

Insulin-like growth factor in cancer: New perspectives (Review)

DUOMING WU^{1,3*}, SHI DONG^{1,3*} and WENCE ZHOU^{3,4}

¹The Second Clinical Medical School, Lanzhou University, Lanzhou, Gansu 730000, P.R. China; ²Department of Breast Surgery,

The First Hospital of Lanzhou University, Lanzhou, Gansu 730000, P.R. China; ³Gansu Province Hepatobiliary

Pancreatic Disease Precision Diagnosis and Treatment Engineering Research Center, Lanzhou, Gansu 730000, P.R. China;

⁴Department of General Surgery, Lanzhou University Second Hospital, Lanzhou, Gansu 730000, P.R. China

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Abstract. The complex nature and heterogeneity of cancer present challenges for cancer treatment. As a class of single-chain peptides, insulin-like growth factors (IGFs) play key roles in cell growth, proliferation, differentiation and metabolic regulation. IGFs promote the proliferation, migration and invasive ability of tumor cells and are closely associated with poor prognosis. Furthermore, IGFs can influence the interactions between immune cells in the tumor microenvironment leading to immune escape. Moreover, the activation of signals associated with IGFs mediates the resistance of tumor cells to chemotherapeutic drugs. With the increasing incidence of tumor events, the desire for new therapies is becoming more urgent. This article comprehensively summarizes the molecular biological mechanisms of IGFs in tumorigenesis and the

development of therapies related to targeting IGFs, with the hope of providing new insights into cancer treatment.

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1. Introduction

With the increasing standard of living, cancer has become a major contributor to the global burden of disease, which continues to grow worldwide, placing a serious economic burden on individuals, families and society (1). According to the Global Agency for Research on Cancer (GARC), 10 cancers accounted for two-thirds of new cases and mortalities worldwide in 2022. It is estimated that there will be >35 million new cancer cases in 2050, an increase of ~77% over the 2022 projections (2,3). In the face of the rapidly growing cancer burden, in addition to the urgent need for improvements in public preventive measures, the enhancement of cancer treatment strategies is equally crucial.

The IGF family consists mainly of two low-molecular-weight protein (IGF-1 and IGF-2), the corresponding receptors (IGF-1R and IGF-2R) and specific binding proteins (4). In 1963, Froesch *et al* (5) discovered the presence of a certain active substance in serum that could not be completely inhibited by insulin antibodies; this substance was subsequently purified by two scientists, Rinderknecht and Humbel (6), and named IGF-1 and IGF-2. IGF-1 is a small polypeptide consisting of 70 amino acids that is synthesized and secreted into the bloodstream mainly by the liver and some IGF-1 is acted upon by the kidneys or skeletal muscles in an autocrine or paracrine manner in their own tissues or periphery (7). The concentration of IGF1 in serum is regulated by insulin-like growth factor-binding proteins (IGFBPs). When IGFBPs are hydrolyzed by proteases, free IGF-1 binds

Correspondence to: Professor Wence Zhou, Department of General Surgery, Lanzhou University Second Hospital, 82 Zuiyingmen, Chengguan, Lanzhou, Gansu 730000, P.R. China
E-mail: zhouwc129@163.com

*Contributed equally

Abbreviations: IGF, insulin-like growth factor; IGFBP, IGF-binding protein; EGFR, epidermal growth factor receptor; IFITM, interferon-induced transmembrane protein; Cyr61, cysteine-rich 61; MMP, matrix metalloproteinase; MCSF, macrophage colony-stimulating factor; HUVEC, human umbilical vein endothelial cells; RPTP- β , protein tyrosine phosphatase β ; ATG4C, autophagy related 4C cysteine peptidase; t-Darpp, PPP1R1B truncated subtype; SOD2, superoxide dismutase 2; ROS, reactive oxygen species; TAM, tumor-associated macrophage; ER α , estrogen receptor α ; TME, tumor microenvironment; KLK10, kallikrein-related peptidase 10; IGFBP-L1, IGFBP-like protein 1; OVA66, ovarian cancer-associated antigen 66; T2DM, type 2 diabetes; TMZ, temozolomide; COX-2, cyclooxygenase-2; PG, prostaglandin; AAT, α 1-antitrypsin; HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor; HA, hyaluronic acid; CK2, casein kinase 2; IR, ionizing radiation

Key words: cancer, insulin-like growth factors, signaling pathway, therapy

to IGF-1R on the cell membrane to mediate the corresponding biological effects (8). In addition, IGF-1 levels are affected by a number of factors, such as age, nutritional status and the release of growth hormones (9). IGF-2 is composed of 67 amino acids and has growth-promoting activity similar to that of IGF-1, but its expression pattern is not controlled by growth hormone (10). IGF-2 is considered to play a critical role in fetal growth and development. Deficiency of IGF-1 inhibits the proliferation and protein synthesis of most cells in the body, predisposing the individual to various diseases, including metabolic bone disease, cardiovascular disease and neurodegenerative diseases (11,12). In addition to inhibiting brain development, reducing IGF-2 affects cell metabolism and stem cell self-renewal (13,14).

IGFs are involved in multiple stages of cancer development. IGF-1 serum levels are markedly higher in patients with advanced gastric cancer than in those with early-stage disease and are associated with a *Helicobacter pylori* positive status (15). Moreover, IGF1R activated by IGF-1 plays a role in epidermal growth factor receptor (EGFR)-mediated primary or secondary resistance to colorectal cancer by upregulating the PI3K/AKT signaling pathway (16). A prospective case-control study suggests that low serum IGF-2 levels are strongly associated with hepatocellular carcinoma risk (17). The IGFs system is involved in the regulation of cancer progression through a variety of signaling pathways, including the MAPK signaling pathway (18), the PI3K/AKT/mTOR signaling pathway (19) and the NF- κ B signaling pathway (20). Therefore, strategies targeting the IGF system may be potential candidates for anti-cancer therapeutic options.

2. Relationship between IGFs and the malignant biological phenotypes of tumors

Tumor cells have a unique malignant biological phenotype, that manifests as a continuous proliferation signal, escape from growth inhibition, unlimited replication ability, continuous angiogenesis, resistance to cell death, invasion and metastasis, genomic instability and mutation, immune escape and other biological phenomena (21). The number of characteristics of cancer add to the complexity of cancer treatment. This section provides insights into the possible mechanisms by which IGFs influence the malignant biological behavior of cancers, providing new strategies for cancer therapy.

