Insulin-like growth factor axis: A potential nanotherapy target for resistant cervical cancer tumors (Review)

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Received December 9, 2021; Accepted September 7, 2022

DOI: 10.3892/ol.2023.13714

Abstract. Cervical cancer is among the most frequently occurring neoplasms worldwide, and it particularly affects individuals in developing countries. Factors such as the low quality of screening tests, the high incidence of locally advanced cancer stages and the intrinsic resistance of certain tumors are the main causes of failure in the treatment of this neoplasm. Due to advances in the understanding of carcinogenic mechanisms and bioengineering research, advanced biological nanomaterials have been manufactured. The insulin-like growth factor (IGF) system comprises multiple growth factor receptors, including IGF receptor 1. These receptors are activated by binding to their respective growth factor ligands, IGF-1 and IGF-2, and insulin, and play an important role in the development, maintenance, progression, survival and treatment resistance of cervical cancer. In the present review, the role of the IGF system in cervical cancer and three nanotechnological applications that use elements of this system are described, namely Trap decoys, magnetic iron oxide nanoparticles and protein nanotubes. Their use in the treatment of resistant cervical cancer tumors is also discussed.

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Key words: cervical cancer resistance, nanotherapy, theranostic, insulin-like growth factor axis

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1. Introduction

Cervical cancer has the fourth highest incidence and mortality among gynecological neoplasms worldwide. In 2018, the annual estimates for cervical cancer were ~570,000 new cases and 311,000 mortalities (1). However, this neoplasm affects each country according to its degree of economic development, social factors and lifestyle, and is an imminent and serious crisis for developing countries. In Mexico from 2011 to 2015, the mortality rate for cervical cancer was 6.45 per 100,000 women (2), indicating that it a highly prevalent health issue. Furthermore, the use of screening programs based on cytology, known as pap smear testing, has not been successful in developing countries due to the poor quality of the tests resulting in high rates of false negatives (3,4). Additionally,

patients frequently first present at health centers with advanced lesions and are diagnosed with locally advanced stages IB2 to IVA according to the FIGO classification (5). The suggested treatment comprises cisplatin (CDDP)-based chemotherapy concomitant with radiation therapy plus brachytherapy, which represents the standard of care in patients with locally advanced disease (6-9). The average prognosis for 5-year survival is 56% (5,10).

Although patients with a poor response to standard treatment are treated with secondary systemic therapies (7,8), there is no standard treatment for patients with progressive or metastatic cervical cancer due to its heterogeneous manifestations (11). Notably, chemotherapeutic treatments for cervical cancer have shown limited success due to the lack of specificity associated with systemic administration. In addition, higher doses are required to achieve a therapeutic effect, which increases the adverse cytotoxic effects that exacerbate those of the first treatment and may reduce the physical integrity of the patient; therefore, survival is limited. The resistance of cancer cells to physical and chemical methods, low efficiency of drug delivery and highly heterogeneous tumor microenvironments represent significant impediments in clinical oncology. Furthermore, even when drug administration is optimized, the efficiency of chemotherapy has several challenges, one of which is the typical hypovascularization of cervical cancer tissues (12), which reduces the efficiency of systemic drug distribution. The cellular origin of cervical cancer also contributes to the development and diversity of the tumor microenvironment, which creates different obstacles to drug transport, even in tumors of the same size and stage. Additionally, it has been shown that the density of the tumor cells and formation of intercellular junctions serve key roles in the pharmacokinetics of chemotherapeutic agents in solid tumors (13).

Nano-oncology is a subdivision of nanomedicine in which nanotechnology is used in the treatment of cancer (14,15). Specific delivery strategies for anticancer agents have been developed, generally in the nanoscale range, using materials such as organic nanoparticles made from lipids, polymers, liposomes, polymeric micelles, dendrimers and engineered peptides and nucleic acids, and inorganic nanoparticles such as carbon, metal and metal oxide nanoparticles (16,17). Nanomaterials have distinctive physical, chemical and optical properties and may be modified with biological molecules to direct them toward specific targets. In this regard, membrane receptors and their ligands have great relevance as biomarkers and therapeutic targets in the treatment of different neoplasms. The insulin-like growth factor (IGF) system has been reported in epithelial and glandular tumors, including prostate cancer, breast cancer and colon cancer, and is an excellent target for nano-oncology (18-20).

The present review provides a brief overview of the IGF system, its relevance in cervical cancer and the development of new nanotechnology-based therapies targeting IGF complex molecules for the treatment of cervical cancer.

