Function of insulin-like growth factor 1 receptor in cancer resistance to chemotherapy (Review)

JINGSHENG YUAN, ZHIJIE YIN, KAIXIONG TAO, GUOBING WANG and JINBO GAO

Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China

Received May 30, 2017; Accepted September 28, 2017

DOI: 10.3892/ol.2017.7276

Abstract. Drug resistance is a primary cause of chemotherapeutic failure; however, how this resistance develops is complex. A comprehensive understanding of chemotherapeutic resistance mechanisms may aid in identifying more effective drugs and improve the survival rates of patients with cancer. Insulin-like growth factor 1 receptor (IGF1R), a member of the insulin receptor family, has been extensively assessed for biological activity, and its putative contribution to tumor cell development and progression. Furthermore, researchers have attended to drugs that target IGF1R since IGF1R functions as a membrane receptor. However, how IGF1R participates in chemotherapeutic resistance remains unclear. Therefore, the present study described the *IGF1R* gene and its associated signaling pathways, and offered details of IGF1R-induced tumor chemoresistance associated with promoting cell proliferation, inhibition of apoptosis, regulation of ATP-binding cassette transporter proteins and interactions with the extracellular matrix. The present study offered additional explanations for tumor chemotherapy resistance and provided a theoretical basis of IGF1R and its downstream pathways for future possible chemotherapy treatment options.

Contents

Correspondence to: Professor Jinbo Gao, Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430022, P.R. China
E-mail: jgao@hust.edu.cn

Key words: insulin-like growth factor 1 receptor, cancer, chemotherapeutic resistance, mechanisms, review

1. Introduction

Insulin-like growth factor 1 receptor (IGF1R) signaling is a complicated and regulated network essential for cells to proliferate and survive. The IGF-IGF1R axis consists of three receptor tyrosine kinases: IGF1R, insulin-like growth factor-2 receptor (IGF2R) and insulin receptor (INSR). The ligands for these receptors are insulin, insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF-2) and serum insulin-like growth factor binding proteins (IGFBPs) (1). IGF-1 and IGF-2 possess autocrine, paracrine and endocrine functions, and activate IGF1R signaling (2). These growth factors and their receptors are commonly overexpressed in malignant tumors; this overexpression may be used to assess cancer through sustained proliferative signals, anti-apoptotic events, invasion, metastasis and drug resistance in cancer cells (3).

IGF1R expression and activity increases in numerous tumor types, including ovarian cancer and rhabdomyosarcoma, and is reported to contribute to cancer cell proliferation and apoptosis (4,5). Since IGF1R functions as a membrane receptor, drugs, including IGF1R tyrosine kinase inhibitors, monoclonal antibodies against IGF1R and monoclonal antibodies against IGF1R ligands targeting this receptor, are of particular interest (6). Recently, the function of IGF1R in chemotherapeutic resistance has gained increasing attention, and relevant mechanisms of inducing resistance in cancer cells include overexpressing multi-drug-resistant proteins, dysregulating cell survival and death and interacting with the tumor microenvironment (7).

2. IGF1R signaling pathway

IGF1R structure and function. IGF1R is an insulin receptor family member, and a disulfide-linked heterotetrameric transmembrane glycoprotein ($\alpha\beta\beta\alpha$) that contains an extracellular ligand-binding domain and an intracellular tyrosine kinase domain (8,9). The ligand-binding specificity determinant is reflected in the amino-terminal cysteine-rich domain of the extracellular α subunit, primarily recognizing and binding to IGF-1 and IGF-2. The intracellular signal transduction depends on the tyrosine kinase activity the ligand in the transmembrane β subunit triggers, permitting specific insulin receptor substrates (IRS-1 to -4) and Src-homology collagen (Shc) to phosphorylate, activating downstream mitogen-activated

protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways (6). The specificity of IGF1R *in vivo* depends on tissue distribution, ligand-binding specificity and receptor differences in intrinsic signaling (10).

IGF1R is often expressed in normal tissues, serving multiple physiological functions in growth, development and feeding (11). The importance of IGF1R in prenatal and postnatal growth has been demonstrated using knockout mice (8). In muscle and bone tissues, IGF1R signaling promotes PI3K/AKT-mediated differentiation and extracellular signal-regulated kinase (ERK) (12). IGF1R also aids in the maintenance of the myocardium and brain (13).

Cardiac-specific IGF1R signaling promotes protective physiological hypertrophy, preserving left ventricular function and inhibiting pathological left ventricular remodeling (14). Furthermore, IGF1R contributes to glucose metabolism and neutrophil physiology (15), and is associated with the occurrence and development of cardiovascular disease, diabetes and inflammation (16,17).

IGF1R is commonly overexpressed in cancer (18). The IGF1R signal promotes non-cancerous cells to malignantly transform (19), and possesses anti-apoptotic and mitogenic activity (20-22). In addition, IGF1R contributes to invasion, metastasis and angiogenesis of cancer (23-25). Excessively activating IGF1R promotes tumors to progress by increasing glycolysis and biomass production (26), and decreases tumor sensitivity to hypoxia, low pH and low glucose environments (27). In addition, expressing IGF1R increases the rate at which tumor cells proliferate and decreases the rate at which they are destroyed (28).

IGF1R gene regulation. The 5'-flanking region promoter of *IGF1R* is enriched in GC, and lacks the effective transcription initiation of the majority of eukaryotic genes usually requiring TATA and CCAAT boxes. This characteristic results in a partial difference in its gene regulation compared with other promoter regions (29,30).

IGF1R gene expression is regulated transcriptionally and post-transcriptionally. Previous studies have suggested that numerous transcription factors regulate the *IGF1R* gene. Transactivation factors include zinc finger protein specificity protein 1 (Sp1), forkhead box protein O3 (Foxo3), E2F1 transcription factor, Krüppel-like factor 6, EWS RNA binding protein 1-Wilms tumor 1 (WT1) fusion protein and high mobility group A1, all of which bind directly to the IGF1R promoter (31-34). In contrast, estrogen, BRCA1 DNA repair associated (*BRCA1*) and von Hippel-Lindau tumor suppressor inhibit *IGF1R* expression by binding to Sp1 (31,35). A previous study confirmed that WT1 specifically binds to co-WT1 *cis*-elements in the *IGF1R* proximal promoter region, and decreases *IGF1R* gene transcription and translation (36). Overexpressing MYB proto-oncogene transcription factor in tumor cells increases the expression of IGF-1 and IGF1R by increasing transcriptional activity (37).