IGFs and tumor proliferation, invasion and metastasis. Continuous proliferation signals, invasion and metastasis are the main characteristics of the malignant phenotype of tumors (22). As an effective mitogen of various cell types, IGF-1 regulates various biological behaviors of tumor cells by binding to IGF-1R. Studies have shown that interferon-induced transmembrane protein (IFITM) is positively associated with gastric cancer progression, recurrence and mortality (23,24). Knocking down IFITM inhibits the proliferation, migration, invasion and epithelial mesenchymal transformation of gastric cancer cells. Further mechanistic studies suggest that IGF-1 induces IFITM2 expression through IGF-1R/STAT3 signal transduction, which ultimately affects tumor growth and metastasis (25). In melanoma, downregulation of IGF-1 reduces the dry character of melanoma initiating cells,

including the expression of dry markers (SOX2, Oct-3/4, CD24 and CD133) and functional properties (melanosphere formation, aldehyde dehydrogenase activity and side population) and eventually inhibiting the proliferation and metastasis of tumor cells (26). Moreover, in breast cancer, IGF-1 mainly upregulates cysteine-rich 61 (Cyr61) by activating the PI3K/AKT pathway and an increase in Cyr61 promotes the growth and invasion of breast cancer cells (27). Notably, key transcription factors such as SOX2, which promote and maintain the dry characteristics of cancer cells, can upregulate the expression and autocrine activity of IGF-2, and IGF-2 then activates the IGF-1R/AKT signaling pathway to enhance the invasive and stemness characteristics of bladder cancer, forming a vicious cycle (28). IGFBP-2, an important member of the insulin-like growth factor binding protein family, is able to regulate a variety of cell signaling pathways to influence tumor progression. In oral cancer, IGFBP-2 promotes the upregulation of matrix metalloproteinase (MMP)2 and MMP9 through the activation of the PI3K/Akt/mTOR signaling pathway, which ultimately leads to the proliferation, migration and invasion of cancer cells (29). In addition, IGFBP-1 can be upregulated by *H. pylori* in a dose-dependent manner, promoting malignant biological processes such as the proliferation, migration and invasion of gastric cancer cells (30). Moreover, IGFBP-7 is also able to regulate the proliferation and migration of cancer cells through the JAK/PI3K signaling axis (31). In conclusion, these findings suggest that targeting IGFs is important for inhibiting cancer proliferation and aggressiveness.

IGFs and tumor angiogenesis. To meet the oxygen and nutrients requirements for continuous proliferation, tumors grow in a variety of ways to stimulate the formation of new blood vessels (32). Especially for solid tumors, new blood vessels are the key link between tumor invasion and metastasis, which also leads to difficulty in tumor treatment. Previous studies have shown that IGFs play an important role in endothelial cell physiology by promoting the expression of the vasodilators NO, VEGF and hypoxia-inducible factor (HIF) (33,34). IGF-1R is involved in most pathophysiological processes mediated by IGFs, including proangiogenic effects. However, IGF-2 also promotes angiogenesis through the insulin receptor (35). Studies have reported that the use of bisphosphonates can delay bone metastasis in patients with breast cancer and improve overall survival (36,37). Mechanistic exploration suggested that pamidronate and clodronate markedly inhibit IGF-1-induced HIF-1 α protein accumulation and VEGF expression in breast cancer cells via the PI-3K/AKT/mTOR signaling pathway and ultimately eliminate IGF-1-induced tumor angiogenesis *in vivo* and *in vitro* (38). In hypoxic epithelial ovarian cancer, as a transcription factor of IGF-1, highly expressed ELF3-mediated secretion of IGF-1 and VEGF promoted endothelial cell proliferation, migration and tumor angiogenesis through activation of the tyrosine kinase pathway, whereas ELF3 silencing attenuated angiogenesis and tumorigenesis in a xenograft mouse model, demonstrating the pro-vascular effect of IGF-1 (39). Moreover, a variety of IGFBPs are also involved in angiogenesis (40,41). In glioblastoma, proteomic results suggest that IGFBP-1 is a key mediator of cancer cell secretion in response to the vascular production-promoting factor macrophage colony-stimulating

factor (MCSF). When conditioned medium from cancer cells was added to human umbilical vein endothelial cells (HUVECs), the silencing of MCSF prevented blood vessel formation. Moreover, IGFBP-1 inhibition in cancer cells also blocked angiogenesis in HUVECs treated with conditioned medium (42). Furthermore, IGF-1R is also involved in the proangiogenic effect of IGFBP-2. IGFBP-2 causes the inactivation of protein tyrosine phosphatase β (RPTP- β) by binding to the RPTP- β receptor and subsequently inhibits the transcription of the tumor suppressor gene PTEN. Inhibition of PTEN mediates the activation of the IGF-I/PI3K/AKT signaling pathway, which in turn promotes vascular smooth muscle proliferation and tumor angiogenesis (43). In addition, other types of IGFBPs can promote or inhibit tumor angiogenesis (44,45). However, the pro-vascular effects of IGFBP seem to be independent of IGF, which provides a new direction for further exploration of the relationship between the IGF system and tumor angiogenesis.

IGFs and tumor autophagy. Autophagy plays a dual role in tumor growth. Early autophagy inhibits cancer progression, but with the continuous growth of tumors, autophagy provides nutrients and energy for tumor survival (46). The basal level autophagy flux is usually associated with tumor inhibition and it is often observed in breast cancer, prostate cancer gastric cancer, hepatocellular carcinoma and other types of cancer in which decreased expression of the-autophagy-associated protein Beclin 1 leads to increased proliferation of tumor cells (47-49). Moreover, deficiency of autophagy regulatory factors such as autophagy-related 4C cysteine peptidase (ATG4C) is more likely to cause cancer (50). However, a number of RAS mutated cancer cells maintain their own growth and metabolism through high levels of autophagy, including those of colorectal cancer and pancreatic cancer (51). IGF signal transduction can activate a number of intracellular kinases to activate and induce a series of reactions, related to apoptosis, autophagy and proliferation (52). In breast cancer cell lines (MCF-7), activation of IGF/PI3K signaling enhances mitochondrial homeostasis by increasing the number of new mitochondria and levels of oxidative phosphorylation and promotes the degradation of damaged mitochondria (mitochondrial autophagy) by increasing BNIP3, a protective mechanism that ultimately influences the cancer treatment response and evolution of the cancer phenotype (53). Moreover, the role of IGF-1 signaling in promoting autophagy has been demonstrated in breast cancer, prostate cancer and osteosarcoma (54). Furthermore, in colorectal cancer, IGF-2 is critical for cancer stem cell formation and IGF-2 preferentially interacts with insulin receptor isoform A rather than with IGF-1R to accelerate autophagy and metabolic remodeling in colorectal cancer (55). IGFBP-3, one of the major members of the insulin-like growth factor binding protein family, has growth inhibitory effects *in vitro* (56). However, high levels of IGFBP-3 in breast tumor tissues are associated with increased xenograft growth in mice and poor prognosis. Specifically, the binding of IGFBP3 to GRP78 increases autophagic site formation and autophagic system flux, thereby promoting breast cancer cell survival even under glucose starvation and hypoxic conditions (57). By contrast, IGFBP-3 has an oncogenic effect on ovarian cancer cells, reflecting the heterogeneity of tumor

tissues and the diverse features of IGFBP-3 functions (58). The pro-autophagic effect of IGFBPs is also reflected in processes such as chemoresistance in hepatocellular carcinoma (59). These studies provide good prospects for in-depth exploration of the regulatory role of the insulin growth factor system in tumor autophagy.