2. IGF axis

The IGF system is a complex network comprising growth factors IGF-1 and -2, cell surface receptors IGF-1R and -2R, the IGF binding protein (IGFBP) family of high-affinity

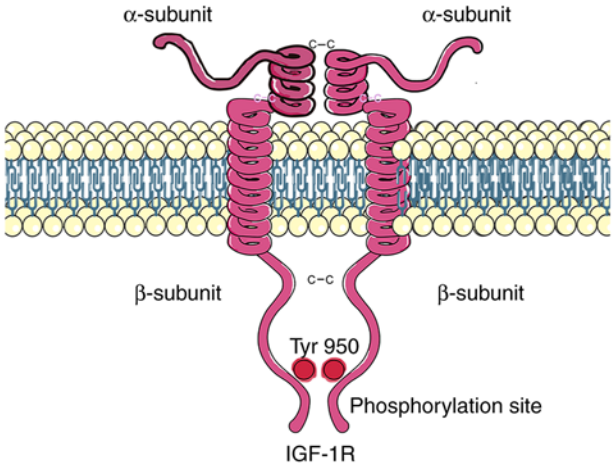

Figure 1. Schematic illustration of IGF-1R. IGF-1R comprises a heterotetramer composed of two α subunits and two β subunits linked by α-α and β-β disulfide bonds.

specific binding proteins (IGFBP-1 to -6) and IGFBP proteases, as well as molecules that interact with IGFBP to regulate and disseminate the actions of IGF in tissues (21). IGFs are peptide hormones from a family that also includes insulin. While the main role of IGF-2 is as a regulator of embryonic and fetal development, IGF-1 is maintained throughout life as a broad-spectrum growth factor (22). These factors bind with a specific receptor on the cell surface and stimulate different signaling pathways.

The sequence of IGF-1R has 60% homology with that of the insulin receptor. It is generated as a polypeptide precursor that is post-translationally modified by glycosylation, proteolytic cleavage and dimerization to form a heterotetramer comprising two α subunits and two β subunits bonded together via α-α and β-β disulfide linkages. The α subunits are located outside the cell and contain the ligand binding site, while the β subunits have extracellular and transmembrane domains and an intracellular portion that contains the tyrosine kinase catalytic domain (Fig. 1) (23). The binding of an IGF ligand to its receptor activates the tyrosine kinase domain, which induces a conformational change allowing autophosphorylation at the Tyr^{950} site. This phosphorylation site is a docking point for substrates such as the insulin receptor substrate 1-4 proteins, where activation of the PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways occurs. The former regulates cell survival and protein synthesis, while the latter regulates gene expression, cell proliferation and differentiation (Fig. 2A) (24). IGF-1R has a tyrosine-kinase domain, whereas IGF-2R does not. Due to this fact and its high affinity for the IGF-2 ligand, it is proposed that the function of IGF-2R is to limit the interaction of IGF-2 with IGF-1R, thereby acting as a tumor suppressor (25,26). The covalent attachment of a small ubiquitin-like modifier (SUMO) family protein to three lysine residues in the b-subunit of IGF-1R via SUMOylation induces its translocation to the nucleus in a ligand-independent manner after (27). In the nucleus, IGF-1R and T cell factor/lymphoid enhancer factor act as transcriptional coactivators to increase the promoter activity and expression of downstream target genes, including cyclin D1 and Axin2 (Fig. 2B), which promote cell cycle progression (19,27).

