Clinical Case Studies: Expert Reviews and Advanced Perspectives

Academixs Open Access Publishers

Research Article

An Update on Targeting Insulin Like Growth Factors& Associated Binding Proteins In Improvements In Cancer Prognosis-A Review

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Received Date: 19.11.2025 **Accepted Date:** 25.11.2025 **Published Date:** 05.12.2025

Abstract

The complexity as well as heterogeneity of cancer possess botherations for cancer therapy. In the form of a class of single-chain peptides, insulin-like growth factors (IGFs) possess pivotal parts in cell growth, proliferation, differentiation in addition to metabolic regulation. IGFs facilitates the proliferation, migration, along with possess the invasive capability of tumor cells as well as are intricately correlated with inimical prognosis. Furthermore, IGFs possess the capacity of affecting the crosstalk amongst immune cells in the tumor micromilieu resulting in immune evasion. Additionally, the activation of signals correlated with IGFs modulates the resistance of tumor cells to chemotherapeutic drugs. With the escalating incidence of tumor processes, the will in reference to generation of innovative treatments is assuming greater urgency. This is an exhaustive narrative article regarding the molecular biological mechanistic modes of IGFs in tumorigenesis as well as the generation of innovative treatments associated to targeting IGFs, with the optimism of yielding novel understanding into cancer therapy. This is subsequent to our earlier review on the advancements in the therapy of advanced ovarian cancer(OC) ,programmed death (PD1) /programmed death ligand1(PDL1) pathway and exhaustive review on high grade serous ovarian carcinoma (HGSOC's) –etiology, emphasizing on intra tumor heterogeneity(ITH); homologous recombination repair (HRR) pathway ; homologous recombination deficiency(HRD) and therapy with PARP hampering agents following neoadjuvant chemotherapy (NACT) -with significance of generation of platinum-resistant(PROC) in addition to tackling inimical toxicity sequelae correlated with PARP hampering agents& platinum-based chemotherapy & recently further updated overcoming such issues by utilizing antibody-drug conjugates for PROC & parts of crosstalk amongst endoplasmic reticulum (ER) stress and ferroptosis.

Keywords: Insulin-Like Growth Factors (Igfs); Insulin-Like Growth Factor-Binding Proteins (IGFBPs); PI3K/AKT/ mTOR), / NFκB/ Wnt/β catenin / COX 2 Signaling Pathway

1. Introduction

With the escalating living standard, cancer accounts for the main worldwide load of disease, which persists to escalate globally, causing addition of robustly cost prohibitive load on persons, families in addition to society [1]. As per the Global Agency for Research on Cancer (GARC), 10 cancers were contributors of two-thirds of new cases in addition to fatalities globally in 2022. It is determined that there will be >35 million new cancer cases in 2050, an escalation of equivalent to77% over the 2022 trajectories [2,3]. In the face of the swiftly escalating cancer load, as well as the emergency requirement for improvements in public methodologies in reference to avoidance of, the increase in cancer treatment approaches possess equivalent pivotal part. The insulin like growth factors (IGF), family comprises basically of two low-molecular-weight protein (IGF-1 along with IGF-2), the akin receptors (IGF-1R in addition to IGF-2R) as well as particular binding proteins [4]. In 1963, Froesch *et al.* [5], advented the existence of a some active compound in serum that dId not possess the capacity of getting fully hampered by insulin antibodies; such compound were later purified by two scientists, Rinderknecht as well as Humbel [6], along with labelled them in the form of IGF-1 in addition to, IGF-2. IGF-1 is a small polypeptide comprising of 70 amino acids which is generated as well as liberated into the bloodstream basically by the liver in addition to certain IGF-1 is worked over by the kidneys or skeletal muscles in an autocrine or paracrine fashion in their own tissues or periphery [7]. The quantities of IGF1 in serum is controlled by insulin-like growth factor-binding proteins (IGFBPs). Once IGFBPs get hydrolyzed by proteases, binding of free IGF-1 takes place to IGF-1R on the cell membrane to modulate the analogous biological actions [8]. Additionally, IGF-1 quantities are influenced by a plethora of factors, for instance i) age, ii) nutritional status, along with theiii) liberation of growth hormones (GH) [9]. IGF-2 consists of 67 amino acids as well as possesses growth- facilitating actions kindred to that of IGF-1, nevertheless its expression design is not regulated by GH [10]. IGF-2 is believed to possess a pivotal part in fetal growth as well as synthesis. Insufficiency of IGF-1hampers the proliferation in addition to protein generation of plethora of cells in the body, escalating the susceptibility of persons to various diseases, inclusive of i) metabolic bone disease, ii) cardiovascular disease (CVD) along with iii) neurodegenerative diseases [11,12]. Apart from hampering i) brain generation, diminishing IGF-2 influenceii) cell metabolism as well asiii) stem cell self renewal [13,14]. IGFs are implicated in plethora of stages of cancer generation. IGF 1 serum quantities are considerably greater i)in patients with advanced gastric cancer in contrast to the ones with early stage disease in addition to are correlated with a *Helicobacter pylori* positive status [15]. Additionally, IGF1R activated by IGF 1 possesses a part in epidermal growth factor receptor (EGFR) modulated primary or secondary resistance to colorectal cancer(CRC) by upregulating the phosphatidyl inositide 3 - receptor kinase(PI3K) / protein kinase B(AKT) signaling pathway [16]. A prospective case control study pointed that lesser serum IGF 2 quantities are robustly correlated with hepatocellular carcinoma (HCC) risk [17]. The IGFs system is implicated in the controlling of cancer via a range of signaling pathways, inclusive of the mitogen activated protein kinase (MAPK) signaling pathway [18]. the PI3K/AKT/ mammalian target of rapamycin (mTOR) signaling pathway [19] along with the nuclear factor κB(NFκB)signaling pathway [20].Thereby, modalities targeting the IGF system plausible candidates for anti cancer therapeutic strategies in reference to improvement of results for OC patients is needed. Earlier we reviewed the advancements in the therapy of advanced ovarian cancer with special emphasis on the programmed death (PD1) programmed death ligand1(PDL1) PD1/PDL1 pathway and reviewed exhaustively,an update on high grade serous ovarian carcinoma – with emphasis on how origination of tumor from the in situ surface epithelium of fallopian tubes in etiology of HGSOC's, emphasizing on intra tumor heterogeneity(ITH); homologous recombination repair (HRR) pathway ; homologous recombination deficiency(HRD) and therapy with PARP hampering agents in such cases following neoadjuvant chemotherapy (NACT) however with significance of generation of platinum agents resistant cancers in addition to tackling inimical toxicity sequelae correlated with PARP hampering agents platinum-based chemotherapy recently we further updated how to overcome such issues utilization of antibody-drug conjugates for platinum-resistant ovarian cancers& parts of crosstalk amongst endoplasmic reticulum (ER) stress and ferroptosis [21-26], here we further update on utilization of targeting IGFs system inclusive of insulin-like growth factor-binding proteins (IGFBPs in variable cancers for addressing-escalating drug resistance in variable cancers leave aside OC.