IGFs and tumor metabolic remodeling. The proposed Warburg effect revealed the important role of metabolic reprogramming in cancer (60). To meet the increased demand for energy and substance synthesis, tumor cells change their flux by adjusting various metabolic pathways and targeting metabolic pathways has gradually become a focus of tumor therapy research (61). However, metabolic adaptability and heterogeneity caused by tumor heterogeneity and plasticity limit metabolic efficacy. IGFs, including IGF-1 and IGF-2, are involved in cellular metabolic signaling and influence glucose and cholesterol uptake and glycogen storage (62,63). Circulating levels of IGF-1 and certain IGFBPs are critical for the maintenance of glucose homeostasis (64). Studies have shown that chronic hyperglycemic diets increase the risk of colon cancer, in part by regulating the insulin/IGF-1 signaling axis by activating the downstream PI3K/AKT/mTOR, Ras/MAPK signaling pathways, glucose transporter proteins (GLUT1) and key enzymes of glycolysis (LDHA and HK2), thereby affecting glucose uptake and aerobic glycolysis in cancer cells (65). In breast cancer, the PPP1R1B truncated subtype (t-Darpp) is upregulated in trastuzumab resistant HER2+ breast cancer. t-Darpp activates IGF-1R/AKT signaling through heterodimerization with EGFR and HER2, promoting and stimulating glucose uptake, glycolysis and trastuzumab resistance in SK-BR-3 cells. Pharmacological inhibition and IGF-1R-targeted knockdown reverse the effects of t-Darpp on metabolic remodeling and drug resistance in tumor cells (66). IGFBP family proteins can bind to IGF-1 and IGF-2, thereby regulating the downstream conduction of IGF signals. IGFBP-1 plays an important role in the regulation of IGF-I signaling and influences a series of downstream biological events such as cell proliferation, survival, movement and metabolism (67). It is shown that IGFBP1 expression and secretion were significantly elevated in cancer cells, and secreted IGFBP-1 inhibits AKT1-mediated phosphorylation of ser27 of mitochondrial superoxide dismutase 2 (SOD2), thereby increasing the activity of SOD2 antioxidant enzymes. Increased SOD2 activity weakens the accumulation of mitochondrial reactive oxygen species (ROS) in spatially constrained cancer cells, thereby supporting the survival of tumor cells in blood vessels in lung tissue and accelerating tumor metastasis in mice (68). However, studies of the IGF system in cancer metabolism are still insufficient, not only the uptake and utilization of glucose, but also the mechanism of changes in lipid and amino acid metabolism still need to be explored.

IGFs and tumor immune escape. The tumor microenvironment (TME) is composed mainly of tumor cells, stromal cells, immune cells and the extracellular matrix, which assume the functions of material exchange, environmental stress and immune regulation (69). In the early stage of tumor

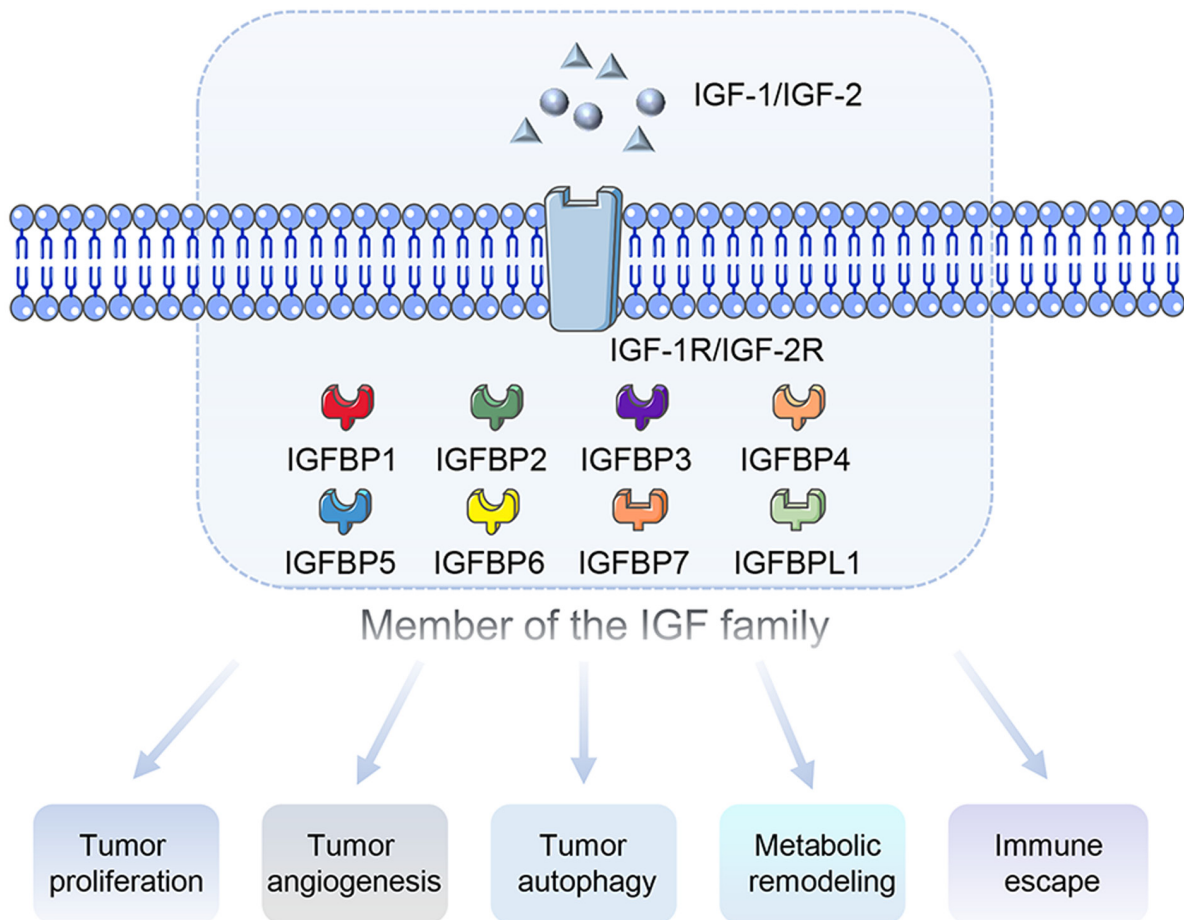


Figure 1. The main members of the IGF family and their roles in tumor progression. The main members of the IGF family include IGF-1/IGF-2 and the corresponding receptors IGF-1R/IGF-2R, as well as a variety of binding proteins. These members are capable of influencing processes such as tumor proliferation, angiogenesis, autophagy, immune escape, and metabolic remodeling. IGFs, insulin-like growth factors; IGFBPs, insulin-like growth factor-binding proteins.