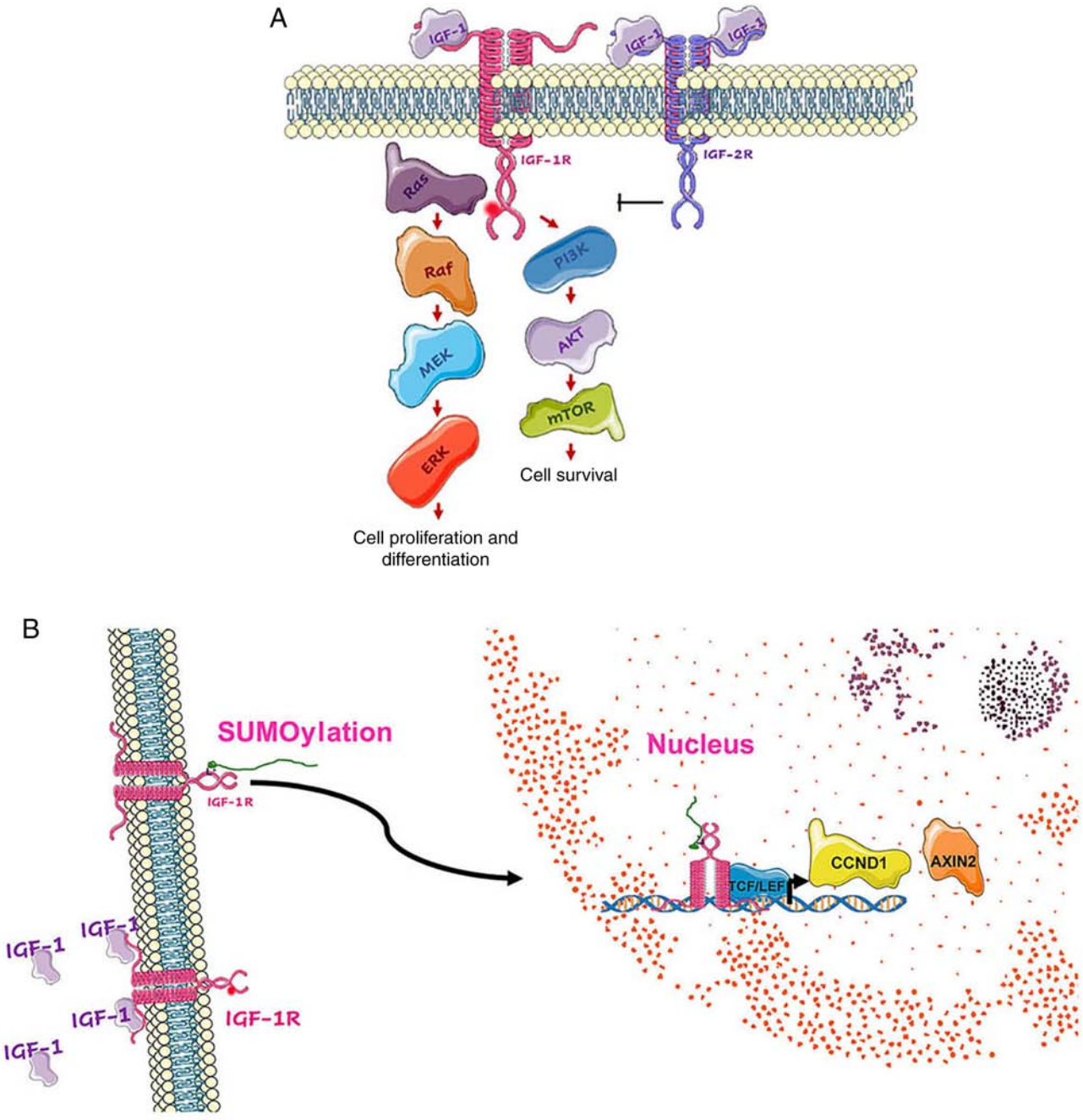

Figure 2. Schematic representation of the regulation of cell proliferation and survival by the IGF axis. (A) Binding of the IGF-1 ligand with IGF-1R causes the autophosphorylation of Tyr^{950}, which induces RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signaling while IGF-2R acts as a negative regulator. (B) The SUMOylation of IGF-1R causes it to migrate to the nucleus where it interacts with TCF/LEF transcriptional factors and activates the transcription of Cyclin D1 and Axin2, which promote cell cycle progression. IGF, insulin-like growth factor; IGF-1R, IGF 1 receptor; IGF-2R, IGF 2 receptor; SUMO, small ubiquitin-like modifier; TCF, T cell factor; LEF, lymphoid enhancer factor; CCND1, cyclin D1.

The actions of IGFs are regulated by interaction with soluble IGFBPs and IGFBP proteases. The IGFBP family comprises six IGFBPs that bind to IGF with high affinity and specificity, and IGFBP-related proteins that are structurally similar to IGFBPs but have lower IGF-binding affinity (22). The six IGFBP proteins are structurally similar to each other but not to cell surface receptors. Each of these binding proteins is the product of different genes and has different functional properties; however, they are all mostly present as high-molecular-weight complexes with IGF-1 and IGF-2 in the circulation and extracellular space, for example, as ~150-kDa complexes with IGFBP-3 and the acid-labile subunit (28,29). These complexes inhibit extravascular transit and help to retain the IGF-1 ligand in the circulation. The IGFBP proteases are critical for modulating the availability of IGF-1 at the cellular level and regulating its half-life via the degradation of IGF-1-containing complexes (Fig. 3A). The dynamic balance of IGF-1, IGFBP and IGFBP proteases constitutes the IGF-1 axis that ultimately determines the extent of the cellular effects dependent on this hormone (30-32). Following dissociation of the ternary complex, the IGFBP/IGF binary complexes are cleared from the circulation via the endothelium, from where