2. Association amongst IGFs along with the malignant biological phenotypes of tumors

Tumor cells possess a distinct malignant biological phenotype, which presents in the form of i)a persistent proliferation signal, ii)evasion from growth hampering, iii)unrestricted capability of reproducibility, iv)persistent angiogenesis, v)resistance to cell demise, vi)invasion as well as metastasis, vii)genomic instability in addition to viii)mutation,ix) immune evasion , along with x)other biological circumstances [27]. The plethora of properties of cancer further escalate the complicated nature of cancer therapy. This section yields understanding into the plausible mechanistic modes by which IGFs affect the malignant biological behavior of cancers, yielding innovative options in reference to cancer treatment.

2.1. IGFs along with tumor proliferation, invasion along with metastasis

Persistent proliferation signals, invasion as well as metastasis represent the basic properties of the malignant phenotype of tumors [28]. In the form of an efficacious mitogen of variable cell kinds, IGF 1 controls variable biological behaviors of tumor cells by binding to IGF 1R. Studies have illustrated that interferon induced transmembrane protein (IFITM) is positively correlated with gastric cancer i)propagation, ii)recurrence in addition to iii)mortality [29,30]. Knocking down IFITM hampers the proliferation, migration, invasion, along with epithelial mesenchymal transition EMT) of gastric cancer cells. Further studies regarding mechanistic modes point that IGF 1 stimulates IFITM2 expression via IGF 1R/ signal transducer and activator of transcription 3(STAT3) signal transduction, that eventually influences tumor growth as well as metastasis [31]. In melanoma, downregulation of IGF 1diminishes the i)dry features of melanoma starting cells, inclusive of the i)expression of dry markers (i)SOX2, ii)Oct 3/4, iii)CD24 as well as iv) CD133) in addition to functional characteristics (i)melanosphere generation, ii)aldehyde dehydrogenase action , along with iii) side population growth as well as ultimately hampering the

proliferation in addition to metastasis of tumor cells[[32]. Furthermore, in breast cancer(BC), IGF 1i) basically upregulates cysteine rich 61 (Cyr61) by a)activating the PI3K/AKT pathway along with b) an escalation in Cyr61 facilitates the,i) growth along with ii)invasion of BC cells [33]. Noticeably,i) vital transcription factors for instance SOX2,a) which facilitate in addition to leads to sustenance of the dry properties of cancer cells possess the capacity of, b) upregulation of the expression , along with c)autocrine action of IGF 2, d) in addition to IGF 2 ii)then followed by a)activation of the IGF 1R/AKT signaling pathway to escalate the i)invasive as well as ii)stemness properties of bladder cancer, forming a vicious cycle [34]. IGFBP 2, a significant member of the insulin like growth factor binding protein family, possesses the capability of controlling a range of cell signaling pathways to affect tumor propagation. Incase of oral cancer, IGFBP 2 facilitates the upregulation of matrix metalloproteinase (MMP)2 in addition to MMP9 via the activation of the PI3K/Akt/mTOR signaling pathway, that eventually result in the proliferation, migration, along with invasion of cancer cells[35]. Additionally, IGFBP 1 possesses the capacity of getting upregulated by *H. pylori* in a dose based fashion, facilitating malignant biological events for instance the i)proliferation, ii)migration as well as iii)invasion of gastric cancer cells [36]. Additionally, IGFBP 7 further possesses the capability of controlling the proliferation in addition to migration of cancer cells via the janus kinase(JAK) JAK/PI3K signaling axis [37]. (Taken together such observations point that targeting IGFs is significant for hampering cancer proliferation along with viciousness.

2.2. IGFs along with tumor angiogenesis.

In reference to seeing through the oxygen as well as nutrient requirements for the i)persistent proliferation, ii) tumor growth in a range of manners to induce the generation of new blood vessels, angiogenesis is needed [38]. Particularly for solid tumors, new blood vessels portray the pivotal association amongst tumor invasion as well as metastasis, that further results in toughness in tumor therapy. Earlier studies have illustrated that IGFs possess a significant part in endothelial cell physiology by facilitating the expression of the vasodilators i) nitric oxide (NO), ii)vascular endothelial growth factors(VEGF) in addition to iii)hypoxia inducible factor (HIF) [39,40]. IGF 1R is implicated in maximum pathophysiological events modulated by IGFs, inclusive of i)proangiogenic actions. Ii) NonethelessIGF 2 further facilitates angiogenesis via the insulin receptor [41]. Studies have documented that the utilization of bisphosphonates possess the capacity of postponement of bone metastasis in patients with breast cancer(BC), in addition to results in improvement of overall survival [42,43]. Evaluation of mechanistic modes pointed that pamidronate as well as clodronate considerably hamper IGF 1 stimulated HIF 1α protein accrual in addition to VEGF expression in BC cells through the PI 3K/AKT/mTOR signaling pathway, along with deplete IGF 1 stimulated tumor angiogenesis in vivo as well as *in vitro* [44]. In hypoxic epithelial ovarian cancer(EOC), in the form of a transcription factor of IGF 1, extensively expressed ETS transcription factor 3 (ELF3,aliasESE-1 and ESX) modulated liberation of IGF 1 in addition to VEGF facilitatedi) endothelial cell proliferation, ii)migration , along with iii)tumor angiogenesis via activation of the tyrosine kinase pathway, whereas ELF3 silencing ameliorated angiogenesis as well as tumorigenesis in a xenograft mouse model, showing the pro vascular actions of IGF 1[45]. Furthermore, a plethora of IGFBPs are further implicated in angiogenesis [46,47]. In glioblastoma, proteomic outcomes point that IGFBP 1 portrays a pivotal modulator of cancer cell hampering liberation in reaction to the vascular generation facilitating factor macrophage colony stimulating factor (MCSF). Addition of conditioned medium from cancer cells to human umbilical vein endothelial cells (HUVECs), the silencing of MCSF resulted in avoidance of blood vessel generation. Furthermore, hampering of IGFBP 1 in cancer cells further barricaded angiogenesis in HUVECs that got treatment with conditioned medium [48]. Moreover, IGF 1R is further implicated in the proangiogenic action of IGFBP 2. IGFBP 2 resulted in the inactivation of protein tyrosine phosphatase β (RPTP β) by binding to the RPTP β receptor as well as gets followed by hampering the transcription of the tumor suppressor gene phosphatase as well as tension homolog(PTEN). Hampering of PTEN modulates the activation of the IGF I/PI3K/AKT signaling pathway, that in turn facilitates vascular smooth muscle proliferation along with tumor angiogenesis [49]. Additionally, other kinds of IGFBPs are capable of facilitating or hampering tumor angiogenesis[50,51].Nevertheless, the pro vascular actions of IGFBP apparently are autonomous of IGF, that yields an innovative trajectory for further asssessment of the association amongst the IGF system in addition to tumor angiogenesis.