IGF1R-associated signaling pathways. IGF1R is associated with multiple signaling pathways via downstream proteins, including IRS and PI3K (38-40). IGF1R, which mediates apoptosis-inhibiting signals, and enhances cell metabolism and protein synthesis via downstream mechanistic target of rapamycin (MTOR) kinase signaling, activates the PI3K/AKT signaling pathway (41-43). IGF1R activates the growth factor receptor bound protein 2 (Grb2)/RAS/RAF/MAPK signaling pathway to transduce cell growth and proliferation signals (44,45). IGF1R activation or overexpression is associated with invasion and metastasis of cancer cells, processes mediated by numerous signal transduction proteins that affect invasiveness (24,25). For example, phosphorylating IRS-1 affects the interactions between epithelial cadherin and β-catenin, and the crosstalk between the IGF axis and integrins (46). A previous study demonstrated that protein tyrosine kinase 6 forms a complex with IGF1R and the adaptor protein IRS-1, which modulates anchorage-independent growth via the regulation of IGF1R expression and phosphorylation (23).

Previously, crosstalk between IGF1R and other signaling pathways has been assessed, with studies focusing on interactions between IGF1R, steroid hormones and other receptor tyrosine kinases (RTKs) (47). The crosstalk between IGF1R and focal adhesion kinase (FAK) signaling pathways (38), IGF1R and the classical Wnt signaling pathways (48,49), and IGF1R and transforming growth factor β (TGFβ) signaling pathways have also been further clarified (50). In addition, certain IGF1R signals have been newly identified, namely RTK heterodimers, including the INSR hybrid receptor, and IGF1R/INSR that function as dependent receptors intervening in IGF1R signaling and its regulation (51).

The IGF1R signaling pathway is regulated at multiple levels; the expression of IGF-2, the presence of IGF2R and high-affinity IGFBPs affects ligand-binding activity (52). In addition, other extracellular factors, including dendritic cells and integrins, may contribute to regulating IGF1R activity (53). Within cells, Notch and apoptosis inducing factor-1 regulates IGF1R kinase activity (54). Downstream, multiple IGF1R effectors participate in IRS/PI3K/AKT signal transmission, including MTOR complex 1, phosphatase and tensin homolog phosphohydrolase, ribosomal protein S6 kinases, ERK and c-Jun N-terminal kinase (5,55,56).

3. IGF1R and chemotherapy resistance

Overexpression of IGF1R is associated with poorer chemotherapy outcomes for patients with gastric cancer compared with those with low expression of IGF1R (57). Patients with co-expression of IGF1R and multi-drug resistance-associated protein 1 (MRP1) have demonstrated a poorer response with adjuvant FOLFOX-4 chemotherapy (58). In patients with human epidermal growth factor receptor 2-negative breast cancer, the decreased expression of IGF1R was correlated with an improved response to chemotherapy (59). Blocking IGF1R signaling facilitates treating bladder cancer cells that are insensitive to chemotherapy (60). Similar phenomena have been reported for prostate and ovarian cancer when IGF1R signaling is blocked (61,62). Although the function of IGF1R in chemotherapy resistance has been confirmed, the mechanism remains to be fully elucidated. The present study assessed IGF1R-associated tolerance mechanisms from multiple aspects, including promoting proliferation, inhibiting apoptosis, and inducing changes to ATP-binding cassette