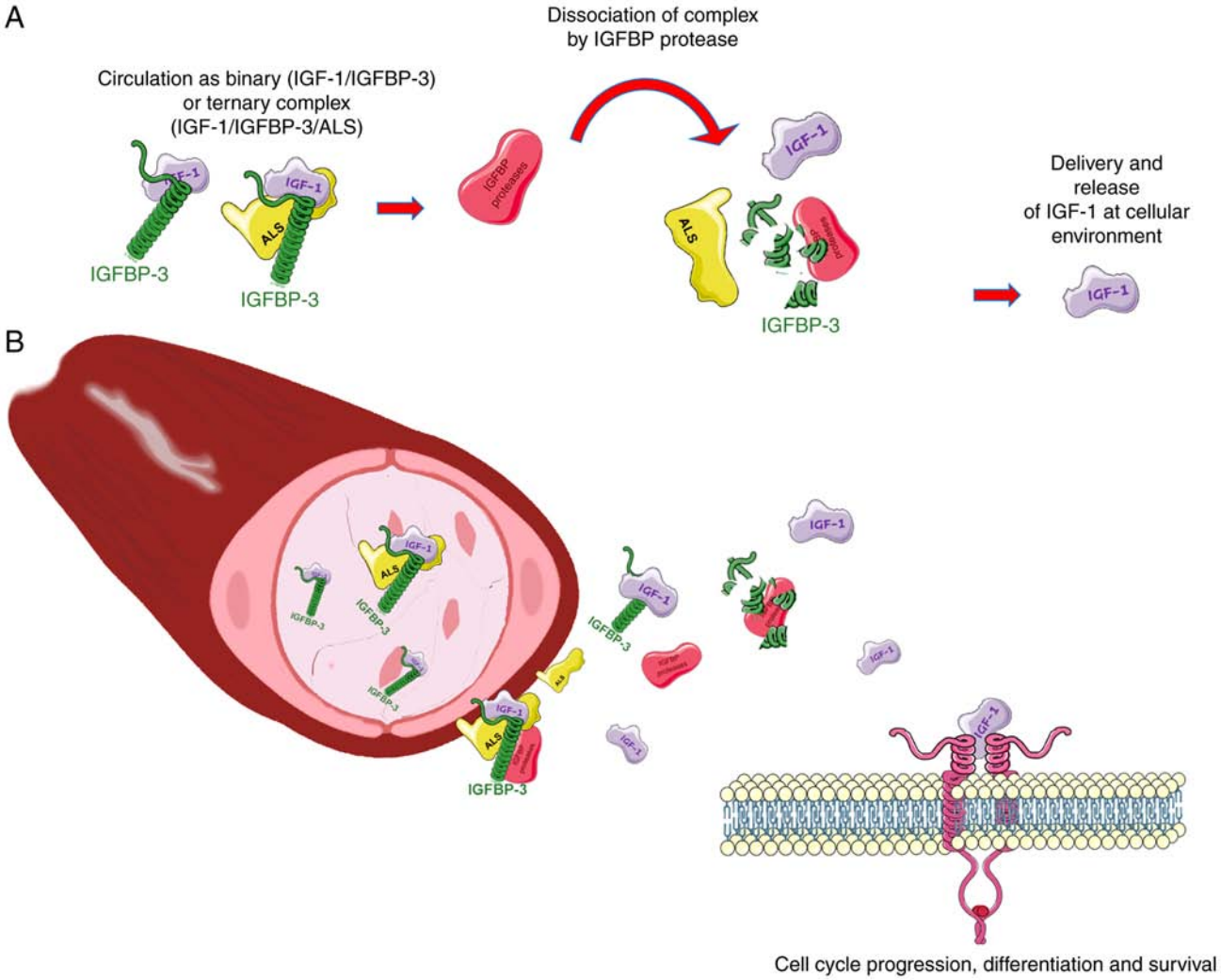

Figure 3. Schematic representation of the regulation of the IGF-1/IGFBP-3/IGFBP protease complex. (A) IGF-1 interacts with the IGFBP protein to form a 150-kDa complex mediated by ALS, which protects, transports and stores IGF-1 in blood capillaries. (B) In the cellular environment the complexes are dissociated by the IGFBP protease and IGF-1 is released. IGF, insulin-like growth factor; IGFBP, IGF binding protein; ALS, acid-labile subunit.

they are delivered to tissues and interact with cell surface receptors (Fig. 3B). Since the binding affinity of IGFs for IGFBPs is higher than that for their receptors, IGFBPs in tissues inhibit the interaction of IGF with its receptors and thereby regulate the action of IGF, promoting a microenvironment that functions as a reservoir for the slow release of ligands. This prolongs the half-life of IGFs in the circulation and prevents them from crossing the capillary barrier (28,33). IGFBP-3 is the most abundant binding protein in human serum; it is present in several glycosylated forms weighing between 40 to 44 kDa and has been shown to regulate the apoptosis induced by p53 (34).

3. IGF axis in cervical cancer

Human papillomavirus (HPV) infection is the primary etiological factor of cervical carcinogenesis (35). The HPV E6 and E7 viral proteins serve well-established oncogenic functions: E6 binds to p53 in a trimeric complex with E6-associated protein, a ubiquitin-ligase, which induces the degradation of p53 in proteasomes (36), while E7 binds to hypophosphorylated retinoblastoma-associated protein (pRB), which is rapidly degraded by proteasomes and constitutively releases the transcription factor E2F (37,38). The HPV-induced loss of function of these two tumor suppressors is a fundamental cause of cervical cancer carcinogenesis. However, additional elements are involved in the inactivation of p53 and pRB (39).

Studies have demonstrated the relationships between viral proteins and members of the IGF system during the neoplastic process. In a study conducted by Kuramoto *et al* (39), it was shown that the expression of IGF-1R is gradually upregulated in cervical intraepithelial neoplasia (CIN) 3 and invasive cancer lesions while its expression is moderate in CIN 1 and 2. The study also suggested that the viral oncoprotein E6 represses p53 and causes transcriptional dysregulation by activating the upregulation of the expression of this receptor. Furthermore, it confirmed that the phosphorylation of IGF-1R increases as the disease progresses. The phosphorylation of IGF-1R activates the MAPK (Ras/Raf/MEK/ERK) and PI3K survival signaling pathways, which contribute to cell survival and drug resistance and thereby serve an important role in progression of the neoplasia (39). It has also been observed in other human neoplasms, including clear cell kidney cancer, colorectal carcinoma and pediatric glioma, that the nuclear translocation