2.3. IGFs along with tumor autophagy.

Autophagy possesses a double part, in tumor growth. Early autophagy hampers cancer propagation, however with the persistent growth of tumors, autophagy yields nutrients as well as energy for tumor survival [52]. The basal concentration autophagy flux is often correlated with tumor hampering in addition to it is usually found in i)breast cancer(BC),ii) prostate cancer iii)gastric cancer, iv)hepatocellular carcinoma(HCC), as well as other kinds of cancer in which diminished expression of the autophagy correlated protein Beclin 1 results in escalated proliferation of tumor cells[53-55, rev by us in ref 56]. Furthermore, insufficiency of autophagy controlling factors for instance i)autophagy associated 4C cysteine peptidase (ATG4C) possessed greater plausibility of resulting in to cancer[57]. Nonetheless, a plethora of RAS mutated cancer cells sustain their own growth as well as metabolism via great quantities of autophagy, inclusive of those of i) colorectal cancer(CRC), in addition to ii)pancreatic cancer [58]. IGF signal transduction possess the capacity of activating a plethora of intracellular kinases in reference to activating , along with stimulating a cascade of responses, associated with i)apoptosis, ii)autophagy as well as iii)proliferation [59]. In BC cell lines (MCF 7), activation of IGF/PI3K signaling escalates mitochondrial homeostasis by escalation of the plethora of new mitochondria in addition to quantities of oxidative phosphorylation , along with facilitates the breakdown of injured mitochondria (mitochondrial autophagy alias mitophagy rev in) by escalation of Bcl-2/adenovirus E1B 19-kDa–interacting protein 3 (BNIP3) , a protection conferring mechanistic mode that eventually affects the cancer therapy reactions as well as evaluation of the cancer phenotype [60]. Furthermore, in CRC the part of IGF 1 signaling in facilitating autophagy has been illustrated in i)breast cancer, ii)prostate cancer as well as iii)osteosarcoma [61]. Additionally, IGF 2 is vital for cancer stem cell generation in addition to IGF 2 predilection in reference to crosstalk with insulin receptor isoform A instead of with IGF 1R to augment autophagy ,

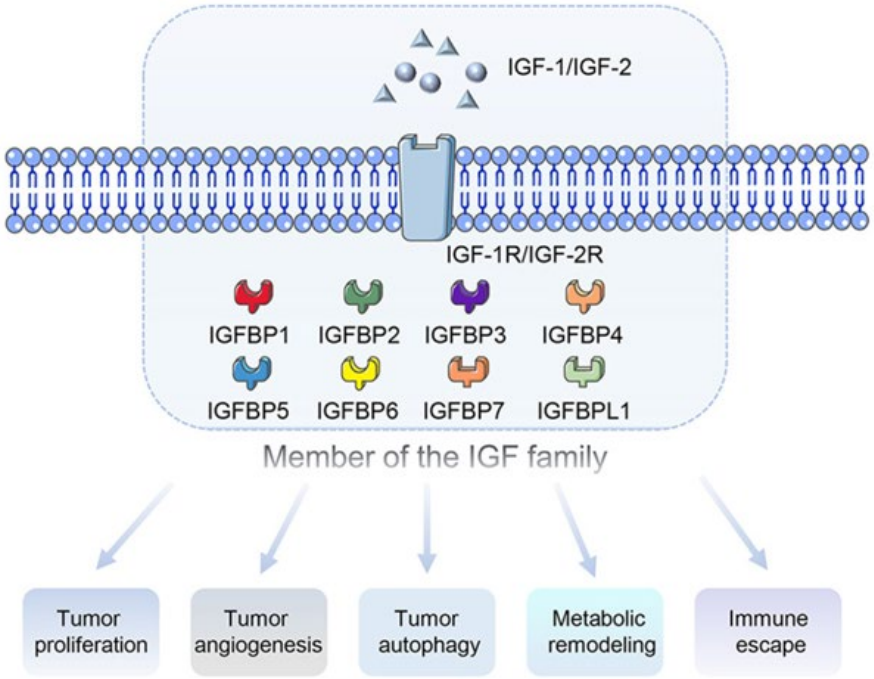
along with metabolic remodeling in CRC [62]. IGFBP 3, one of the main members of the insulin like growth factor binding protein family, possesses the growth hampering actions in vitro [63]. Nonetheless, great quantities of IGFBP 3 in breast tumor tissues are associated with escalated xenograft growth in mice as well as inimical prognosis. Particularly, the binding of IGFBP3 to GRP78 escalates autophagic region generation in addition to autophagic system flux, thereby facilitating BC cell survival despite under glucose starvation in addition to hypoxic situations[64]. Compared to that, IGFBP 3 possesses an oncogenic action on OC cells, representing the heterogeneity of tumor tissues along with the variable characteristics of IGFBP 3 working[65].The pro autophagic action of IGFBPs is further portrayed in events for instance i)chemoresistance in HCC [66]. Such studies yield promising prospects in reference to deep evaluation of the controlling part of the insulin growth factor system in tumor autophagy.

2.4. IGFs along with tumor metabolic remodeling.

The posited Warburg actions documented the significant part of metabolic reprogramming in cancer [67]. To see off the escalated needs for energy as well as generation of substance, tumor cells alter their flux by adapting variable metabolic pathways in addition to targeting metabolic pathways has slowly become a concentration of tumor for scientific researchers in reference to treatment [68]. Nevertheless, metabolic flexibility, along with heterogeneity resulting from tumor heterogeneity as well as plasticity restrict metabolic efficaciousness. IGFs, inclusive of IGF 1 in addition to IGF 2, are implicated in cellular metabolic signaling, along with impact glucose as well as cholesterol uptake in addition to glycogen storage [69,70]. Circulating quantities of IGF 1, along with certain IGFBPs are vital for the sustenance of glucose homeostasis [71]. Studies have illustrated that chronic hyperglycemic diets escalate the risk of colon cancer, in part by controlling the insulin/IGF 1 signaling axis by activating the downstream PI3K/AKT/ mTOR, Ras/MAPK signaling pathways, glucose transporter proteins (GLUT1) as well as critical enzymes of glycolysis (5-lactate dehydrogenase A (LDHA) in addition to hexokinase II hexosekinase(HK II]), thereby affecting glucose uptake along with aerobic glycolysis in cancer cells [72]. In BC, the PPP1R1B truncated subtype (t Darpp) is upregulated in trastuzumab resistant HER2+ breast cancer. t Darpp activates IGF 1R/AKT signaling via heterodimerization with EGFR as well as HER2, facilitating in addition to triggering i) glucose uptake, ii) glycolysis , along with iii) trastuzumab resistance in SK BR 3 cells. Lenz et al[73],isolated transcripts of the PPP1R1B gene, which encodes the dopamine- and cAMP-regulated neuronal phosphoprotein 32 (Darpp-32) as well as a truncated isoform (t-Darpp), as being up-regulated in trastuzumab-resistant HER2+ breast cancer .Pharmacological hampering as well as IGF 1R targeted knockdown revert the actions of t Darpp on metabolic remodeling in addition to drug resistance in tumor cells [73]. IGFBP family proteins possess the capacity of binding to IGF 1 along with IGF 2, therefore controlling the downstream conduction of IGF signals. IGFBP 1 possesses a significant part in the controlling of IGF I signaling as well as impacts a cascade of downstream biological processes for instance i) cell proliferation, ii) survival, iii) movement in addition to iv) metabolism [74]. It is illustrated that IGFBP1 expression along with liberation were significantly escalated in cancer cells, as well as liberated IGFBP 1 hampers AKT1 modulated phosphorylation of ser27 of mitochondrial superoxide dismutase 2 (SOD2), therefore escalating the actions of SOD2 antioxidant enzymes. Escalated SOD2 action enhance the inimicality of accrual of mitochondrial reactive oxygen species (ROS) in spatially laboured cancer cells, therefore embracing the survival of tumor cells in blood vessels in lung tissue as well as amplifying tumor metastasis in mice [75]. Nevertheless, studies of the IGF system in cancer metabolism even currently are inadequate, apart from the uptake in addition to utilization of glucose, however further, the mechanistic modes of alterations in lipid in addition to amino acid metabolism continue to be uncharted.