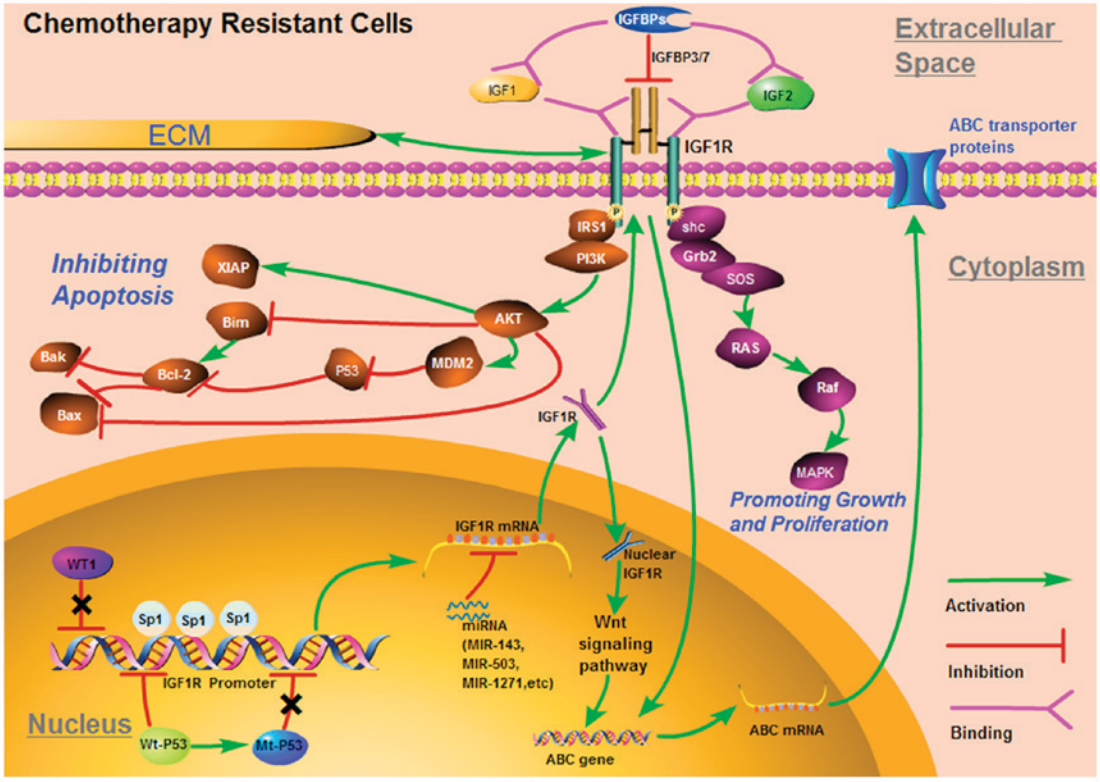

Figure 1. IGF1R signaling pathway and its relevant drug resistance mechanisms: Promoting proliferation, inhibiting apoptosis and inducing changes to ABC transporter proteins and the ECM. Silencing WT1 and mutant p53 causes loss of the inhibitory effects of the *IGF1R* promoter. Downregulating microRNAs, including miR-143, miR-503, miR-1271, causes the loss of IGF1R mRNA degradation and IGF1R translation inhibitory activity. Serum insulin-like growth factor binding proteins decrease the inhibitory effects of IGF1R post-transcriptionally, increasing IGF1R expression and activity. This may promote downstream phosphatidylinositol 3-kinase/protein kinase B and Grb2/RAS/RAF/mitogen-activated protein kinase signaling cascades, thereby enhancing cell proliferation and anti-apoptotic activity. In addition, IGF1R signaling pathways participate in regulating *ABC* genes and alter cell responses to chemotherapy. The ECM and IGF1R stabilize and activate the activity of one another. IGF1R, insulin-like growth factor 1 receptor; ABC, ATP-binding cassette; ECM, extracellular matrix; WT1, Wilms tumor 1; miR, microRNA; Grb2, growth factor receptor bound protein 2.

(ABC) transporter proteins and the extracellular matrix (ECM) (Fig. 1).

Promoting proliferation. A characteristic of tumor cells, persistent proliferation may be acquired in multiple ways (3). As chemotherapeutic resistance develops, certain signals elevate receptor proteins on tumor cell surfaces and permit cells to avoid growth signal control (57). Changing the receptor's molecular structure, which alters ligand restriction and promotes the downstream signal to activate, may achieve the same effect (63).

The Grb2/RAS/RAF/MAPK cascades serve crucial functions in cell proliferation and survival and are aberrantly activated in drug-tolerant cells. Numerous mechanisms increase IGF1R expression and activate IGF1R, thereby promoting signaling cascades and proliferation (64). WT1 is reportedly silenced in drug-resistant cells, which may degrade the inhibitory effect of WT1 on IGF1R transcription (65). Similar effects are reflected in the feedback loop between Foxo3, IGF1R and AKT (31). Micro (mi) RNA inhibits IGF1R expression by directly targeting the 3' untranslated regions but CpG methylating the miRNA promoter region results in the downregulation, and the loss of the inhibitory effects, of IGF1R expression (66,67). MIR-143, MIR-503 and MIR-1271 regulate cisplatin resistance in human gastric cancer cell lines by targeting IGF1R (66-69). Normally, insulin-like growth factor binding protein-7 (IGFBP7) directly binds to IGF1R and inhibits its function post-transcriptionally; however, studies indicate that, in chemotherapy-resistant cells, IGFBP7 expression significantly decreased (70). Therefore, IGF1R is overactivated once IGFBP7 inhibitory activity has decreased (71). Furthermore, inactivating IGF1R inhibits tumor cell proliferation by blockading G0/G1 and IGF1R binds to non-IGF ligands from extracellular spaces, cell membranes and the cytoplasm, which regulates cell proliferation and survival IGF-independently during chemoresistance (72,73).

In addition to overexpression, IGF1R over-activation is also important with respect to chemotherapeutic tolerance. Phosphorylated IGF1R increased in chemotherapeutic drug-resistant cell lines (74-76) and multiple mechanisms contribute to the over-activation of IGF1R, including increased constitutively secreted IGF-1 (63), transgelin overexpression (77) and the effect of the Src oncogene on IGF1R (78). By these processes, IGF1R signals promote tumor cells to proliferate and induce resistance by over-activating Grb2/RAS/RAF/MAPK cascades (64).

Inhibiting apoptosis. Anti-apoptosis is common to numerous tumors and chemotherapy-resistant cells evolve diverse strategies to limit or avoid apoptosis (3). The most common strategy is to eliminate the tumor suppressor function of p53 (79). Resistant cells also downregulate pro-apoptotic

factors or increase the expression of anti-apoptotic factors to avoid apoptosis (80). IGF1R participates in apoptosis inhibition predominantly via the PI3K/AKT signaling pathway in drug-resistant cell lines but multiple other mechanisms are associated with IGF1R overexpression and inhibition of apoptosis in drug-resistant cells (81,82).

Previous studies have indicated that cancer chemotherapy is associated with inducing p53-dependent apoptosis responses (79). p53 is one of the most frequently mutated tumor suppressors and IGF1R overexpression inhibits wild-type p53 (WT-p53) via phosphorylated (p) AKT (80). This enhances the ubiquitination-promoting function of murine double minute 2, which decreases p53 protein production (79). Reciprocally, WT-p53 renders tumor cells more chemosensitive by inhibiting Sp1-induced transactivation of the *IGF1R* promoter and increasing the expression of pro-apoptotic protein p21 (81). Mutant p53 stimulates *IGF1R* promoter function in chemotherapeutic resistant cell lines (82). Furthermore, IGF1R regulates cisplatin resistance by targeting proto-oncogene *Bcl-2*, which is anti-apoptotic and affects drug resistance by binding to and inhibiting Bcl 2-associated X protein (BAX) and Bcl 2 homologous antagonist killer protein (83). IGF1R activation is also associated with decreased expression of IGFBP7, which is associated with the expression of the anti-apoptotic gene *Bim* and chemotherapy tolerance-associated genes, including annexin A4 and protein kinase C 1 (84). Conversely, overexpressing IGFBP7 induces apoptosis and reverses tumor drug resistance (70).