of IGF-1R is associated with advanced disease and poor prognosis (19,40). In the study of Codony-Servat *et al* (19), it was observed that the treatment of patients with metastatic colorectal cancer using IGF-1R blocking antibodies induced an increase in nuclear translocation, suggesting that receptor nuclear sequestration may contribute to resistance. In another study, in which the upregulation of IGF-1R was shown to be associated with resistance to radiotherapy in patients with HPV-16-positive cervical cancer, IGF-1R was proposed as a predictive biomarker of the response to radiation (41). Similarly, in a recent study IGF-2R was proposed as a poor prognostic biomarker for patients with cervical cancer since it may be involved in the recurrence of the disease. In that study, Takeda *et al* (42) describe an oncogenic mechanism of IGF-2R, in which it participates in the regulation of lysosomal transport via Golgi bodies, together with cathepsins B and L loaded with mannose-6-phosphate, resulting in increased lysosomal homeostasis and decreased apoptosis. Thus, IGF-2R appears to have a dual oncogenic role in cervical cancer.

The upregulation of the IGF receptors in tumors resistant to radiation therapy indicates that they are potential targets for alternative therapies. Furthermore, the expression of ligands of the IGF system has been reported in different events that contribute to the pathogenesis and progression of various neoplasms (43,44). In non-small cell lung cancer, a study reported that the expression of IGF-1 and IGF-1R was upregulated and associated with progression and poor prognosis, and suggested that the autocrine/paracrine activity of IGF-1 may play an important role in the development of lung cancer (45). In cervical cancer, a review of the IGF axis indicated that the presence of IGF-1 may contribute to each stage of tumor progression, from malignant transformation, tumor growth, local invasion, distal metastasis and resistance to treatment (46). Elevated levels of IGF-1 and IGF-2 promote signaling via the stimulation of IGF-1R in cervical cancer from the CIN phase (47,48), with a dose-dependent effect on the growth and invasiveness of tumor cells, mainly mediated by IGF-1. Furthermore, an unexpected role of IGF-1 as a stimulator of the invasion and proliferation of cervical cells through interaction with IGF-1R with the cooperation of integrin $\alpha_v\beta_3$ has been reported (49). It is important to note that relatively low IGF-2 mRNA levels have been reported in primary tumor samples and cervical tumor cell models (29,50,51). Therefore, it appears that the production of IGF-2 by cervical epithelial cells is insufficient to transduce a strong mitogenic signal. Nevertheless, Steller *et al* (50) proposed that the autocrine function of IGF-2 in cervical cancer cells involves the mitogenic signaling of epidermal growth factor (EGF).

Studies on IGF-binding proteins in cervical neoplasia have mainly reported on IGFBP-2 and -3. The role of IGFBP-2 in tumorigenesis is complex and multifaceted, as it can both promote and suppress tumors. The prolonged expression of HPV16 E6 and E7 suppresses IGFBP-2 expression; IGFBP-2 generally inhibits the actions of IGF and thereby inhibits mitogenesis, differentiation, survival and other cellular processes, which may be due to the ability of IGFBP-2 to compete with IGF-1R or -2R for the binding of IGF-1 or -2 ligands (47,52). However, IGFBP-2 has also been demonstrated to interact with integrins to exert oncogenic effects that promote cell proliferation and invasion and suppress apoptosis. Specifically, studies have shown that IGFBP-2 is associated with metastasis and uses integrin-dependent mechanisms to reduce cell adhesion and promote invasion, suggesting that IGFBP-2 has IGF-independent oncogenic effects (52-54). By contrast, IGFBP-3 is known to protect against cancer via the p53-mediated activation of apoptosis. However, IGFBP-3 upregulation is a late event after E6/E7 expression in infected cells, after which E6 inhibits p53 activity and consequently blocks apoptosis (55). Additionally, E7 impedes the ability of IGFBP-3 to induce apoptosis. This appears to be mediated via the binding of E7 to the nuclear localization sequence of IGFBP-3 in the nucleus, which reduces the half-life of nuclear IGFBP3 and subsequently induces the polyubiquitination and proteolysis of IGFBP-3 in cervical cancer cells (28,56). However, the functions of IGFBP-3 in the nucleus are not clearly understood, although it may regulate transcription and modify cellular functions through intranuclear pathways (57). Notably, a study of 226 patients found that a high nuclear concentration of IGFBP-3 was a powerful predictor of recurrence in prostate cancer (57,58).