colonization or growth, activated immune cells contribute to a tumor-suppressive inflammatory microenvironment that hinders tumor development, whereas long-term persistent antigenic stimulation, the activation of immunosuppressive cells and metabolic stress prompt the tumor to escape from the surveillance of the immune system and continue to grow, which is known as immune escape of the tumor (70,71). Modification changes in the tumor cells themselves and changes in the immune microenvironment lead to complexity of the immune escape process. Remodeling the positive immune microenvironment and stimulating or restoring the innate tumor suppression ability of the immune system are crucial for improving the malignant progression of tumors. IGF-1/IGF-1R was found to be critical in regulating the activity of a number of immune cells, including T cells. In a mouse model of hepatocellular carcinoma, regulatory T cells (Tregs) with high IGF-1R expression presented increased PI3K/AKT/mTOR signaling and were able to produce more ATP, lactate and ROS, which contribute to enhanced immunosuppressive effects (72). Tumor-associated macrophages (TAMs), important immunosuppressive cells in the microenvironment, are able to activate the Gli2/IGF-2/ERK1/2 signaling axis to promote TGF- β secretion and thus mediate the migration, invasion and EMT of hepatocellular carcinoma cells (Huh-7 cells) (73). Moreover, M2-type TAMs, through

the secretion of IGF-1 and IGF-2, activate PI3K/AKT/mTOR signaling and enhance the malignant proliferation and stemness characteristics of cancer cells (74). In addition, adipose tissue in the microenvironment is also capable of secreting IGF-1 to support microenvironmental remodeling (75). IGF-1 serves as a key mediator that communicates between the microenvironment and cancer cells and targeting IGF-1 has become a critical part of the fight against tumor immunosuppression. Nevertheless, the relationships between IGFs and numerous microenvironmental components, such as NK cells, neutrophils and even the microbiota, remain to be elucidated and incorporating other targets or combination therapies to address the individual and tissue heterogeneity of tumors is crucial. Fig. 1 shows the role of IGF family members in tumor progression.

3. IGFs regulate signaling pathways associated with cancer progression

During the malignant progression of tumors, a variety of signaling pathways are activated to participate in the proliferation, migration, angiogenesis and metabolic remodeling of tumor cells, among which IGFs play important regulatory roles (76). This section summarizes the key signaling pathways involved in the regulation of IGFs in tumor progression.

IGFs regulate the PI3K/AKT signaling pathway. In an oncogenic context, the IGF family regulates a number of biological processes such as cancer cell proliferation, apoptosis, metabolism and protein synthesis, which are closely associated with the activation of PI3K/AKT signaling, which subsequently promotes the transcription of downstream pro-oncogenic target genes such as c-Myc and HIF-1 α (77). In colorectal cancer, IGF-2 secreted by cancer-associated fibroblasts binds to IGF-1R on cancer cells to activate the PI3K/AKT/mTOR and Hippo-YAP1 signaling pathways to promote cancer cell proliferation, migration and invasion; after knock-down of IGF-1R or inhibition of IGF-1R with the IGF-1R inhibitor picropodophyllin, the tumor-promoting effects are reversed (78). In another study, IGF-1 was shown to regulate glucose metabolism in cancer cells with the involvement of kallikrein-related peptidase 10 (KLK10) and the knockdown of KLK10 markedly inhibited glucose metabolism and PI3K/Akt/mTOR signaling activation, a process that could be reversed by IGF-1, suggesting that IGF-1 and KLK10 serve as potential targets for regulating metabolic remodeling in colon cancer (79). As an important noncoding RNA, microRNA (miR)-186-3p is involved in the proliferation, migration and apoptosis of a number of cancer cells, especially cervical cancer cells. It can inhibit the activation of PI3K/AKT signaling through the inverse regulation of IGF-1 expression and ultimately suppress the tumorigenesis of cervical cancer cells (80). Moreover, IGF-1 mediates the activation of the PI3K/AKT/mTOR pathway in uterine smooth muscle tumors, gliomas and pancreatic cancer (81-83). Numerous components of the microenvironment are also involved in malignant tumor progression. M2 macrophages, as infiltration-rich immunosuppressive cells, are able to activate the PI3K/AKT/mTOR signaling axis by secreting IGF-1 and IGF-2, which promotes thyroid cancer cell invasion and the expression of stemness markers (Oct4, SOX2 and CD133), exacerbating the immunosuppressive effects of cancer (74). IGFBP-like protein 1 (IGFBP-L1), a key member of the IGFBP family, regulates its function by binding to IGF (84). In esophageal cancer, the methylation process of IGFBP-L1 was associated with tumor size and TNM stage. Relevant *in vivo* and *in vitro* experiments have confirmed that IGFBP-L1 methylation exerts a pro-oncogenic effect by promoting PI3K/AKT phosphorylation and IGFBP-L1 methylation has become a potential marker for the early detection of esophageal cancer, as well as a predictive marker for PI3K-targeted therapy in esophageal cancer (85).

IGFs regulate the NF- κ B signaling pathway. NF- κ B is a general term for a group of protein complexes, including mainly subunits such as RelA (p65), RelB, c-Rel, p50/p105 (NF- κ B1) and p52/p100 (NF- κ B2), which play important roles in cell proliferation, immune regulation and the stress response (86). High-level NF- κ B activation is involved in tumorigenesis, angiogenesis, microenvironmental remodeling and chemoresistance (87). Activation of the NF- κ B pathway under the influence of IGFs mediates the transcription of downstream signals and a range of tumorigenic activities. IGF-1, as a nutrient-responsive growth factor, activates NF- κ B and the expression of downstream genes (Ccdn1, Vegf, Birc5 and Ptg2) to promote the growth of pancreatic cancer *in vitro* and *in vivo* (88). Furthermore, the cross-talk between IGF-1

and ROS is involved in the occurrence and development of a variety of cancers, including liver, cervical and colorectal cancers. Further studies revealed that IGF-1 activates the inflammatory signals NF- κ B and NLRP3 in cancer cells and that this activation depends on the accumulation of ROS and NOX2. The inhibition of the IGF-1 receptor substrates IRS-1 and NOX2 effectively prevents the development of cancer-related inflammation (89). IGFBP-3, a secreted glycoprotein, can regulate the mitogenic activity of IGF-1R. Recent studies have shown that high expression of IGFBP-3 can increase the radiosensitivity of cancer cells and induce their apoptosis by activating apoptosis-related proteins. Under irradiation, IGFBP-3 induces apoptosis and ROS production by activating NF- κ B signaling and ROS further promote IGFBP-3 mediated signaling activity. The positive circuit of NF- κ B activation and ROS production can accumulate more ROS in irradiated OSCC cells and this positive feedback regulation overcomes the pro-survival effect of NF- κ B/IL-6 signaling (90). In another study, IGFBP-3 was able to enhance etoposide-induced cell growth inhibition by blocking the NF- κ B signaling pathway in gastric cancer cells, confirming that IGFBP-3 has become a key target and marker for cancer therapy and further exploration of its in-depth regulatory mechanisms is worthwhile (91).