2.5. IGFs along with tumor immune evasion.

The tumor microenvironment (TME) basically comprises of i) tumor cells, i) stromal cells, iii) immune cells as well as iv) the extracellular matrix(ECM), that become the working of i) material exchange, ii) environmental stress in addition to iii) immune controlling [76]. In the early stage of tumor colonization or growth, activated immune cells account for a tumor reppressive inflammatory micromilieu that hampers tumor generation, while i) long term persistent antigenic stimulation, ii)the activation of immunoreppressive cells along with iii) metabolic stress stimulate the tumor to evade from the surveillance of the immune system as well as persist to escalate, that is referred to as immune evasion of the tumor [77,78]. Modification alterations in the tumor cells themselves in addition to alterations in the immune micromilieu result in complicated nature of the immune evasion event . Remodeling the positive immune micromilieu as well as inducing or rectification of the innate tumor reppression rectification capability of the immune system are pivotal for causing improvementof the malignant propagation of tumors. IGF 1/IGF 1R was observed to be pivotal in controlling the activity of several immune cells, inclusive of i)T cells. In a mouse model of HCC, i)regulatory T cells (Tregs) withii) greater IGF 1R expression posed escalated PI3K/AKT/ mTOR signaling possessed the capacity of greater ATP, lactate in addition to ROS, that allow for escalated immunoreppressive actions[79].Tumor associated macrophages (TAMs), portray significant immunoreppressive cells in the micromilieu ,ii) possessed the capacity of activating the Gli2/IGF 2/ERK1/2 signaling axis to facilitate transforming growth factorβ (TGF-β) liberation, along with thereby modulate the migration, invasion as well as EMT of HCC cells (Huh 7 cells) [80]. Furthermore, M2 kind TAMs, via the liberation of IGF 1 in addition to IGF 2, activate PI3K/AKT/mTOR signaling , along with enhance the malignant proliferation along with stemness properties of cancer cells [81]. Additionally, adipose tissue(AT) in the micromilieu possesses the capability of liberating IGF 1 to embrace remodeling of micromilieu [82]. IGF 1 working in the form of a crucial modulator which connects amongst the micromilieu as well as cancer cells in addition to targeting IGF 1 has assumed a pivotal role in reference to addressing tumor immunoreppression. Nevertheless, the association amongst IGFs, along with numerous micromilieu constituents, for instance i) NK cells, ii)neutrophils in addition to theiii) microbiota as well, continues to be elucidated as well as integrating other targets or combination therapies for tackling the individual along with tissue heterogeneity of tumors is critical. Fig. 1 illustrate the part of IGF family members in tumor propagation[rev in ref 83].



Legend for Figure1
Courtesy ref no-83-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

3. IGFs control signaling pathways associated with cancer propagation

At the time of the malignant propagation of tumors, a plethora of signaling pathways get activated to take part in the proliferation, migration, angiogenesis as well as metabolic remodeling of tumor cells, of which IGFs possess significant controlling part [84]. This section narrates the crucial signaling pathways implicated in the controlling of IGFs in tumor propagation.

3.1. IGFs control the PI3K/AKT signaling pathway.

In an oncogenic backdrop, the IGF family controls a plethora of biological events for instance i)cancer cell proliferation,ii) apoptosis, iii)metabolism in addition to iv)protein generation, that are intricately correlated with the activation of PI3K/AKT signaling, that gets followed by facilitating the transcription of downstream pro oncogenic target genes for instance i)c Myc as well as ii) Hypoxia inducible factor 1 α (HIF 1 α) [85]. In CRC, IGF 2 liberated by cancer associated fibroblasts(CAF) binding takes place to IGF 1R on cancer cells to activate the PI3K/ AKT/mTOR in addition to Hippo/Yes-associated protein (YAP1) signaling pathways to facilitate cancer cell proliferation, migration, along with invasion; subsequent to knock down of IGF 1R or hampering of IGF 1R with the IGF 1R hampering agent picropodophyllin, the tumor facilitating actions get reverted [86]. In case of a separate study, IGF 1 was illustrated to control glucose metabolism in cancer cells with the kallikrein related peptidase 10 (KLK10) getting implicated as well as the knockdown of KLK10 considerably hampered glucose metabolism in addition to, PI3K/ Akt/mTOR signaling activation, an event that possesses the capability of getting reverted by IGF 1, pointing that IGF 1 in addition to KLK10 acts in the form of plausible targets for controlling metabolic remodeling in colon cancer [87]. In the form of a significant noncoding RNA, microRNA (miR) 186 3p is implicated in the proliferation, migration along with apoptosis of a plethora of cancer cells, particularly cervical cancer cells. It possess the capacity of hampering the activation of PI3K/ AKT signaling via the inverse controlling of IGF 1 expression as well as eventually reppress the tumorigenesis of cervical cancer cells [88]. Furthermore, IGF 1modulates the activation of the PI3K/AKT/mTOR pathway ini) uterine smooth muscle tumors, ii)gliomas in addition to iii)pancreatic cancer [89-91]. (Plethora of constituents of the microenvironment are further implicated in malignant tumor propagation. M2 macrophages, due to infiltration rich immunoreppressive cells, possess the capacity of activating the PI3K/AKT/ mTOR signaling axis by liberating IGF 1 along with IGF 2, that facilitates iv)thyroid cancer cell invasion as well as the expression of stemness markers (Oct4, SOX2 in addition to CD133), aggravating the immunosuppressive actions of cancer[81]. IGFBP like protein 1 (IGFBP L1), represents a crucial member of the IGFBP family, controls its working by binding to IGF[92].In esophageal cancer, the methylation event of IGFBP L1 was correlated with tumor size , along with TNM stage. Germane *in vivo* as well as *in vitro* experiments have corroborated that IGFBP L1 methylation elicits a pro oncogenic action by facilitating PI3K/AKT phosphorylation as well as IGFBP L1 methylation has assumed a plausible marker part for the early estimation of esophageal cancer, in addition to an anticipative marker for PI3K targeted treatment in esophageal cancer [93].

3.2IGFs control the NF κB signaling pathway.

