. Hartog, H.; Horlings, H.M.; van der Vegt, B.; Kreike, B.; Ajouaou, A.; van de Vijver, M.J.; Marike Boezen, H.; de Bock, G.H.; van der Graaf, W.T.; Wesseling, J. Divergent effects of insulin-like growth factor-1 receptor expression on prognosis of estrogen receptor positive versus triple negative invasive ductal breast carcinoma. *Breast Cancer Res. Treat.* **2011**, *129*, 725–736. [CrossRef]
130. Davison, Z.; de Blacquiere, G.E.; Westley, B.R.; May, F.E. Insulin-like growth factor-dependent proliferation and survival of triple-negative breast cancer cells: Implications for therapy. *Neoplasia* **2011**, *13*, 504–515. [CrossRef]