4. IGF axis members as therapeutic targets in cervical cancer

As explained above, the components of the IGF system are activated in an aberrant way during carcinogenesis and, importantly, the expression of certain components confers resistance to the treatments used for this neoplasia, making them a key target for new therapeutic strategies. Several approaches have been used to target components of the IGF system, in particular IGF-1R, due to its involvement in cancer cell growth. These include interference RNAs, antisense oligonucleotides and RNAs, triple helix-forming oligonucleotides, specific kinase inhibitors, single chain antibodies and humanized anti-IGF-1R monoclonal antibodies. Tyrosine kinase inhibitors and monoclonal antibodies are among the most useful; they include ganitumab (AMG-479), dalotuzumab (MK-0646), cixutumumab (IMC-A12), teprotumumab (R1507) and figitumumab (CP-751,871), which are fully human recombinant monoclonal antibodies commonly used to target IGF-1R. They prevent IGF-1 from binding to IGF-1R and inhibit downstream signaling via the PI3K/Akt pathway (18,59-63). The PI3K/Akt pathway is known to promote cell growth and survival in response to extracellular signals. However, a study investigating advances in the treatment of solid tumors with these IGF-1R inhibitory antibodies, alone or in combination with other therapies, revealed they had non-significant effects on overall survival and progression-free survival, and furthermore, adverse effects were observed for dalotuzumab in the breast, colorectal and prostate cancer subgroups (63). Although monoclonal antibodies are highly selective, their development as therapeutic agents is challenging due to their poor tumor penetration and high production costs (28).

5. Extracellular domain of IGF-1R used as a trap nanoparticle

The action of cell surface receptors can be effectively blocked via the use of soluble decoys that specifically bind to a ligand with high affinity, thereby limiting the bioavailability of the ligand and the signaling it would otherwise mediate at the

membrane receptor (64,65). Furthermore, other studies have demonstrated that the efficiency of these decoys is significantly improved by the addition of the Fc domain of human IgG_1 to form a more stable chimeric protein known as a 'Trap'. Specific Traps have been used to treat various diseases, including rheumatoid arthritis (66), cryopyrin-associated periodic syndromes (67), wet macular degeneration and metastatic colorectal cancer (65). In addition, an EGFR-Fc fusion decoy comprising the truncated extracellular domains of EGFR/ErbB-1 and ErbB-4 was shown to have high affinity for EGF-like growth factor and inhibit the proliferation, invasion and metastasis of breast cancer cells (64,68).

The identification of elements of the IGF system as therapeutic targets in different tumors has stimulated the development of decoys based on the IGF receptor system. A study conducted by Samani *et al* (69) initially designed a truncated protein of IGF-1R comprising the first 933 amino acids of the native receptor and encompassing its extracellular domain. This protein was expressed in H-59 highly metastatic murine lung carcinoma cells and detected as a secreted heterotetramer (β^m-α-α-β^m) that exogenously neutralized the IGF-1 ligand and inhibited the proliferation, invasion and resistance to apoptosis of the cells via the regulation of IGF-1R signaling. Similarly, the expression of this protein markedly reduced the metastatic potential of the H-59 cells following their intrasplenic/portal inoculation in mice, reducing the formation of liver metastases by 90% and significantly extending the disease-free survival time. In a second study, a gutless adenovirus expressing soluble IGF-1R (sIGFIR) was intravenously injected into mice, which led to the production of measurable plasma levels of sIGFIR for up to 21 days and significantly inhibited liver metastasis (70). Subsequently, to optimize this soluble decoy for translation to the clinic, its pharmacokinetic properties and therapeutic potential were improved via fusion with the Fc portion of human IgG_1 to form sIGFIR/hFc-IgG_1. The addition of the Fc fragment did not alter the binding kinetics of the recombinant protein. Furthermore, this IGF-Trap decoy had high binding affinity for hIGF-1, moderately lower affinity for mouse IGF-2 and IGF-1, and a three-log lower affinity for insulin (20). IGF-Trap displayed similar effects to sIGFIR, with the ability to inhibit IGF-1, IGF-2 and IGF-1R-regulated cell signaling and functions in various types of carcinoma cells *in vitro*, including breast, lung and colon carcinoma cells. However, the pharmacokinetic profile of IGF-TRAP was more favorable than that of sIGFIR *in vivo*, as demonstrated by half-lives of 47.5 and 21.9 h, respectively, which confirmed that the two Fc domains improved the stability of the protein *in vivo* (20,64).

A frequent limitation of fusion proteins is that they may form high-molecular-weight complexes via the formation of disulfide bonds between Fc fragments. This is an issue for the IGF-Trap decoy, a tetramer that comprises two subunits each fused to an IgG_1 Fc domain, in which the proximity of adjacent Fc domains facilitates the formation of disulfide bonds and large molecular complexes. For this reason, the IGF-Trap decoy was redesigned by the replacement of cysteine with serine in the hinge region of the Fc fragment of human IgG_1, and the introduction of a longer, more flexible linker between the IGF-1R ectodomain and the Fc domain (Fig. 4).