NF κB is a more common word for a group of protein complexes, inclusive of basically subunits for instance i)RelA (p65), ii)RelB, iii)c Rel iv), p50/p105 (NF κB1) as well as v) p52/p100 (NF κB2), that possess significant parts in cell proliferation, immune controlling in addition to the stress reactions [94]. Greater quantity NF κB activation is implicated in tumorigenesis, angiogenesis,

remodeling of micromilieu along with chemoresistance [95]. Activation of the NF κB pathway under the impact of IGFs modulates the transcription of downstream signals as well as a variety of tumorigenic actions. IGF 1, in the form of a nutrient reactive growth factor, activates NF κB in addition to the expression of downstream genes (i)Ccdn1, ii)Vegf,iii) Birc5 as well as iv)Ptgs2) to facilitate the growth of pancreatic cancer in vitro in addition to in vivo [96]. Additionally, the interactions amongst IGF 1, along with ROS is implicated in the phenomenon as well as production of a variety of cancers, inclusive of liver, cervical in addition to CRC. Further studies documented that IGF 1 activates the inflammatory signals NF κB as well as nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing (NLRP3) inflammasome in cancer cells in addition to that such activation is based on the accrual of ROS, along with NADPH Oxidase(NOX2). The hampering of the IGF 1 receptor substrate (IRS 1) as well as NOX2 efficaciously causes avoidance of the generation d el of cancer correlated inflammation [97]. IGFBP 3, portraying a liberated glycoprotein, possesses the capability of controlling the mitogenic actions of IGF 1R. Recent studies have illustrated that greater expression of IGFBP 3 is capable of the radio sensitivity of cancer cells as well as stimulates their apoptosis by activating apoptosis correlated proteins. Under irradiation, IGFBP 3 stimulates apoptosis in addition to ROS production by activating NF κB signaling, along with ROS further facilitate IGFBP 3 modulated signaling actions. The positive circuit of NF κB activation as well as ROS generation possess the capacity of accrual of greater ROS in irradiated OSCC cells as well as such positive feedback controlling tackles the pro survival action of NF κB/IL 6 signaling [98]. In a separate study, IGFBP 3 had the capacity of escalating etoposide stimulated cell growth hampering by blocking the NF κB signaling pathway in gastric cancer cells, validating that IGFBP 3 has assumed a pivotal target in addition to marker for cancer therapy , along with further deep evaluation of its deep controlling mechanistic modes might be further helpful [99].

3.3. IGFs control the MAPK signaling pathways

MAPK is a pivotal transmitter of signals from the cell surface to the nucleus as well as possesses the capability of being activated by factors for instance i)cytokines,ii) hormones, iii)stressors in addition to others to control cell growth, differentiation, inflammation as well as other physiological, along with pathological events[100]. In the backdrop of cancer propagation, MAPK signals are implicated in variable activities of cancer cells, inclusive of proliferation, apoptosis as well as immune evasion. Nevertheless, only targeting persistent MAPK correlated signals has not been efficacious in treating cancer [101]. The working of IGFs in the MAPK signaling pathway yields an innovative trajectory in the fight against cancer. IGF 1R is believed tobe a plausible cellular oncogene, particularly in breast cancer (BC), where greater expression with IGF 1R is a guide of the malignant phenotype. in case of persistent IGF 1 induction, IGF 1R/MAPK/PI3K signaling is activated, resulting in resistance to estrogen tamoxifen in addition to fluvestrant. Low doses of tamoxifen work in the form of agonists in IGF 1 stimulated BC cells, along with further escalate IGF 1 expression. Pivotal constituents implicated in the IGF 1/IGF 1R signaling network have become plausible targets for combined antiestrogen treatment [102]. Ovarian cancer associated antigen 66 (OVA66) was first illustrated in OC by diminishing IGF 1R expression as well as downstream phosphorylation of ERK1/2 Hsp27 signaling. Deeper studies regarding mechanistic modes have illustrated that OVA66 possesses the capability of cross talk with MDM2 to control the activation of the IGF 1R ERK1/2 signaling pathway to facilitate tumorigenesis [103]. Research has illustrated that type 2 diabetes (T2DM) is correlated with an escalated risk of colon cancer, as well as escalated insulin along with IGF 1. Insulin in addition to loneIGF 1 or in combination facilitated the proliferation of MC38 colon cancer cells, along with diminished apoptosis. Nonetheless, the utilization of extracellular signal –regulated kinase (ERK1/2) or c-Jun-N-terminal kinase (JNK) hampering agents, hampered the growth of colon cancer cells *in vivo* in addition to *in vitro*, pointing that the activation of ERK1/2 as well as JNK signaling by insulin along with IGF 1 is anyhow partly implicated as well in the generation of T2DM associated colon cancer [104]. Such studies efficaciously corroborated the pivotal part of the IGF 1/ IGF 1R/MAPK signaling axis in malignant tumor propagation.

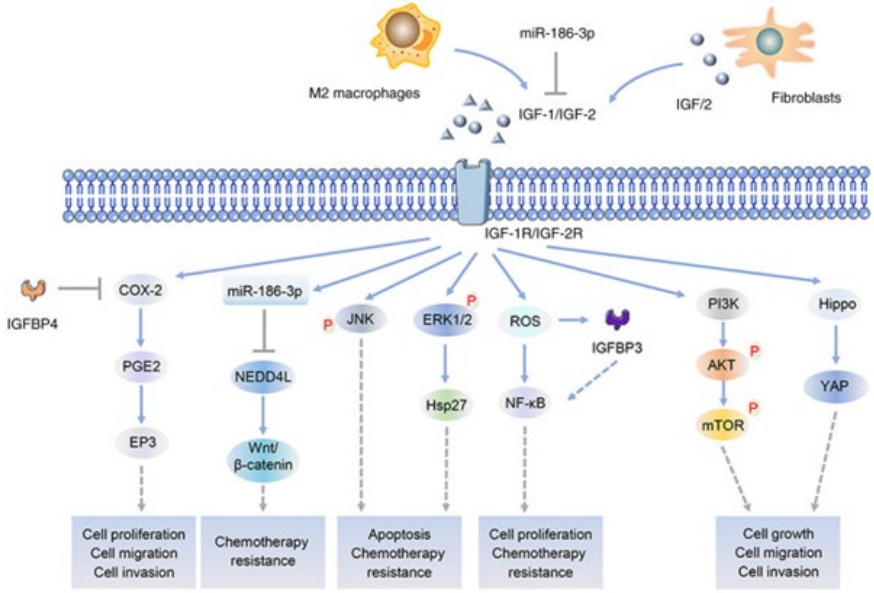
3.4. IGFs control regulate the Wnt/β catenin signaling pathway.