IGFs regulate the MAPK signaling pathway. MAPK is a key transmitter of signals from the cell surface to the nucleus and can be activated by factors such as cytokines, hormones, stressors and others to regulate cell growth, differentiation, inflammation and other physiological and pathological processes (92). In the context of cancer progression, MAPK signals are involved in various activities of cancer cells, including proliferation, apoptosis and immune escape. However, simply targeting MAPK-related signals has not been effective in treating cancer (93). The function of IGFs in the MAPK signaling pathway provides a new direction in the fight against cancer. IGF-1R is considered a potential cellular oncogene, especially in breast cancer, where high expression with IGF-1R is a driver of the malignant phenotype. Under continuous stimulation of IGF-1, IGF-1R/MAPK/PI3K signaling is activated, leading to resistance to estrogen tamoxifen and flutestrant. Low doses of tamoxifen act as agonists in IGF-1-stimulated breast cancer cells and further increase IGF-1 expression. Key components involved in the IGF-1/IGF-1R signaling network have become potential targets for combined antiestrogen therapy (94). Ovarian cancer-associated antigen 66 (OVA66) was first shown to play a role in ovarian cancer by reducing IGF-1R expression and downstream phosphorylation of ERK1/2-Hsp27 signaling. In-depth mechanistic studies have shown that OVA66 can interact with MDM2 to coregulate the activation of the IGF-1R-ERK1/2 signaling pathway to promote tumorigenesis (95). Research has shown that type 2 diabetes (T2DM) is associated with an increased risk of colon cancer, along with increased insulin and IGF-1. Insulin and IGF-1 alone or in combination promoted the proliferation of MC38 colon cancer cells and reduced apoptosis. However, the use of ERK1/2 or JNK inhibitors inhibited the growth of colon cancer cells *in vivo* and *in vitro*, suggesting that the activation of ERK1/2 and JNK signaling by insulin and IGF-1 is at least partially responsible for the development of T2DM-associated

colon cancer (96). These studies effectively confirmed the critical regulatory role of the IGF-1/IGF-1R/MAPK signaling axis in malignant tumor progression.

IGFs regulate the Wnt/ β -catenin signaling pathway. The Wnt signaling pathway is mainly mediated by the activation of β -catenin and the sustained accumulation of β -catenin into the nucleus initiates the transcription of target genes by binding to T-cell factor (TCF)/lymphoid enhancer-binding factor transcription factors (97). The Wnt/ β -catenin signaling pathway is closely related to stem cell differentiation and organ regeneration. Studies have shown that the activation of Wnt signaling in colorectal cancer is associated with the loss of function of the tumor regulator APC and the involvement of Wnt signaling has been reported in a variety of malignancies, including breast and stomach cancer (98,99). Nevertheless, targeting the Wnt pathway alone presents significant challenges for cancer therapy, including poor drug response and toxic side effects (100). As a receptor for IGF-1 and IGF-2, IGF1R-mediated phosphorylation of Akt and GSK3 β promotes β -catenin stability and nuclear localization (101). Moreover, the nuclear localization of IGF-1R is mediated mainly by its C-terminal domain. Following its nuclear localization, IGF-1R promotes TCF-mediated β -catenin transcriptional activity, which has been confirmed in hepatocellular carcinoma cells (102). In colorectal cancer cell lines (HT-29 and SW620), knockdown of IGF-1R by small interfering RNA resulted in a blockade of the downstream PI3K/Akt and typical Wnt signaling pathways, which ultimately inhibited cancer cell proliferation and promoted apoptosis (103). To identify IGF-1-mediated miRNA regulatory networks that cause temozolomide (TMZ) to be insensitive to glioblastoma multiforme treatment, on the basis of comprehensive analysis of multiple databases and *in vitro* experiments, Chen *et al.* (104) confirmed that IGF-1 upregulated miR-513a-5p signaling reduced the sensitivity of glioma cells to TMZ by inhibiting the NEDD4L-inactivated Wnt/ β -catenin pathway. The mining of this signaling pathway provides a feasible target for improving the drug sensitivity of TMZ.

IGFs regulate the COX-2 signaling pathway. Cyclooxygenase-2 (COX-2) is a key regulatory molecule that catalyzes the synthesis of arachidonic acid to prostaglandin (PG), which is expressed in large quantities when cells are stimulated by inflammation, accelerating the occurrence of inflammatory storms (105). COX-2 is highly expressed in most tumors and promotes tumor proliferation, migration and angiogenesis (106). Moreover, the overexpression of COX-2 is often closely associated with chemotherapy resistance and immune escape processes in tumors, suggesting that COX-2 is an attractive therapeutic target in tumors (107). Nevertheless, the regulation of COX-2-related signaling pathways remains to be elucidated. The IGF-1/IGF-1R system has been shown to be an important promoter of tumor growth in various cancers, promoting tumor progression and metastasis by regulating multiple signaling pathways, such as those of PI3K/AKT and MAPK/ERK signaling (78,94). Notably, COX-2 expression is also affected by the IGF-1/IGF-1R signaling pathway (108). In a study of colon cancer cells, COX-2 expression and PGE2 synthesis were upregulated by the IGF-2/

IGF-1R autocrine pathway and IGF-1R blockade decreased COX-2 activity and inhibited tumor cell proliferation and promoted apoptosis (103). Stoeltzing *et al.* (109) reported that IGF-I selectively upregulates COX-2 through the MAPK/(ERK1/2) pathway in pancreatic cancer and that treatment with anti-IGF-1R antibodies can effectively inhibit IGF-1R and MAPK/ERK activation and reduce COX-2 expression in parental cells. Furthermore, in a BK5.IGF-1 mouse model of breast cancer, elevated levels of IGF-1 expression activated the COX-2/PGE2/EP3 signaling pathway, accompanied by increased VEGF expression and tumor angiogenesis (110). Celecoxib treatment resulted in a 45% reduction in mammary PGE2 levels and attenuated mast cell influx and angiogenesis, suggesting that COX-2-selective inhibitors may be useful in the prevention or treatment of breast cancer associated with elevated human IGF-1 levels (110). As a member of the IGFBP family, IGFBP-4 influences the inflammatory regulation of the tumor microenvironment. In lung cancer tissues, the expression of IGFBP-4 was markedly lower than that in normal tissues adjacent to the cancer, but the expression of COX-2 was greater in lung cancer tissues. In addition to inhibiting the expression of COX-2 in lung cancer cells, IGFBP-4 also inhibited the proliferation, migration and metastasis of cancer cells through the modulation of the PI3K/AKT, ERK and CREB pathways, which highlights the anticancer value of IGFBP-4 (111). These findings suggest that the regulation of the COX-2-related signaling axis by the IGF system could be a potential target for cancer therapy and deserves further exploration. Fig. 2 shows the key signaling pathways involved in the regulation of IGFs in tumor progression.

4. Application of IGFs in cancer therapy

The treatment of cancer is very complex and IGF-related signals affect multiple processes of cancer cell proliferation, invasion and metastasis. Moreover, IGFs also mediate tumor resistance to chemotherapy and confer resistance to immunotherapy (112). Therefore, IGFs are promising targets for cancer treatment. This section focusses on the application and related mechanisms of targeting IGFs in cancer therapy.