Regulating ABC transporter proteins. The ABC is the largest protein transporter superfamily present in all organisms (85). This family of genes codes for different proteins (importers and exporters) and its increased expression decreases drug influx and increases efflux, decreasing therapeutic response (86). IGF1R signals participate in regulating ABC genes, including multidrug resistance protein 1 (MDR1), MRP1, multidrug resistance-associated protein 2 (MRP2), multidrug resistance-associated protein 3 (MRP3) and breast cancer resistance protein (BCRP) (59,87-89). As such, IGF1R increases tumor resistance by increasing the expression of MDR1, a protein implicated in chemotherapeutic resistance (88). Expression of MRP3 and BCRP decreases or disappears in the presence of an IGF1R inhibitor (87) and overexpressing IGF1R results in increased MRP2 promoter activity via increased pAKT and nuclear factor erythroid 2-related factor 2 in resistant cells (59,88). In addition, *IGF1R* silencing increases chemotherapeutic sensitivity via transcription inhibition of MRP-2 (59). Previous studies have demonstrated that overexpressing IGF1R and MRP1 was associated with chemotherapeutic resistance and poorer prognosis compared with malignancies with normal or low expression of IGF1R and MRP1, indicating that the co-expression of IGF1R/MRP1 in tumors may predict chemotherapeutic effects (88,89).

Interacting with ECM. The ECM is predominantly composed of fibrin (collagen and laminin) and proteoglycans (hyaluronic acid), which forms the structural framework for the majority of tissues (90). The ECM transfer signals to the cells via integrin binding and activation, which modulate cell proliferation, survival and migration and influence the tumor response to anti-cancer therapies (91,92).

Previous studies have indicated that IGF1R stabilizes the molecular structure of β1 integrin by protecting it from proteasomal degradation and promoting tumor cells to grow and proliferate (93). FAK, a substrate protein of IGF1R, is activated by integrin, affecting epithelial transformation, invasion and metastasis of tumor cells IGF1R-independently (38). Extracellular fibronectin increases the activity of β1 integrin to increase the abundance of MAPK-phosphatase-1 and the receptor of activated C kinase (RACK-1) (62). In addition, establishing crosstalk between β1 integrin and IGF1R retains the phosphorylation of IGF1R, which helps stimulate downstream signaling of IGF1R, and contributes to cell proliferation and transformation (94). Previous studies have revealed that, in the presence of IGF1R, the β1 integrin receptor increased the recruitment of RACK-1 and mediated tumor cell migration (62). These changes contribute to chemotherapeutic tolerance.

Other mechanisms. Previous studies have revealed that IGF1R is sumoylated and translocated to the nucleus, which permits the receptor to interact with chromatin, and function as a transcriptional regulator (95-97). Nuclear IGF1R specifically binds to and functions as a transcriptional activator of its own promoter, and interferes with signaling pathways (98). Specifically, nuclear IGF1R interferes with Wnt signaling, which upregulates ABC drug transporters and modulates drug responses (99). Regarding the tumor microenvironment, activating IGF1R results in stabilizing hypoxia-inducible factor (HIF)-1α and HIF-2α, and the upregulation of vascular endothelial growth factor (100). A previous study demonstrated that overexpressing HIF-1α increased the expression of Bcl-2, decreased the expression of BAX, and induced the expression of MDR1 and MRP1 (101). These results offer novel insights into IGF1R-mediated chemotherapeutic resistance.

4. Conclusions

Chemotherapeutic resistance commonly results in cancer treatment failing, with previous studies confirming multiple resistance-associated mechanisms (102,103). Therefore, understanding how tumors develop resistance may help to identify improved drugs and increase patient survival rates.

Changes in drug transporter proteins, activating signaling pathways and ineffectively inducing cell death are primary mechanisms of chemotherapeutic resistance. IGF1R-mediated resistance includes promoting cells to proliferate, inhibiting apoptosis, inducing increased expression of ABC transporter proteins on cell membranes and inducing changes in the ECM. Transcription factors and miRNAs also intervene in regulating IGF1R transcriptionally and cause downstream signaling pathways to excessively activate by promoting increased IGF1R expression or loss of inhibitory effects to the *IGF1R* promoter. IGFBPs participate in regulating IGF1R post-transcriptionally, with the loss of IGF1R inhibition and enhanced expression of anti-apoptotic and chemotherapy resistance-associated genes. Following overexpression and over-activation, IGF1R predominantly triggers the Grb2/RAS/RAF/MAPK and PI3K/AKT cascades, which induce proliferation and inhibit apoptosis in chemotherapy-resistant tumor cell lines. IGF1R

signaling regulates the expression of ABC transporter proteins via multiple mechanisms and renders chemotherapy less effective. The ECM interacts synergistically with IGF1R activity as chemotherapy-resistant cells develop; however, how this occurs remains unclear.

Overall, IGF1R signaling serves a crucial function in tumor chemotherapeutic tolerance. Recently, drug combinations that target predicted or identified chemoresistance markers have been suggested as the future direction of cancer treatment. As a membrane receptor, IGF1R is of particular interest in cancer drug targeting; however, IGF1R-mediated resistance mechanisms require further study. Furthermore, RTK heterodimer and IGF1R nuclear translocation may be associated with drug resistance, though few reports of this exist in the literature.

Acknowledgements

The present study was supported by the National Natural Science Foundation of China (grant no. 81572411).