The Wnt signaling pathway is basically modulated by the activation of β catenin as well as the sustained accrual of β catenin into the nucleus, starts the transcription of target genes by binding to T cell factor (TCF)/lymphoid enhancer binding factor transcription factors [105]. The Wnt/β catenin signaling pathway is intricately associated with stem cell differentiation in addition to organ regeneration. Studies have illustrated that the activation of Wnt signaling in CRC is correlated with the elimination of working of the tumor controller adenomatous polyposis coli (APC) along with the implication of Wnt signaling has been documented in a range of malignancies, inclusive of BC, as well as stomach cancer [106,107]. However, targeting the lone Wnt pathway poses significant botherations for cancer therapy, inclusive of inimical drug reaction in addition to toxic inimical sequelae [108]. In the form of a receptor for IGF 1 along with IGF 2, IGF1R modulated phosphorylation of Akt as well as glycogen synthase kinase 3 β (Gsk3β) facilitates β catenin stability in addition to nuclear localization [109]. Additionally, the nuclear localization of IGF 1R is modulated basically by its C terminal domain. Subsequent to its nuclear localization, IGF 1R facilitate TCF modulated β catenin transcriptional action, that has been corroborated in HCC cells [110]. In CRC cell lines (HT 29 , along with SW620), knockdown of IGF 1R by small interfering RNA caused a blockade of the downstream PI3K/Akt , along with canonical Wnt signaling pathways, that eventually hampered cancer cell proliferation in addition to facilitated apoptosis [111]. Regarding isolation of IGF 1 modulated miRNA controlling networks which resulted in temozolomide (TMZ) to be insensitive to glioblastoma multiforme (GBM) therapy, dependent on the exhaustive assessment of plethora of databases as well as in vitro experiments, Chen et al. [112], corroborated that IGF 1 upregulated miR 513a 5p signaling diminished the sensitivity of glioma cells to TMZ by hampering the neural precursor cell-expressed developmentally downregulated 4-like (NEDD4L)(an E3 ubiquitin protein ligase), inactivated Wnt/β catenin pathway. The prospecting of such signaling pathway yields a plausible target regarding improvements in the drug sensitivity of TMZ [112].

3.5. IGFs control the COX 2 signaling pathway.

Cyclooxygenase 2 (COX 2) is a pivotal controlling molecule which

catalyzes the generation of arachidonic acid to prostaglandin (PG), that is expressed in considerably greater concentration when cells are stimulated by inflammation, augmentation of the circumstance of inflammatory storms [113]. COX 2 is extensively expressed in maximum tumors as well as facilitate tumor proliferation, migration in addition to angiogenesis [114]. Additionally, the overexpression of COX 2 is usually intricately correlated with chemotherapy resistance, along with immune evasion events in tumors, pointing that COX 2 is an attractive promising therapeutic target in tumours [115]. However, the controlling of COX 2 associated signaling pathways continue to be uncharted. The IGF 1/IGF 1R system has been illustrated to be a significant facilitate of tumor growth in variable cancers, facilitating tumor propagation as well metastasis by controlling plethora of signaling pathways, for instance those of PI3K/AKT as well as MAPK/ERK signaling [86,102]. Noticeably, COX 2 expression is further influenced by the IGF 1/IGF 1R signaling pathway [112]. In a study of colon cancer cells, COX 2 expression as well as PGE2 s generation were upregulated by the IGF 2/ IGF 1R autocrine pathway in addition to IGF 1R blockade diminished COX 2 activity, along with hampered tumor cell proliferation as well as facilitated apoptosis [111]. Stoeltzing et al. [117], documented that IGF I selectively upregulates COX 2 via the MAPK/ (ERK1/2) pathway in pancreatic cancer along with that therapy with anti IGF IR antibodies possess the capacity of efficaciously hampering IGF IR in addition to MAPK/ERK activation, along with diminished COX 2 expression in parental cells [117]. Moreover, in a BK5.IGF 1 mouse model of BC, escalated quantities of IGF 1 expression activated the COX 2/PGE2/EP3 signaling pathway, correlated with elevated VEGF expression as well as tumor angiogenesis [118]. Celecoxib therapy led to a 45% decrease in mammary PGE2 quantities as well as ameliorated mast cell influx in addition to angiogenesis, pointing that COX 2 selective hampering agents might be of utility in the avoidance of or therapy of BC correlated with escalated human IGF 1 quantity [118]. In the form of a member of the IGFBP family, IGFBP 4 impacts the inflammatory controlling of the tumor microenvironment. In lung cancer tissues, the expression of IGFBP 4 was considerably lesser in contrast to that in normal tissues nearby to the cancer, however the expression of COX 2 was greater in lung cancer tissues. Apart from hampering the expression of COX 2 in lung cancer cells, IGFBP 4 further hampered the proliferation, migration as well as metastasis of cancer cells via the modulation of the PI3K/AKT, ERK in addition to, cyclic adenosine triphosphate(AMP) response element binding proteins (CREBP) pathways, which the anticancer usefulness of IGFBP 4[119].Such observations point that the controlling of the COX 2 associated signaling axis by the IGF system possesses the capability of be a feasible target for cancer therapy in addition to warrants further evaluation. Fig. 2 illustrates the pivotal signaling pathways I implicated in the controlling of IGFs in tumor propagation.



Legend for Figure2

Courtesy ref no-83-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-κB, 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-κB, nuclear factor κB; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; EP3, PGE2 receptor 3; YAP, yes-associated protein; NEDD4L, NEDD4-like E3 ubiquitin protein ligase.

4. Implementation of IGFs in cancer treatment

The therapy of cancer is extensive complicated along with IGF correlated signals influence plethora of events of i) cancer cell proliferation, ii) invasion as well as metastasis. Furthermore, IGFs further modulate tumor resistance to chemotherapy in addition to confer resistance to immunotherapy[120]. Thereby, IGFs are attractive targets for cancer therapy. The concentration of this section is in reference to the implementation along with correlated mechanistic modes of targeting IGFs in cancer treatment.

4.1. Targeted treatment.

Targeting the IGF 1R signaling pathway is believed to be a plausible advent in anticancer treatment as well as a plethora

of small molecule hampering agents in addition to monoclonal antibodies targeting IGF 1R, for instance BIIB 022, BMS 754807, along with Teprotumumab, have been generated as well as evaluated in clinical trials [121-123]. Nevertheless, due to their restricted anticancer action or drug toxicity, a plethora of clinical trials targeting IGF 1R have been given up in addition to occasional drugs have precisely gained entry into clinical utilization. The distinct benefits which natural substances possess in cancer propagation enables targeting IGF 1R feasible. For instance, the combination of curcumin, along with resveratrol hampers NF κB action by targeting IGF 1R signaling, eventually resulting in apoptosis as well as cell cycle arrest in natural colon cancer cells, implying that IGF 1R might be a promising anticancer strategy [124]. Quercetin, that possesses enrichment in fruits, vegetables, leaves in addition to grains, further possess the capacity of hampering skin cancer proliferation by targeting IGF 1R [125]. Epigallocatechin gallate, a polyphenolic constituents of green tea, hampers the propagation of variable cancers, inclusive of glioma, BC as well as liver cancers, by hampering IGF 1R via the phosphorylation of the tyrosine kinase IGF 1R [126-128]. Our group has reviewed all abovementioned natural substances regarding their actions via targeting IGFs system in T2D&obesity& curcumin as well as resveratrol in cancer [129-133]. Targeting circulating IGF 1 as well as IGF 2 quantities is a separate anticancer approach. Nevertheless, despite serum IGF quantities are intricately correlated with tumor propagation, IGF further possesses a significant controlling part regarding normal life actions, For instance sustenance of skeletal muscle growth in addition to generation, islet proliferation, along with cell metabolism. What is the manner of maximization of hampering tumor growth without disrupting normal physiological actions is a pivotal concern in the generation of IGF 1/2 hampering agents. For instance, MEDI 573 hampers IGF 1R signaling as well as tumor growth in vivo by neutralizing IGF 1 in addition to IGF 2. MEDI 573 yielded a plausible targeted therapy approach for cancer [134]. Plethora of studies have illustrated that IGFBPs further possesses the capacity of influencing the malignant biological behaviour of tumours in an IGF autonomous way. Thereby targeting IGFBPs has further assumed an IGFs dependent cancer treatment [135,136]. α1 Antitrypsin (AAT) is a member of the serine protease hampering agent superfamily as well as possesses anti inflammatory in addition to tissue protection conferring actions. It possesses the capacity of decreasing colitis, along with chronic ileitis by hampering cytokine development in addition to escalating intestinal barrier working. In a mouse model of colon cancer, the quantities of IGFBP 3 diminished extensively under the effect of serine protease as well as the utilization of AAT reverted such results, leading to anticancer actions [137]. Plethora of studies have illustrated that methyltransferase-like 3 (METTL3), possesses a significant controlling part in prostate cancer proliferation, migration, invasion, apoptosis, drug resistance androgen stimulated splicing in addition to glycolipid metabolism sustenance[138,139]. The hampering agent STM2457 possesses the capacity of decreasing the m6A quantities in cancer cells by hampering the IGFBP3/AKT signaling axis, thereby eliciting anticancer actions effects in vitro as well as in vivo [140]. Such studies corroborate that targeting IGFs is a significant approach for cancer treatment.