Targeted therapy. Targeting the IGF-1R signaling pathway is considered a potential breakthrough in anticancer therapy and a number of small molecule inhibitors and monoclonal antibodies targeting IGF-1R, such as BIIB-022, BMS-754807 and Teprotumumab, have been developed and evaluated in clinical trials (113-115). However, owing to their limited anticancer activity or drug toxicity, a number of clinical trials targeting IGF-1R have been abandoned and few drugs have actually entered clinical use. The unique advantages that natural compounds have in cancer progression make targeting IGF-1R possible. For example, the combination of curcumin and resveratrol inhibits NF- κ B activity by targeting IGF-1R signaling, ultimately leading to apoptosis and cell cycle arrest in natural colon cancer cells, suggesting that IGF-1R may be an anticancer approach (116). Quercetin, which is abundant in fruits, vegetables, leaves and grains, can also inhibit skin cancer proliferation by targeting IGF-1R (117). Epigallocatechin gallate, a polyphenolic component of green tea, inhibits the progression of various cancers, including

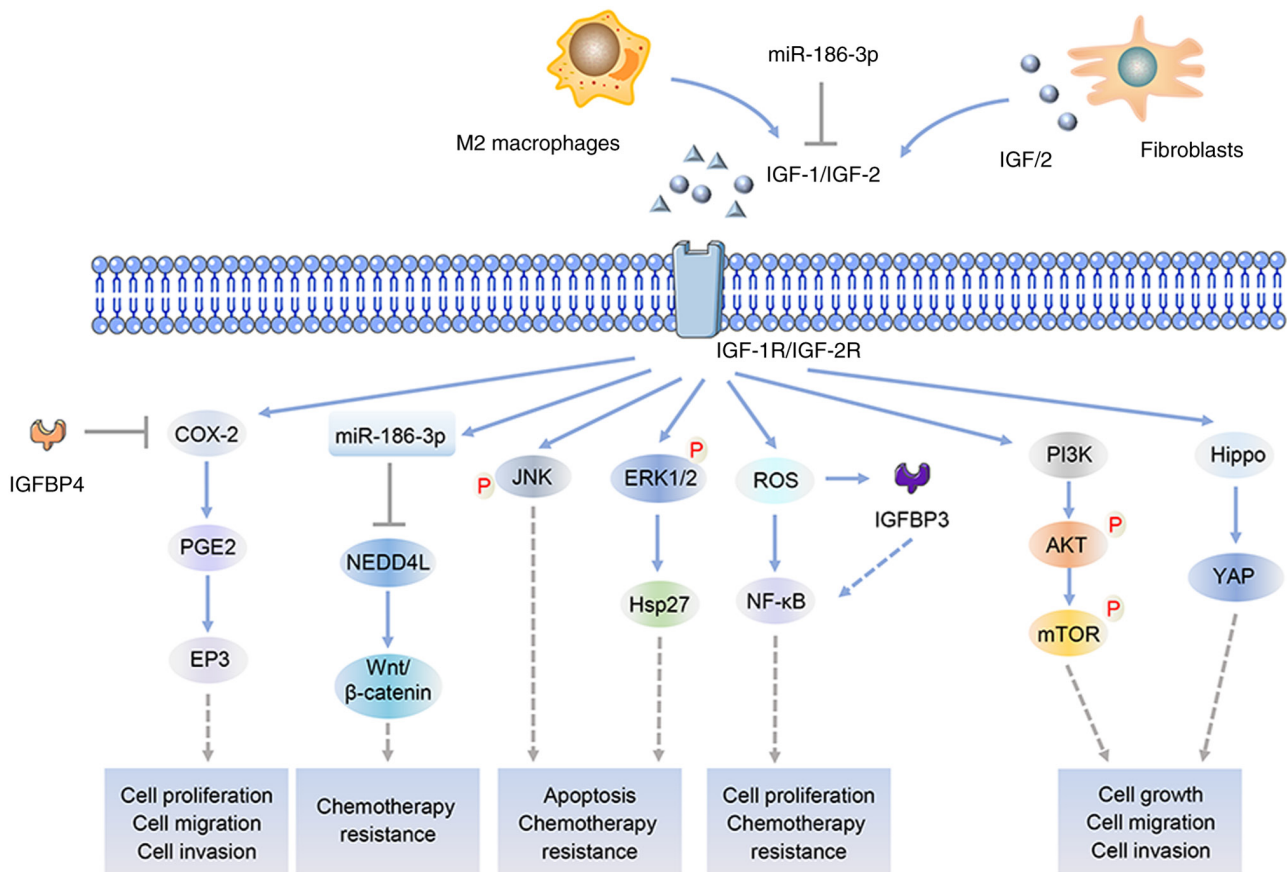


Figure 2. Relevant signaling pathways of major IGF family members affecting tumor progression. IGF family members are able to influence the processes of tumor growth, proliferation, invasion, and chemoresistance by mediating the PI3K/AKT, NF- κ B, MAPK, Wnt/ β -Catenin and COX signaling pathways and downstream signaling molecules. IGFs, insulin-like growth factors; IGFBPs, insulin-like growth factor-binding proteins; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide-3-kinase; AKT, protein kinase B; mTOR, mammalian target of the rapamycin; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; NF- κ B, nuclear factor κ B; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; EP3, PGE2 receptor 3; YAP, yes-associated protein; NEDD4L, NEDD4-like E3 ubiquitin protein ligase.

glioma, breast and liver cancers, by inhibiting IGF-1R via the phosphorylation of the tyrosine kinase IGF-1R (118-120). Targeting circulating IGF-1 and IGF-2 levels is another anticancer strategy. However, although serum IGF levels are closely associated with tumor progression, IGF also plays an important regulatory role in normal life activities, such as maintaining skeletal muscle growth and development, islet proliferation and cell metabolism. How to maximally inhibit tumor growth without interfering with normal physiological activities is a key issue in the development of IGF-1/2 inhibitors. For example, MEDI-573 inhibits IGF-1R signaling and tumor growth *in vivo* by neutralizing IGF-1 and IGF-2. MEDI-573 offers a potential targeted treatment strategy for cancer (121). Numerous studies have shown that IGFBPs can also affect the malignant biological behavior of tumors in an IGF-independent manner. Therefore, targeting IGFBPs has also become an IGFs-based cancer therapy (122,123). α 1-Antitrypsin (AAT) is a member of the serine protease inhibitor superfamily and has anti-inflammatory and tissue protective effects. It can reduce colitis and chronic ileitis by inhibiting cytokine production and enhancing intestinal barrier function. In a mouse model of colon cancer, the level of IGFBP-3 decreased markedly under the action of serine protease and the use of AAT reversed this outcome, resulting anticancer effects (124). Several studies

have shown that METTL3 plays important regulatory roles in prostate cancer proliferation, migration, invasion, apoptosis, drug resistance androgen-induced splicing and glycolipid metabolism maintenance (125,126). The inhibitor STM2457 can reduce the m6A level in cancer cells by inhibiting the IGFBP3/AKT signaling axis, thus exerting anticancer effects *in vitro* and *in vivo* (127). These studies confirm that targeting IGFs is an important strategy for cancer therapy.

Chemotherapy. For most cancers, chemotherapy is the mainstay of late-stage intervention, a treatment strategy that helps improve prognosis and overall survival. However, with the frequent occurrence of drug resistance, chemotherapeutic agents have become less effective in treating cancer (128,129). Therefore, researchers have begun to explore the potential mechanisms of tumor drug resistance with the aim of improving the efficacy of chemotherapy. Studies have confirmed that IGFs play important roles in drug resistance in tumors, including the IGF-1/IGF-2/IGF-1R signaling axis and the IGFBP family members that reduce the susceptibility of cancers such as lung and breast cancers to chemotherapy resistance (130,131). Therefore, targeting IGFs may help solve the problem of tumor drug resistance. Her2-positive breast cancer resistant to trastuzumab therapy severely affects prognosis.