References

1. Cascieri MA and Bayne ML: Analysis of the interaction of IGF-I analogs with the IGF-I receptor and IGF binding proteins. Adv Exp Med Biol 343: 33-40, 1993.
2. Hayashi Y, Asuzu DT, Gibbons SJ, Aarsvold KH, Bardsley MR, Lomberk GA, Mathison AJ, Kendrick ML, Shen KR, Taguchi T, *et al*: Membrane-to-nucleus signaling links insulin-like growth factor-1- and stem cell factor-activated pathways. PLoS One 8: e76822, 2013.
3. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
4. Amutha P and Rajkumar T: Role of insulin-like growth factor, insulin-like growth factor receptors, and insulin-like growth factor-binding proteins in ovarian cancer. Indian J Med Paediatr Oncol 38: 198-206, 2017.
5. Wan X, Harkavy B, Shen N, Grohar P and Helman LJ: Rapamycin induces feedback activation of akt signaling through an igf-1R-dependent mechanism. Oncogene 26: 1932-1940, 2007.
6. Chen HX and Sharon E: IGF-1R as an anti-cancer target-trials and tribulations. Chin J Cancer 32: 242-252, 2013.
7. Shi WJ and Gao JB: Molecular mechanisms of chemoresistance in gastric cancer. World J Gastrointest Oncol 8: 673-681, 2016.
8. Liu JP, Baker J, Perkins AS, Robertson EJ and Efstratiadis A: Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igf1r). Cell 75: 59-72, 1993.
9. Ward CW and Garrett TP: Structural relationships between the insulin receptor and epidermal growth factor receptor families and other proteins. Curr Opin Drug Discov Devel 7: 630-638, 2004.
10. Siddle K: The insulin receptor and type I IGF receptor: Comparison of structure and function. Prog Growth Factor Res 4: 301-320, 1992.
11. Wit JM and Walenkamp MJ: Role of insulin-like growth factors in growth, development and feeding. World Rev Nutr Diet 106: 60-65, 2013.
12. Yakar S, Kim H, Zhao H, Toyoshima Y, Pennisi P, Gavrilova O and Leroith D: The growth hormone-insulin like growth factor axis revisited: Lessons from IGF-1 and IGF-1 receptor gene targeting. Pediatr Nephrol 20: 251-254, 2005.
13. Russo VC, Gluckman PD, Feldman EL and Werther GA: The insulin-like growth factor system and its pleiotropic functions in brain. Endocr Rev 26: 916-943, 2005.
14. Laustsen PG, Russell SJ, Cui L, Entingh-Pearsall A, Holzenberger M, Liao R and Kahn CR: Essential role of insulin and insulin-like growth factor 1 receptor signaling in cardiac development and function. Mol Cell Biol 27: 1649-1664, 2007.
15. Moody G, Beltran PJ, Mitchell P, Cajulis E, Chung YA, Hwang D, Kendall R, Radinsky R, Cohen P and Calzone FJ: IGF1R blockade with ganitumab results in systemic effects on the GH-IGF axis in mice. J Endocrinol 221: 145-155, 2014.
16. Delafontaine P, Song YH and Li Y: Expression, regulation, and function of IGF-1, IGF-1R, and IGF-1 binding proteins in blood vessels. Arterioscler Thromb Vasc Biol 24: 435-444, 2004.
17. Gao S, Wassler M, Zhang L, Li Y, Wang J, Zhang Y, Shelat H, Williams J and Geng YJ: MicroRNA-133a regulates insulin-like growth factor-1 receptor expression and vascular smooth muscle cell proliferation in murine atherosclerosis. Atherosclerosis 232: 171-179, 2014.
18. Werner H: Tumor suppressors govern insulin-like growth factor signaling pathways: Implications in metabolism and cancer. Oncogene 31: 2703-2714, 2012.
19. Schayek H, Bentov I, Sun S, Plymate SR and Werner H: Progression to metastatic stage in a cellular model of prostate cancer is associated with methylation of the androgen receptor gene and transcriptional suppression of the insulin-like growth factor-I receptor gene. Exp Cell Res 316: 1479-1488, 2010.
20. O'Connor R, Kauffmann-Zeh A, Liu Y, Lehar S, Evan GI, Baserga R and Blättler WA: Identification of domains of the insulin-like growth factor I receptor that are required for protection from apoptosis. Mol Cell Biol 17: 427-435, 1997.
21. Resnicoff M, Abraham D, Yutanawiboonchai W, Rotman HL, Kajstura J, Rubin R, Zoltick P and Baserga R: The insulin-like growth factor I receptor protects tumor cells from apoptosis in vivo. Cancer Res 55: 2463-2469, 1995.
22. Valentinis B and Baserga R: The IGF-I receptor protects tumor cells from apoptosis induced by high concentrations of serum. Biochem Biophys Res Commun 224: 362-368, 1996.
23. Baserga R: The IGF-I receptor in cancer research. Exp Cell Res 253: 1-6, 1999.
24. Samani AA, Yakar S, LeRoith D and Brodt P: The role of the IGF system in cancer growth and metastasis: Overview and recent insights. Endocr Rev 28: 20-47, 2007.
25. Pollak M: The insulin and insulin-like growth factor receptor family in neoplasia: An update. Nat Rev Cancer 12: 159-169, 2012.
26. Ter Braak B, Siezen CL, Lee JS, Rao P, Voorhoeve C, Ruppin E, van der Laan JW and van de Water B: Insulin-like growth factor 1 receptor activation promotes mammary gland tumor development by increasing glycolysis and promoting biomass production. Breast Cancer Res 19: 14, 2017.
27. Peretz S, Kim C, Rockwell S, Baserga R and Glazer PM: IGF1 receptor expression protects against microenvironmental stress found in the solid tumor. Radiat Res 158: 174-180, 2002.
28. Werner H, Sarfstein R, LeRoith D and Bruchim I: Insulin-like growth factor 1 signaling axis meets p53 genome protection pathways. Front Oncol 6: 159, 2016.
29. Mamula PW and Goldfine ID: Cloning and characterization of the human insulin-like growth factor-I receptor gene 5'-flanking region. DNA Cell Biol 11: 43-50, 1992.
30. Werner H, Bach MA, Stannard B, Roberts CT Jr and LeRoith D: Structural and functional analysis of the insulin-like growth factor I receptor gene promoter. Mol Endocrinol 6: 1545-1558, 1992.
31. Singh RK, Gaikwad SM, Jinager A, Chaudhury S, Maheshwari A and Ray P: IGF-1R inhibition potentiates cytotoxic effects of chemotherapeutic agents in early stages of chemoresistant ovarian cancer cells. Cancer Lett 354: 254-262, 2014.
32. Schayek H, Bentov I, Rotem I, Pasmanik-Chor M, Ginsberg D, Plymate SR and Werner H: Transcription factor E2F1 is a potent transactivator of the insulin-like growth factor-I receptor (IGF-IR) gene. Growth Horm IGF Res 20: 68-72, 2010.
33. Huo X, Liu S, Shao T, Hua H, Kong Q, Wang J, Luo T and Jiang Y: GSK3 protein positively regulates type I insulin-like growth factor receptor through forkhead transcription factors FOXO1/3/4. J Biol Chem 289: 24759-72470, 2014.
34. Finkeltov I, Kuhn S, Glaser T, Idelman G, Wright JJ, Roberts CT Jr and Werner H: Transcriptional regulation of IGF-I receptor gene expression by novel isoforms of the EWS-WT1 fusion protein. Oncogene 21: 1890-1898, 2002.
35. Werner H and Sarfstein R: Transcriptional and epigenetic control of IGF1R gene expression: Implications in metabolism and cance. Growth Horm IGF Res 24: 112-118, 2014.
36. Idelman G, Glaser T, Roberts CT Jr and Werner H: WT1-p53 interactions in insulin-like growth factor-I receptor gene regulation. J Biol Chem 278: 3474-3482, 2003.
37. Kim SO, Park JG and Lee YI: Increased expression of the insulin-like growth factor I (IGF-I) receptor gene in hepatocellular carcinoma cell lines: Implications of IGF-I receptor gene activation by hepatitis B virus X gene product. Cancer Res 56: 3831-3836, 1996.