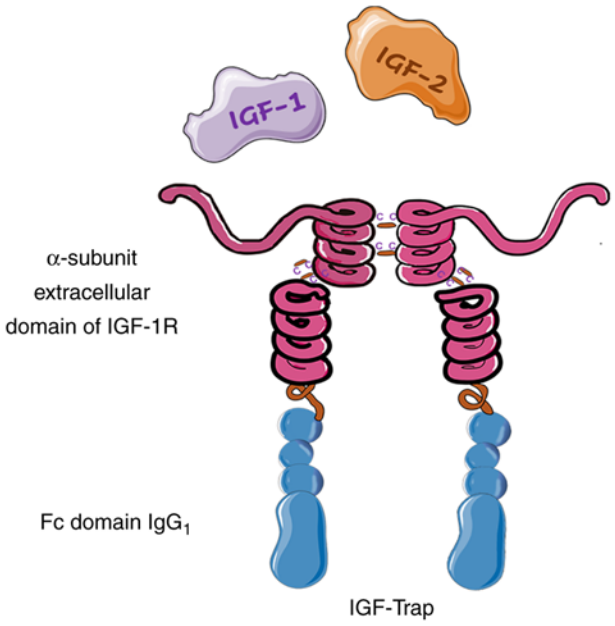

Figure 4. IGF Trap decoy for IGF-1 and -2 ligands. Redesigned with two extracellular domains of IGF-1R subunits, each fused to an IgG1 Fc domain. IGF, insulin-like growth factor; IGF-1R, IGF 1 receptor.

This modification decreased the formation of high molecular weight complexes by this Trap and increased its stability, thereby improving its pharmacodynamic properties (64,71). Using the kinase receptor activation (KIRA) assay, it was shown that the serum bioavailability of IGF-1 is closely associated with the pharmacokinetic/pharmacodynamic profile of the IGF-Trap. In this assay, the bioavailability of the ligand was measured via quantification of the phosphorylated IGF-1 receptor. Unlike traditional endpoint bioassays that measure the downstream effects of IGF-1R activation, the KIRA assay directly measures receptor activation, thereby eliminating the confounding effects of other factors that may also activate downstream signaling pathways. In addition, since the bioavailability and bioactivity of IGF-1 are affected by IGF-BP and naturally occurring proteases in the circulation, the KIRA assay provides a more accurate measure of bioactive ligands (72). The aforementioned studies indicate that IGF-Trap has high specificity for IGF-1 and IGF-2 and low affinity for insulin, and therefore should minimally influence the physiological functions of insulin. In addition, the penetration and diffusion of IGF-Trap into solid tumors may exert beneficial effects via the neutralization of locally produced IGFs. Furthermore, reducing the bioavailability of IGFs using IGF-Trap may affect various components of the tumor microenvironment and thereby provide an enhanced growth inhibiting effect. These data also suggest that IGF-Trap could provide a surrogate marker for response assessment and a potential tool for the classification of patients with resistant cervical tumors.

6. Nanoparticles targeting IGF-1R with theragnostic advantages

Magnetic nanoparticles (MNPs) have shown promising results in the personalized therapy and clinical management of patients

with resistant tumors. Due to the unique physicochemical properties of MNPs, they may be used for multiple applications simultaneously, particularly for theragnostic purposes, such as imaging combined with the administration of therapeutic drugs. Magnetic iron oxide nanoparticles (IONPs) are biocompatible and biodegradable with low toxicity. Therefore, various types of IONPs have been used clinically and have been shown to be safe. Furthermore, IONPs have unique paramagnetic properties that provide T2- and T2*-weighted images with a strong contrast, and a T1 effect at very low concentrations (73,74).

Biodegradable IONPs have been generated and directed against different target receptors, including the urokinase plasminogen activator (uPA) receptor (uPAR). In one study, amphiphilic polymer-coated IONPs were conjugated to the amino-terminal fragment of uPA, the natural high-affinity ligand for uPAR (75). In addition, the polymer coating was modified to allow the encapsulation of hydrophobic chemotherapeutic drugs to form nanoparticulate drug delivery vehicles that are also sensitive to magnetic resonance imaging (MRI). The fluorescent hydrophobic drug doxorubicin (Dox) was efficiently encapsulated into the IONPs to form compact Dox-loaded nanoparticles that were stable at pH 7.4 but released Dox at an acidic pH of 4.0-5.0 within 2 h. These Dox-encapsulating IONPs were observed to retain their T2 MRI contrast effect following their internalization in tumor cells (75). Notably, this IONP system can be conjugated with different ligands and thus be directed to different target receptors to perform theranostic functions. IGF-1R appears to be an ideal target receptor due to its upregulation in tumor cells resistant to treatments. In another study, Zhou *et al* (76) aimed to exploit the theranostic capacities of IONPs directed at this receptor by loading IONPs with Dox and conjugating them with recombinant human IGF-1 for targeting purposes (Fig. 5). The efficacy of these theranostic IONPs, referred to as IBF-1-IONP-Dox, was evaluated using human patient-derived xenograft (PDX) models in which pancreatic cancer tissue was implanted into severe combined immunodeficient mice. The repeated systemic administration of the IGF-1-targeted theragnostic IONPs was monitored by optical imaging and near infrared magnetic resonance, and the results revealed that IGF-1-IONP-Dox induced a significantly greater reduction in PDX growth than was achieved using free Dox or undirected IONP-Dox in both subcutaneous and orthotopic locations. In summary, theragnostic nanoparticles that can easily be modified using a variety of targeting molecules and therapeutic agents, such as antibodies, peptides, small molecules and aptamers, via several conjugation strategies have been directed to specific targets including IGF-1R.