In trastuzumab-resistant Her2-positive breast cancer cells, IGFBP-3 expression was reduced, leading to the inhibition of Wnt signaling pathway release and increased Cullin7 expression mediated by TCF7L2. Cullin7 was subsequently involved in the degradation of IRS-1 in an mTOR/S6K-dependent manner to increase drug resistance. Intervention with IGFBP-3 or Cullin7 partially restored trastuzumab sensitivity in trastuzumab-resistant Her2-positive breast cancer cells, which is important for selecting the optimal therapeutic strategy for Her2-positive breast cancer (132). Tamoxifen, a selective estrogen receptor modulator and antagonist of ER α in breast tissue, is a commonly used adjuvant therapy for patients with ER α -positive breast cancer (133). However, tamoxifen resistance is becoming more common. Studies have shown that tamoxifen resistance is associated with IGFBP-1 accumulation and that the overexpression of IGFBP-1 promotes tamoxifen resistance in breast cancer cells by activating the ERK pathway, which can be reversed by knocking down IGFBP-1 (134). Moreover, in hepatocellular carcinoma (HCC), antiangiogenic tyrosine kinase inhibitors (TKIs) are effective therapeutic agents and the main therapeutic effect is to induce severe hypoxia in the tumor microenvironment (TME) through depletion of the vascular density of tumor. However, patients with HCC often develop resistance to TKIs and this resistance development is associated with increased IGFBP-1 expression, the aggregation mechanism manifested by TKI-induced hypoxia increasing IGFBP-1 expression through activation of HIF-1 α and HIF-2 α . Tumor-derived IGFBP-1 induces tumor angiogenesis by activating integrin $\alpha 5 \beta 1$ /focal adhesion kinase/extracellular signal-regulated kinase signaling. The acquired resistance of tumor cells to TKIs is partially reversed by inhibiting IGFBP-1 and the combination of antiangiogenic TKIs and IGFBP-1 inhibitors may be a promising therapeutic strategy for HCC (135). IGFBP-2 is a secreted protein that prevents IGF-1/IGF-2 from binding to its receptor and it also participates in the regulation of the TME in a macrophage-dependent manner. IGFBP-2 is highly expressed in the blood of lung tumors and patients with lung cancer and high levels of IGFBP-2 are associated with poor survival and metastasis in patients with lung cancer. *In vitro* and *in vivo* experiments have shown that IGFBP-2 plays an important role in the acquisition of gefitinib resistance. Mechanistically, IGFBP-2 can activate STAT3 to increase the transcriptional activity of C-X-C motif ligand 1 (CXCL1), thereby increasing the intracellular expression level of CXCL1, which contributes to the survival of lung cancer cells in the gefitinib environment (136). The aforementioned results suggest the potential of IGFBP-2 as a biomarker of gefitinib resistance and a potential target for intervention. In addition, decreased survival of human lung cancer cells is associated with increased IGFBP-3 expression. IGFBP-3 plays an anticancer role by exerting cytotoxic effects on cell survival through a mechanism dependent on the interaction between the glycosaminoglycan hyaluronic acid (HA) and CD44. Loss of IGFBP-3 expression decreases the sensitivity of lung cancer cells to cisplatin. Casein kinase 2 (CK2) is an antiapoptotic kinase that maintains cell survival. Phosphorylation of IGFBP-3 by CK2 blocks the binding of IGFBP-3 to HA, activates HA-CD44 signaling and leads to reduced apoptosis, increased cell survival and cisplatin

resistance. Blocking CK2 and IGFBP-3 phosphorylation may be an effective strategy to increase lung cancer susceptibility to cisplatin (137). Therefore, further exploration of the mechanism of IGFs in tumor drug resistance is important for improving tumor sensitivity to chemotherapy drugs.

Immunotherapy. Immunotherapy is another innovative cancer treatment strategy following surgery, chemoradiotherapy and targeted therapy, opening a new era of cancer treatment. This means that working on cancer cells alone will not achieve the goal of completely eliminating the tumor and new treatment strategies should consider the TME, that is, the surrounding immune cell components. Some inherent mechanisms of the tumor itself help tumor cells escape the surveillance and killing effects of the immune system, so tumor immune escape is also one of the bottlenecks to improving the current therapeutic effect on tumors (138). How to solve the immune escape and secondary drug resistance of tumor has become a difficult problem for the wide application of tumor immunotherapy. Ovarian cancer is the deadliest gynecological malignancy. Immune checkpoint inhibitors have shown good therapeutic efficacy in most malignancies, but have limited efficacy in patients with ovarian cancer. The main reason is that the large amount of extracellular matrix deposition in the ovarian cancer microenvironment leads to tumor vascular collapse, reduced vascular perfusion, poor drug delivery and blocked migration of cytotoxic T cells to the tumor area (139). As a widely used antihypertensive drug, losartan enhances vascular perfusion, thereby enhancing drug delivery and intratumoral invasion of immune effector cells and, on the other hand, enhances chemotherapy sensitivity by inhibiting IGF-1 signaling to reshape ovarian cancer and the microenvironment (140). Several studies have shown that IGF-2 in the tumor microenvironment is derived mainly from CAFs and that high levels of IGF-2 inhibit the infiltration and cytotoxicity of CD8 $^{+}$ T cells, exacerbating the immunosuppressive effect of tumors (78,141). Mechanistically, autocrine IGF-2 promotes self-activation by binding to the IGF-1 receptor (IGF-1R) on CAFs and activating PI3K/AKT signaling, followed by the secretion of various chemokines and cytokines (CCL5 and CXCL12) by CAFs to influence the infiltration of T cell. Furthermore, CAFs interact with T cells via the PD-1/PD-L1 and CD73/adenosine axes and inhibit their activation, proliferation and effector responses. Genetic inhibition or the targeted inhibitor of IGF-2, lincitinib, markedly enhances the response to immune checkpoint blockade, suggesting the potential of IGF-2 as a biomarker and therapeutic target in immunotherapy (141). In a mouse model of pancreatic cancer liver metastasis, the use of IGF-1R inhibitor IGF-Trap reshaped the local immunosuppressive microenvironment of liver tumors, reduced the recruitment of bone marrow-derived suppressor cells, reversed innate immune cell polarization and inhibited metastatic expansion. Moreover, when IGF-1R was combined with an anti-PD-1 antibody, the growth of experimental pancreatic ductal adenocarcinoma liver metastases was inhibited and the response of T cell was further enhanced. These results suggest that blocking IGFs has the dual effects of reshaping the immune microenvironment and enhancing immunotherapy (142). Current research confirms that single-agent immunotherapy is not advantageous in cancer treatment and that cotargeting

Table I. Summary of studies on the application of targeted IGFs in cancer therapies and related mechanisms of action.