38. Taliaferro-Smith L, Oberlick E, Liu T, McGlothen T, Alcaide T, Tobin R, Donnelly S, Commander R, Kline E, Nagaraju GP, *et al*: FAK activation is required for IGF1R-mediated regulation of EMT, migration, and invasion in mesenchymal triple negative breast cancer cells. Oncotarget 6: 4757-4772, 2015.
39. Dearth RK, Cui X, Kim HJ, Hadsell DL and Lee AV: Oncogenic transformation by the signaling adaptor proteins insulin receptor substrate (IRS)-1 and IRS-2. Cell Cycle 6: 705-713, 2007.
40. Koval AP, Blakesley VA, Roberts CT Jr, Zick Y and Leroith D: Interaction in vitro of the product of the c-Crk-II proto-oncogene with the insulin-like growth factor I receptor. Biochem J 330: 923-932, 1998.
41. Kulik G and Weber MJ: Akt-dependent and -independent survival signaling pathways utilized by insulin-like growth factor I. Mol Cell Biol 18: 6711-6718, 1998.
42. Peruzzi F, Prisco M, Dews M, Salomoni P, Grassilli E, Romano G, Calabretta B and Baserga R: Multiple signaling pathways of the insulin-like growth factor 1 receptor in protection from apoptosis. Mol Cell Biol 19: 7203-7215, 1999.
43. Brazil DP, Yang ZZ and Hemmings BA: Advances in protein kinase B signalling: AKTion on multiple fronts. Trends Biochem Sci 29: 233-242, 2004.
44. Pollak M: Insulin, insulin-like growth factors and neoplasia. Best Pract Res Clin Endocrinol Metab 22: 625-638, 2008.
45. Greer EL and Brunet A: FOXO transcription factors at the interface between longevity and tumor suppression. Oncogene 24: 7410-7425, 2005.
46. Playford MP, Bicknell D, Bodmer WF and Macaulay VM: Insulin-like growth factor 1 regulates the location, stability, and transcriptional activity of beta-catenin. Proc Natl Acad Sci USA 97: 12103-12108, 2000.
47. Liu C, Zhang Z, Tang H, Jiang Z, You L and Liao Y: Crosstalk between IGF-1R and other tumor promoting pathways. Curr Pharm Des 20: 2912-2921, 2014.
48. Rota LM, Albanito L, Shin ME, Goyeneche CL, Shushanov S, Gallagher EJ, LeRoith D, Lazzarino DA and Wood TL: IGF1R inhibition in mammary epithelia promotes canonical Wnt signaling and Wnt1-driven tumors. Cancer Res 74: 5668-5679, 2014.
49. Zhang QY, Wang L, Song ZY and Qu XJ: Knockdown of type I insulin-like growth factor receptor inhibits human colorectal cancer cell growth and downstream PI3K/Akt, WNT/β-catenin signal pathways. Biomed Pharmacother 73: 12-18, 2015.
50. Alsina-Sanchis E, Figueras A, Lahiguera Á, Vidal A, Casanovas O, Graupera M, Villanueva A and Vinals F: The TGFβ pathway stimulates ovarian cancer cell proliferation by increasing IGF1R levels. Int J Cancer 139: 1894-4903, 2016.
51. Tognon CE and Sorensen PH: Targeting the insulin-like growth factor 1 receptor (IGF1R) signaling pathway for cancer therapy. Expert Opin Ther Targets 16: 33-48, 2012.
52. Firth SM and Baxter RC: Cellular actions of the insulin-like growth factor binding proteins. Endocr Rev 23: 824-854, 2002.
53. Triplett TA, Cardenas KT, Lancaster JN, Hu Z, Selden HJ, Jasso GJ, Balasubramanyam S, Chan K, Li L, Chen X, *et al*: Endogenous dendritic cells from the tumor microenvironment support T-ALL growth via IGF1R activation. Proc Natl Acad Sci USA 113: E1016-E1025, 2016.
54. Medyouf H, Gusscott S, Wang H, Tseng JC, Wai C, Nemirovsky O, Trumpp A, Pflumio F, Carboni J, Gottardis M, *et al*: High-level IGF1R expression is required for leukemia-initiating cell activity in T-ALL and is supported by Notch signaling. J Exp Med 208: 1809-1822, 2011.
55. Manning BD and Cantley LC: AKT/PKB signaling: Navigating downstream. Cell 129: 1261-1274, 2007.
56. Kim EK, Kim JH, Kim HA, Seol H, Seong MK, Lee JY, Byeon J, Sohn YJ, Koh JS, Park IC and Noh WC: Phosphorylated S6 kinase-1: A breast cancer marker predicting resistance to neoadjuvant chemotherapy. Anticancer Res 33: 4073-4079, 2013.
57. Sui P, Cao H, Meng L, Hu P, Ma H and Du J: The synergistic effect of humanized monoclonal antibodies targeting insulin-like growth factor 1 receptor (IGF-1R) and chemotherapy. Curr Drug Targets 15: 674-680, 2014.
58. Ge J, Chen Z, Wu S, Chen J, Li X, Li J, Yin J and Chen Z: Expression levels of insulin-like growth factor-1 and multidrug resistance-associated protein-1 indicate poor prognosis in patients with gastric cancer. Digestion 80: 148-158, 2009.