4.1. AChemotherapy.

For maximum cancers, chemotherapy is the major approach of late stage mediation, a treatment approach which aids in improvements in prognosis as well as overall survival. Nevertheless, with the common circumstance of drug resistance, chemotherapeutic agents have assumed lesser efficacy in treating cancer [141,142]. Thereby, scientific workers have initiated evaluation of the plausible mechanistic modes of tumor drug resistance with the objective of improvement in the effectiveness of chemotherapy. Studies have corroborated that IGFs possess significant parts in drug resistance in tumors, inclusive of the IGF 1/IGF 2/IGF 1R signaling axis, along with the IGFBP family members that diminish the proneness of cancers for instance BC as well as lung cancers to chemotherapy resistance [143,144].

i) Thereby, targeting IGFs might aid in tackling the concerns of tumor drug resistance. A) Her2 positive BC resistant to trastuzumab therapy robustly impacts prognosis. In trastuzumab resistant Her2 positive BC cells, IGFBP 3 expression was diminished, resulting in the hampering of Wnt signaling pathway liberation as well as escalated Cullin7 expression modulated by TCF7L2. Escalated Cullin7 was followed by implication in the breakdown of IRS 1 in an mTOR/S6K based fashion to escalate drug resistance. Part rectification of trastuzumab sensitivity in trastuzumab resistant Her2 positive BC cells took place, on arbitration with IGFBP 3 or Cullin7 which is significant for choice of the ideal therapeutic approach for Her2 positive BC cells [145].

B) Tamoxifen, a selective estrogen receptor modulator in addition to antagonist of ERα in breast tissue, is a commonly utilized adjuvant therapy for patients with ERα positive BC [146]. Nevertheless, tamoxifen resistance is assuming greater frequency. Studies have illustrated that tamoxifen resistance is correlated with IGFBP 1 accrual, along with that the overexpression of IGFBP 1 facilitates tamoxifen resistance in BC cells by activating the ERK pathway, which possesses the capability of getting reverted by knocking down IGFBP 1[147].

ii)Furthermore, in HCC, antiangiogenic tyrosine kinase hampering agents (TKHAs) are efficacious therapeutic agents in addition to the major therapeutic activity is to stimulate robust hypoxia in the TME via elimination of the vascular density of tumor. Nevertheless, patients with HCC (their tumor cells usually generated resistance to TKHAs via robust hypoxia in the TME as well as evaded this situation by escalation of the expression of IGFBP-1 in the form of the downstream protein of HIF-1α and -2α signaling, the agglomeration mechanistic modes presented by TKHAs stimulated hypoxia escalating IGFBP 1 expression. Tumor obtained IGFBP 1stimulates tumor angiogenesis by activating integrin α5β1/focal adhesion kinase (FAK)/ ERK1/2 signaling. Part rectification of the attained resistance of tumor cells takes place to TKHAs by hampering IGFBP 1 as well as the combination of antiangiogenic TKHAs in addition to IGFBP 1 hampering agents might be an attractive therapeutic approach for HCC [148].

iii)IGFBP 2 is a liberated protein that results in avoidance of IGF 1/IGF 2 from binding to its receptor along with it further takes part in the controlling of the TME in a macrophage based fashion. IGFBP 2 is extensively expressed in the blood of lung tumors as well as patients with lung cancer in addition to greater quantities of IGFBP 2 are correlated with inimical survival, along with metastasis in patients with lung cancer. In vitro as well as in vivo experiments have illustrated that IGFBP 2 possesses a significant part in the achieving of gefitinib

resistance. According to mechanistic modes, IGFBP 2 possesses the capability of activating STAT3 to escalate the transcriptional activity of C X C motif ligand 1 (CXCL1), thereby escalating the intracellular expression level of CXCL1, that assist in the survival of lung cancer cells in the gefitinib environment [149]. The abovementioned outcomes pointed to the plausible part of IGFBP 2 in the form of a biomarker of gefitinib resistance in addition to a plausible target for arbitration. B) Additionally, reduced survival of human lung cancer cells is correlated with escalated IGFBP 3 expression. IGFBP 3 possesses an anticancer part by eliciting cytotoxic actions on cell survival via a mechanistic mode based on the crosstalk amongst the glycosaminoglycan hyaluronic acid (HA), along with CD44. Elimination of IGFBP 3 expression diminishes the sensitivity of lung cancer cells to cisplatin. Casein kinase 2 (CK2) is an antiapoptotic kinase that sustains cell survival. Phosphorylation of IGFBP 3 by CK2 adds a barricade to the binding of IGFBP 3 to HA, which activates HA CD44 signaling as well as results in decreased apoptosis, escalated cell survival in addition to cisplatin resistance. Blocking CK2 as well as IGFBP 3 phosphorylation might be an efficacious approach to escalate lung cancer proneness to cisplatin [150]. Thereby, further evaluation of the mechanistic modes of IGFs in tumor drug resistance is significant for improvements in tumor sensitivity to chemotherapy agents.