First author/s, year	Intervention	Target	Mechanism of action	<i>In vitro/</i> <i>in vivo</i>	(Refs.)
Zhang <i>et al</i> , 2018	Curcumin and resveratrol	IGF-1R	Inhibition of NF-κB activity ultimately leads to apoptosis and cycle arrest of cancer cells	Both	(116)
Jung <i>et al</i> , 2013	Quercetin	IGF-1/IGF-1R	Inhibition of phosphorylation of IRS-1, Akt and S6K	Both	(117)
Le <i>et al</i> , 2018	EGCG	IGF-1/IGF-2/IGF-1R	Inhibition of p-ERK, p-Akt, p-Stat-3 and p-GSK-3β protein levels	<i>In vitro</i>	(118)
Gao <i>et al</i> , 2011	MEDI-573	IGF-1/IGF-2/IGF-1R	Blocking the binding of IGF-1 and IGF-2 to IGF-1R	Both	(121)
Cai <i>et al</i> , 2022	AAT	IGFBP-3	Reversing the inhibitory effect of serine protease on IGFBP-3 expression	Both	(124)
Chen <i>et al</i> , 2024	STM2457	IGFBP3	Reducing m6A levels in cancer cells by inhibiting the IGFBP3/AKT pathway	Both	(127)
Qiu <i>et al</i> , 2019	Cullin7	IGFBP-3	Promoting IRS-1 degradation and IGFBP-3 downregulation activates PI3K/AKT pathway and enhancing trastuzumab resistance in breast cancer	Both	(132)
Zheng <i>et al</i> , 2020	shRNA	IGFBP-1	Increasing the sensitivity of breast cancer cells to tamoxifen by inhibiting the IGFBP-1/ERK signaling pathway	<i>In vitro</i>	(134)
Suzuki <i>et al</i> , 2023	TKI	IGFBP-1	Activation of integrin α5β1/FAK/ERK signaling induces tumor angiogenesis	Both	(135)
Lu <i>et al</i> , 2024	shRNA	IGFBP2	Inhibition of the IGFBP2/STAT3/ CXCL1 signaling axis	Both	(136)
Coleman <i>et al</i> , 2023	CK2	IGFBP-3	Blocking the binding of IGFBP-3 and HA, activating HA-CD44 signaling and reducing the sensitivity of lung cancer cells to cisplatin	<i>In vitro</i>	(137)
Sun <i>et al</i> , 2024	Losartan	IGF-1	Remodeling the tumor microenvironment and increasing the level of intratumoral infiltration of immune cells	Both	(140)
Song <i>et al</i> , 2024	Lincetinib	IGF2	Inhibition of the interaction between CAFs and T cells	Both	(141)
Hashimoto <i>et al</i> , 2021	IGF-Trap	IGF-1R	Enhancement of T cell responses by remodeling the immunosuppressive microenvironment	Both	(142)
Chen <i>et al</i> , 2017	NVP-ADW742	IGF-1R	Increasing the sensitivity of colon cancer cells to radiation	<i>In vitro</i>	(146)
Chen <i>et al</i> , 2018	Antrocin	IGF-1R	Regulation of cancer cell cycle and apoptosis by inhibition of IGF-1R/β-catenin signaling pathway	Both	(149)

IGFs, insulin-like growth factors; IGFBPs, insulin-like growth factor-binding proteins; p-, phosphorylated; CXCL1, C-X-C motif chemokine ligand 1; CAFs, cancer-associated fibroblasts; HA, hyaluronan; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase.

IGFs offers a new therapeutic strategy to improve the efficacy of immunotherapy.

Radiotherapy. Radiotherapy plays a pivotal role in controlling and eradicating tumors as an adjuvant cancer treatment,

either alone or in combination with other modalities (surgery, chemotherapy, immunotherapy and targeted therapy) (143). Despite the continuous progress in radiation technology, which allows for more precise radiotherapy of local tumor tissues while reducing the effect on normal tissues, problems such as

radioresistance and tumor recurrence remain major challenges in the application of radiation therapy (144). Improving the sensitivity of tumor tissues to radiotherapy is the main direction of current research. Studies have shown that IGFs are closely related to radiation response and tumor radiosensitivity. Among them, IGF/IGF-1R signals can improve radiotherapy sensitivity by activating a series of signal transduction events involved in DNA damage repair. In colon cancer cells (HT-29 and SW480 cells), genetic knockout of IGF-1R or the use of the IGF-1R inhibitor NVP-ADW742 enhanced the killing effect of radiation on cancer cells, confirming that depletion of IGF-1R improves radiosensitivity to colon cancer therapy (145,146). Antrocin is a sesquiterpene lactone isolated from camphor that is used as a dietary supplement for cancer prevention and liver protection. In addition, antrocin has been shown to effectively antagonize a variety of cancers, including breast, lung, liver and colon cancers (147,148). In prostate cancer, the combination of antrocin and ionizing radiation (IR) synergistically inhibits the proliferation of radioresistant prostate cancer cells and induces apoptosis. Specifically, antrocin regulates the cell cycle and apoptosis through the inhibition of β -catenin mediated by IGF-1R, suggesting the potential value of antrocin as a potent therapeutic agent to overcome radioresistance (149). Due to the heterogeneity of tumor tissues, the challenges posed by radioresistance are increasingly significant. An in-depth exploration of the important role of IGFs in tumor radioresistance can provide potential therapeutic targets for improving tumor radiosensitivity. The application of targeted IGFs in cancer therapies and related mechanisms of action are summarized in Table I.

5. Summary and prospects

Cancer is a major social, economic and public safety issue in the 21st century and increasing morbidity and mortality rates have placed great burdens on the worldwide population. Despite advances in technology, the treatment and prevention of cancer are still in their infancy. Recently, as the function of IGFs has gradually been revealed, the important role that IGFs play in cancer progression has brought new hope for cancer treatment. The present review introduced the role of IGFs in cancer and their molecular mechanism, focusing on the application of IGFs in current cancer therapies, with the goal of providing a theoretical basis for comprehensive cancer diagnosis and treatment.

Inhibition of IGF-1R signaling is considered a promising strategy for inhibiting tumor growth and improving survival rates in a variety of cancers. However, several drugs, including teprotumumab and BIIB-022, which target IGF-1R, have not shown good therapeutic effects in clinical trials, possibly due to the lack of reliable IGF-1R inhibition biomarkers. Moreover, IGF-related molecular mechanisms not only play a role in tumor cells but also affect other nontumor cell components in the microenvironment, such as fibroblasts, macrophages and T cells, demonstrating that targeting IGFs alone cannot completely inhibit tumor growth and progression. Furthermore, owing to the heterogeneity and diversity of tumor cells themselves, the role of IGFs is not necessarily only as a tumor suppressor, so the development of related inhibitors must fully consider the impact on the tumor and its surrounding environment. With the advance of combination

therapy, the combination of targeted IGFs and other technologies for the treatment of tumors has shown advantages, which not only increase the efficacy but also effectively prevent the occurrence of drug resistance. Future research should focus on exploring the use of combination therapy in cancer treatment. Moreover, with the advancement of multiomics technology, the importance of precision therapy and individualized treatment is increasingly emphasized and multidimensional and different levels of cancer-related mechanisms need to be explored to develop more reliable inhibitors, which, combined with a more rational target delivery mechanism, is the direction of cancer treatment in the future. In conclusion, targeting IGFs can provide more therapeutic options for cancer patients.

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Authors' contributions

DW prepared and wrote the original draft and was responsible for supervision and project administration. SD prepared and wrote the original draft and was responsible for visualization. WZ prepared and wrote the original draft and was responsible for supervision, project administration and funding acquisition. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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