59. de Groot S, Charehbili A, van Laarhoven HW, Mooyaart AL, Dekker-Ensink NG, van de Ven S, Janssen LG, Swen JJ, Smit VT, Heijns JB, *et al*: Insulin-like growth factor 1 receptor expression and IGF1R 3129G > T polymorphism are associated with response to neoadjuvant chemotherapy in breast cancer patients: Results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Res 18: 3, 2016.
60. Sun HZ, Wu SF and Tu ZH: Blockage of IGF-1R signaling sensitizes urinary bladder cancer cells to mitomycin-mediated cytotoxicity. Cell Res 11: 107-115, 2001.
61. Thomas F, Holly JM, Persad R, Bahl A and Perks CM: Fibronectin confers survival against chemotherapeutic agents but not against radiotherapy in DU145 prostate cancer cells: involvement of the insulin like growth factor-1 receptor. Prostate 70: 856-865, 2010.
62. Eckstein N, Servan K, Hildebrandt B, Pölitz A, von Jonquières G, Wolf-Kümmeth S, Napierski I, Hamacher A, Kassack MU, Budczies J, *et al*: Hyperactivation of the insulin-like growth factor receptor I signaling pathway is an essential event for cisplatin resistance of ovarian cancer cells. Cancer Res 69: 2996-3003, 2009.
63. Montazami N, Aghapour M, Farajnia S and Baradaran B: New insights into the mechanisms of multidrug resistance in cancers. Cell Mol Biol (Noisy-le-grand) 61: 70-80, 2015.
64. Worrall C, Nedelcu D, Serly J, Suleymanova N, Oprea I, Girnita A and Girnita L: Novel mechanisms of regulation of IGF-1R action: Functional and therapeutic implications. Pediatr Endocrinol Rev 10: 473-484, 2013.
65. Chen MY, Clark AJ, Chan DC, Ware JL, Holt SE, Chidambaram A, Fillmore HL and Broaddus WC: Wilms' tumor 1 silencing decreases the viability and chemoresistance of glioblastoma cells in vitro: A potential role for IGF-1R de-repression. J Neurooncol 103: 87-102, 2011.
66. Qian X, Yu J, Yin Y, He J, Wang L, Li Q, Zhang LQ, Li CY, Shi ZM. Xu Q, *et al*: MicroRNA-143 inhibits tumor growth and angiogenesis and sensitizes chemosensitivity to oxaliplatin in colorectal cancers. Cell Cycle 12: 1385-1394, 2013.
67. Wang T, Ge G, Ding Y, Zhou X, Huang Z, Zhu W, Shu Y and Liu P: MiR-503 regulates cisplatin resistance of human gastric cancer cell lines by targeting IGF1R and BCL2. Chin Med J (Engl) 127: 2357-2362, 2014.
68. Yang M, Shan X, Zhou X, Qiu T, Zhu W, Ding Y, Shu Y and Liu P: miR-1271 regulates cisplatin resistance of human gastric cancer cell lines by targeting IGF1R, IRS1, mTOR, and BCL2. Anticancer Agents Med Chem 14: 884-891,2014.
69. Zhuang M, Shi Q, Zhang X, Ding Y, Shan L, Shan X, Qian J, Zhou X, Huang Z, Zhu W, *et al*: Involvement of miR-143 in cisplatin resistance of gastric cancer cells via targeting IGF1R and BCL2. Tumour Biol 36: 2737-2745, 2015.
70. Verhagen HJ, de Leeuw DC, Roemer MG, Denkers F, Pouwels W, Rutten A, Celie PH, Ossenkoppele GJ, Schuurhuis GJ and Smit L: IGFBP7 induces apoptosis of acute myeloid leukemia cells and synergizes with chemotherapy in suppression of leukemia cell survival. Cell Death Dis 5: e1300, 2014.
71. Baxter RC: Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities. Am J Physiol Endocrinol Metab 278: E967-E976, 2000.
72. Bach LA: Insulin-like growth factor binding proteins-an update. Pediatr Endocrinol Rev 13: 521-530, 2015.
73. Beattie J, Allan GJ, Lochrie JD and Flint DJ: Insulin-like growth factor-binding protein-5 (IGFBP-5): A critical member of the IGF axis. Biochem J 395: 1-19, 2006.
74. Beech DJ, Perer E, Helms J, Gratzer A and Deng N: Insulin-like growth factor-I receptor activation blocks doxorubicin cytotoxicity in sarcoma cells. Oncol Rep 10: 181-184, 2003.
75. Dallas NA, Xia L, Fan F, Gray MJ, Gaur P, van Buren G II, Samuel S, Kim MP, Lim SJ and Ellis LM: Chemoresistant colorectal cancer cells, the cancer stem cell phenotype, and increased sensitivity to insulin-like growth factor-I receptor inhibition. Cancer Res 69: 1951-1957, 2009.
76. Sun Y, Zheng S, Torossian A, Speirs CK, Schleicher S, Giacalone NJ, Carbone DP, Zhao Z and Lu B: Role of insulin-like growth factor-1 signaling pathway in cisplatin-resistant lung cancer cells. Int J Radiat Oncol Biol Phys 82: e563-e572, 2012.
77. Kim TR, Cho EW, Paik SG and Kim IG: Hypoxia-induced SM22α in A549 cells activates the IGF1R/PI3K/Akt pathway, conferring cellular resistance against chemo- and radiation therapy. FEBS Lett 586: 303-309, 2012.
78. Werner H and Le Roith D: New concepts in regulation and function of the insulin-like growth factors: Implications for understanding normal growth and neoplasia. Cell Mol Life Sci 57: 932-942, 2000.