4.1. B Immunotherapy

Immunotherapy is one more innovative cancer therapy approach, following surgery, chemoradiotherapy as well as targeted therapy, opening a novel era of cancer treatment. This implies that lone working on cancer cells would not attain the objective of fully depleting the tumor in addition to innovative therapy approaches illustrated actions to be taken into account in the TME, that is, the encompassing immune cell constituents. Certain fundamental mechanistic modes of the tumor itself aid in tumor cells the surveillance in addition to fatal actions of the immune system, so tumor immune evasion is further one of the obstructions to improvements in the present therapeutic actions on tumors [151]. What is the manner of resolving the immune evasion in addition to secondary drug resistance of tumor has assumed a tough botheration for the broader implementation of tumor immunotherapy. Ovarian cancer (OC) is the maximum lethal gynecological malignancy. Immune checkpoint hampering agents have illustrated great therapeutic effectiveness in maximum malignancies, but possesses restricted effectiveness in patients with OC. The major exposition is that the greater quantities of ECM accumulation in the OC micromilieu results in tumor vascular collapse, reduced vascular perfusion, inimical drug administration as well as barricade to the migration of cytotoxic T cells to the tumor region [152]. In the form of a broadly utilized antihypertensive drug, losartan escalates vascular perfusion, therefore escalating drug administration in addition to intratumoral invasion of immune effector cells, along with, Conversely, escalates chemotherapy sensitivity by hampering IGF 1 signaling to reshape OC as well as the microenvironment [153]. Plethora of studies have illustrated that IGF 2 in the TME is obtained basically from CAFs in addition to that greater quantities of IGF 2hamper the infiltration, along with cytotoxicity of CD8+ T cells, aggravating the immunosuppressive action s of tumours [86,154]. According to mechanistic modes, results in autocrine IGF 2 facilitates self activation by binding to the IGF 1 receptor (IGF 1R) on CAFs as well as activating PI3K/AKT signaling, with following the liberation of variable chemokines in addition to cytokines (CCL5, along with CXCL12) by CAFs to impact the infiltration of T cell. Additionally, CAFs crosstalk with T cells through the PD 1/PD L1 as well as CD73/adenosine axes as well as hamper their activation, proliferation in addition to effector reactions. Genetic hampering or the targeted hampering agent of IGF 2, lincitinib, extensively escalated the reactions to immune checkpoint barricade, implying the plausibility of IGF 2 in the form of a biomarker, along with therapeutic target in immunotherapy [154]. In a mouse model of pancreatic cancer liver metastasis, the use of IGF IR hampering agent IGF Trap reshaped the local immunosuppressive micromilieu of liver tumours, decreased the enrolment of bone marrow derived suppressor cells (BMSC), reverted innate immune cell polarization, along with hampered metastatic protractedness. Furthermore, once IGF 1R in combination with an anti PD 1 antibody, hampered the growth of experimental pancreatic ductal adenocarcinoma liver metastases as well as the reaction of T cell was further escalated. Such outcomes point that blocking IGFs has the double actions of refashioning reshaping the immune micromilieu in addition to escalating immunotherapy [155]. At present research validates that single agent immunotherapy is not of benefit in cancer therapy , along with that cotargeting IGFs offers a new therapeutic strategy to improve the efficacy of immunotherapy.

4.1. C. Radiotherapy.

Radiotherapy possesses a crucial part in regulating as well as eliminating tumors in the form of an adjuvant cancer therapy, lone or in combination with other methodologies (surgery, chemotherapy, in addition to immunotherapy targeted treatment) [156]. Although there is persistence of propagation in radiation technology, that aid in greater exactitude of radiotherapy of local tumor tissues whereas diminishing the actions on normal tissues, concerns for instance radio resistance as well as tumor recurrence continues to be major botheration's in the implementation of radiation treatment [157]. Improvements in the sensitivity of tumor tissues to radiotherapy is the major trajectory of present research. Studies have illustrated that IGFs are intricately associated to radiation reactions in addition to tumor radio sensitivity. Among them, IGF/IGF 1R signals possess the capacity of improvements in radiotherapy sensitivity by activating a cascade of signal transduction events implicated in DNA damage repair. In colon cancer cells (HT 29, along with SW480 cells), genetic knockout of IGF 1R or the utilization of the IGF 1R hampering agent NVP ADW742 escalated the fatal actions of radiation on cancer cells, corroborating that elimination of IGF 1R improvements in radio sensitivity to colon cancer therapy [158,159]. Antrocin is a sesquiterpene lactone isolated from camphor that is utilized in the form of a dietary supplement for cancer avoidance of as well as protection conferring actions to liver. Additionally, antrocin has been illustrated to efficaciously antagonize a range of cancers, inclusive of breast, lung, liver in addition to colon cancers [160,161]. In prostate cancer, the combination of antrocin, along with ionizing radiation (IR) synergistically hampers the proliferation of radioresistant prostate cancer cells as well as stimulates apoptosis. Particularly, antrocin controls the cell cycle in addition to apoptosis via the actions of β catenin modulated by IGF 1R, pointing the plausible importance of antrocin in the form of a robust therapeutic agent to overcome radio resistance [162]. Owing to the heterogeneity of tumor tissues, the concerns presented by radio resistance

are escalating important. A deep evaluation of the significant part of IGFs in tumor radio resistance possess the capacity of yielding plausible therapeutic targets for improvements in tumor radiosensitivity.

5. Conclusions along with Directions for Future

Cancer portrays a main social, cost prohibitive as well as public safety concern in the 21st century in addition to escalating morbidity, along with mortality rates have added considerable load in reference to global population. Although there have been advancements in technologies, the treatment as well as avoidance of cancer are still in their budding state. Recently, the manner working of IGFs has progressively been documented, the significant part that IGFs possess in cancer propagation has yielded innovative optimism for cancer therapy. The current review has presented the part of IGFs in cancer as well as their molecular mechanistic modes, with concentration on the implementation of IGFs in present cancer treatments, with the objective of yielding a theoretical ground for exhaustive cancer diagnosis as well as treatment. Hampering of IGF 1R signaling is believed tobe an attractive approach for hampering tumor growth in addition to improvements in survival rates in a range of cancers. Nevertheless, variable drugs, inclusive of teprotumumab, along with BIIB 022, which target IGF 1R, have not illustrated greater therapeutic actions in clinical trials, probably owing to the absence of dependable IGF 1R hampering biomarkers. Furthermore, IGF correlated molecular mechanistic modes, apart from possessing a part in tumor cells, further influence other nontumor cell constituents in the micromilieu, for instance fibroblasts, macrophages as well as T cells, illustrating that targeting lone IGFs do not possess the capacity of fully hampering tumor growth along with propagation. Additionally, due to the multifaceted nature as well as variability of tumor cells themselves, the part of IGFs is not imperatively just in the form of a tumor reppressor, thereby the generation of correlated hampering agents need to completely take into account the affect on the tumor in addition to its encompassing milieu. With the advancements of combination treatments, the combination of targeted IGFs in addition to other modalities for the therapy of tumors has illustrated benefits, which apart from escalating the effectiveness further efficaciously results in avoidance of circumstance of drug resistance. Future research needs concentration on evaluation of the utilization of combination therapy in cancer therapy. Furthermore, with the advancement of multiomics modality, the significance of precision treatment, along with personalized therapy is escalatingly highlighted as well as multidimensional (MD) in addition to variable magnitude of cancer- correlated mechanistic modes need to be asssessed regarding generating greater dependable hampering agents, that in combination with a greater germane target administration mechanistic modes, is the trajectory of cancer therapy in the future. Therefore, conclusions drawn are targeting IGFs possess the capacity of yielding greater therapeutic modalities for cancer patients.

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Citation: Kaur, K. K.,Allahbadia, G. N., Singh, M. (2025). An Update on Targeting Insulin Like Growth Factors& Associated Binding Proteins In Improvements In Cancer Prognosis-A Review. *Clin. Case Stud. Exp. Rev. Adv. Perspect. 1*(1), 1-5.