79. Tracz AF, Szczylik C, Porta C and Czarnecka AM: Insulin-like growth factor-1 signaling in renal cell carcinoma. BMC Cancer 16: 453, 2016.
80. Buck E and Mulvihill M: Small molecule inhibitors of the IGF-1R/IR axis for the treatment of cancer. Expert Opin Investig Drugs 20: 605-621, 2011.
81. Ozaki T and Nakagawara A: P53: The attractive tumor suppressor in the cancer research field. J Biomed Biotechnol 2011: 603925, 2011.
82. Larsson O, Girnita A and Girnita L: Role of insulin-like growth factor 1 receptor signalling in cancer. Br J Cancer 96 (Suppl): R2-R6, 2007.
83. Adams JM and Cory S: Bcl-2-regulated apoptosis: Mechanism and therapeutic potential. Curr Opin Immunol 19: 488-496, 2007.
84. Kashyap MK: Role of insulin-like growth factor-binding proteins in the pathophysiology and tumorigenesis of gastro-esophageal cancers. Tumour Biol 36: 8247-8257, 2015.
85. Jiang ZS, Sun YZ, Wang SM and Ruan JS: Epithelial-mesenchymal transition: Potential regulator of ABC transporters in tumor progression. J Cancer 8: 2319-2327, 2017.
86. Zhang YK, Wang YJ, Gupta P and Chen ZS: Multidrug resistance proteins (MRPs) and cancer therapy. AAPS J 17: 802-812, 2015.
87. Benabbou N, Mirshahi P, Bordu C, Faussat AM, Tang R, Therwath A, Soria J, Marie JP and Mirshahi M: A subset of bone marrow stromal cells regulate ATP-binding cassette gene expression via insulin-like growth factor-I in a leukemia cell line. Int J Oncol 45: 1372-1380, 2014.
88. Shen K, Cui D, Sun L, Lu Y, Han M and Liu J: Inhibition of IGF-IR increases chemosensitivity in human colorectal cancer cells through MRP-2 promoter suppression. J Cell Biochem 113: 2086-2097, 2012.
89. Benabbou N, Mirshahi P, Cadillon M, Soria J, Therwath A and Mirshahi M: Hospicells promote upregulation of the ATP-binding cassette genes by insulin-like growth factor-I via the JAK2/STAT3 signaling pathway in an ovarian cancer cell line. Int J Oncol 43: 685-694, 2013.
90. Gilkes DM, Semenza GL and Wirtz D: Hypoxia and the extracellular matrix: Drivers of tumour metastasis. Nat Rev Cancer 14: 430-439, 2014.
91. Elliott T and Sethi T: Integrins and extracellular matrix: A novel mechanism of multidrug resistance. Expert Rev Anticancer Ther 2: 449-459, 2002.
92. L Addison C: Modulation of response to tumor therapies by the extracellular matrix. Future Oncol 2: 417-429, 2006.
93. Sayeed A, Fedele C, Trerotola M, Ganguly KK and Languino LR: IGF-IR promotes prostate cancer growth by stabilizing α5β1 integrin protein levels. PLoS One 8: e76513, 2013.
94. Prokop I, Konończuk J, Surażyński A and Pałka J: Cross-talk between integrin receptor and insulin-like growth factor receptor in regulation of collagen biosynthesis in cultured fibroblasts. Adv Med Sci 58: 292-297, 2013.
95. Packham S, Warsito D, Lin Y, Sadi S, Karlsson R, Sehat B and Larsson O: Nuclear translocation of IGF-1R via p150(Glued) and an importin-β/RanBP2-dependent pathway in cancer cells. Oncogene 34: 2227-2238, 2015.
96. Aleksic T, Chitnis MM, Perestenko OV, Gao S, Thomas PH, Turner GD, Protheroe AS, Howarth M and Macaulay VM: Type 1 insulin-like growth factor receptor translocates to the nucleus of human tumor cells. Cancer Res 70: 6412-6419, 2010.
97. Sehat B, Tofigh A, Lin Y, Trocmé E, Liljedahl U, Lagergren J and Larsson O: SUMOylation mediates the nuclear translocation and signaling of the IGF-1 receptor. Sci Signal 3: ra10, 2010.
98. Sarfstein R, Pasmanik-Chor M, Yeheskel A, Edry L, Shomron N, Warman N, Wertheimer E, Maor S, Shochat L and Werner H: Insulin-like growth factor-I receptor (IGF-IR) translocates to nucleus and autoregulates IGF-IR gene expression in breast cancer cells. J Biol Chem 287: 2766-2776, 2012.
99. Vesel M, Rapp J, Feller D, Kiss E, Jaromi L, Meggyes M, Miskei G, Duga B, Smuk G, Laszlo T, *et al*: ABCB1 and ABCG2 drug transporters are differentially expressed in non-small cell lung cancers (NSCLC) and expression is modified by cisplatin treatment via altered Wnt signaling. Respir Res 18: 52, 2017.
100. Huang YH, Lin MH, Wang PC, Wu YC, Chiang HL, Wang YL, Chang JH, Huang YK, Gu SY, Ho HN and Ling TY: Hypoxia inducible factor 2α/insulin-like growth factor receptor signal loop supports the proliferation and Oct-4 maintenance of mouse germline stem cells. Mol Hum Reprod 20: 526-537, 2014.
101. Treins C, Giorgetti-Peraldi S, Murdaca J, Monthouël-Kartmann MN and Van Obberghen E: Regulation of hypoxia-inducible factor (HIF)-1 activity and expression of HIF hydroxylases in response to insulin-like growth factor I. Mol Endocrinol 19: 1304-1317, 2005.
102. Popeda M, Pluciennik E and Bednarek AK: Proteins in cancer multidrug resistance. Postepy Hig Med Dosw (Online) 68: 616-632, 2014 (In Polish).
103. Genois MM, Paquet ER, Laffitte MC, Maity R, Rodrigue A, Ouellette M and Masson JY: DNA repair pathways in trypanosomatids: From DNA repair to drug resistance. Microbiol Mol Biol Rev 78: 40-73, 2014.