These IONPs constitute a novel model for the imaging and targeted administration of drugs for the treatment of tumors (77). Human pancreatic PDX models, which are highly similar to tumors in patients in terms of their intratumoral heterogeneity, histological features and tumor microenvironments, were used to assess the effect of IONPs. The strategy of using IGF-1 for the targeted therapy of pancreatic cancer is promising. Although this system has not been tested in cervical tumors, it appears to be a promising innovation for the management of resistant tumors.

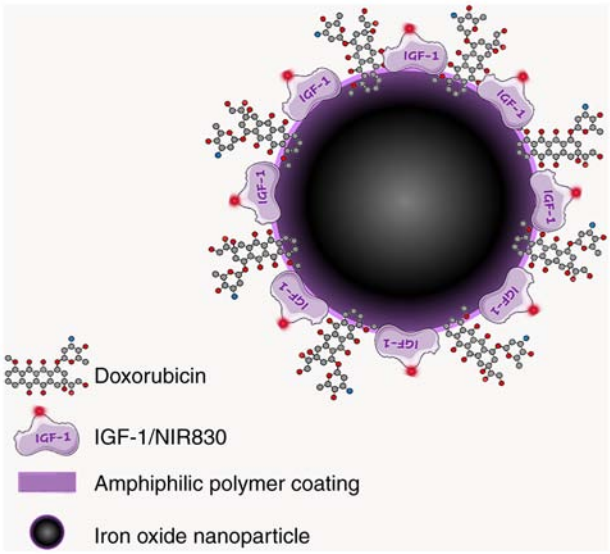

Figure 5. Theranostic nanoparticles targeting IGF-1R. Magnetic iron oxide nanoparticles are conjugated with the near infrared dye NIR 830 and recombinant human IGF-1 targeting molecules and loaded with the hydrophobic drug doxorubicin. IGF, insulin-like growth factor.

7. Protein nanotubes

The self-assembly of peptides to form nanostructured materials is a research area in which the non-covalent interactions within or between peptide building blocks have been investigated for their contribution to the self-assembly process (78). Based on the role of IGFBPs in the initiation, development, progression and survival of cancer and their function as natural antagonists of IGFs, IGFBP mimetics have been created as potential alternative therapies for cancer treatment using IGFBP-2 as a template. It was observed that by fragmenting the IGFBP-2 protein at the single tryptophan residue within the conserved CWCV motif, the carboxyl terminal fragment was stable and able to inhibit the binding of IGF-1 to IGF 1R (79). Therefore, this fragment was subjected to further investigation.

The native sequence of the hIGFBP-$2^{249\text{-}289}$ fragment includes two cysteine residues in its primary sequence, and cysteine-rich regions have been observed to increase the specificity of the ligand (79). Previously, in a study by Binkert *et al* (80), the amino acid sequences of the mature forms of human IGFBP-1, IGFBP-2 and the rat BRL-BP proteins were aligned, and they observed that the three IGFBPs share a cysteine-rich region homologous at its amino terminus, plus an RGD motif embedded in a conserved pentapeptide. However, there are differences between the three proteins of this family. IGFBP-2 has the highest number of cysteines at its carboxyl end and carries an Arg-Gly-Asp (RGD) motif embedded in a conserved pentapeptide, which implies a structural or functional relevance (80). Therefore, following the addition of an extra cysteine at residue 281, an hIGFBP-$2^{249\text{-}289}$ (R281C) polypeptide with an odd number of cysteines was obtained (79,81,82), which spontaneously self-assembled to form soluble nanotubular structures via the formation of intermolecular disulfide bonds. The formation and disassembly of the nanotubes can be controlled by the choice of appropriate redox conditions.

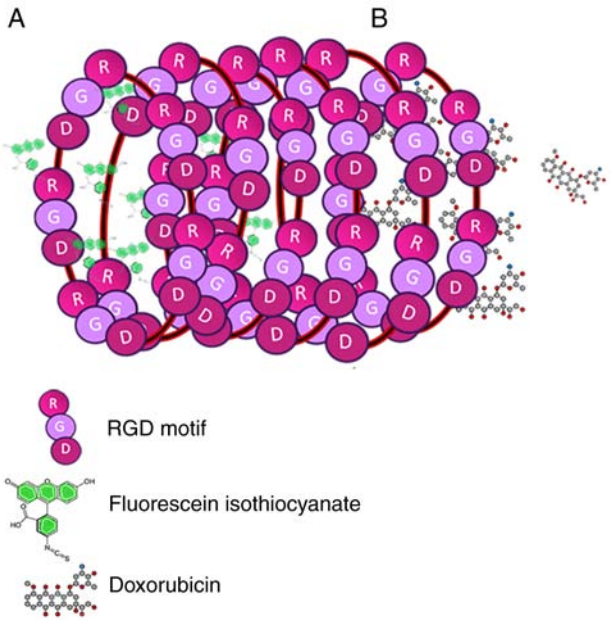

Figure 6. Schematic representation of the organization of nanotubes based on repeated motifs of RGD and their theragnostic potential. (A) Nanotube loaded with fluorescein isothiocyanate for its diagnostic activity. (B) Nanotube loaded with doxorubicin for its therapeutic activity. RGD, Arg-Gly-Asp.

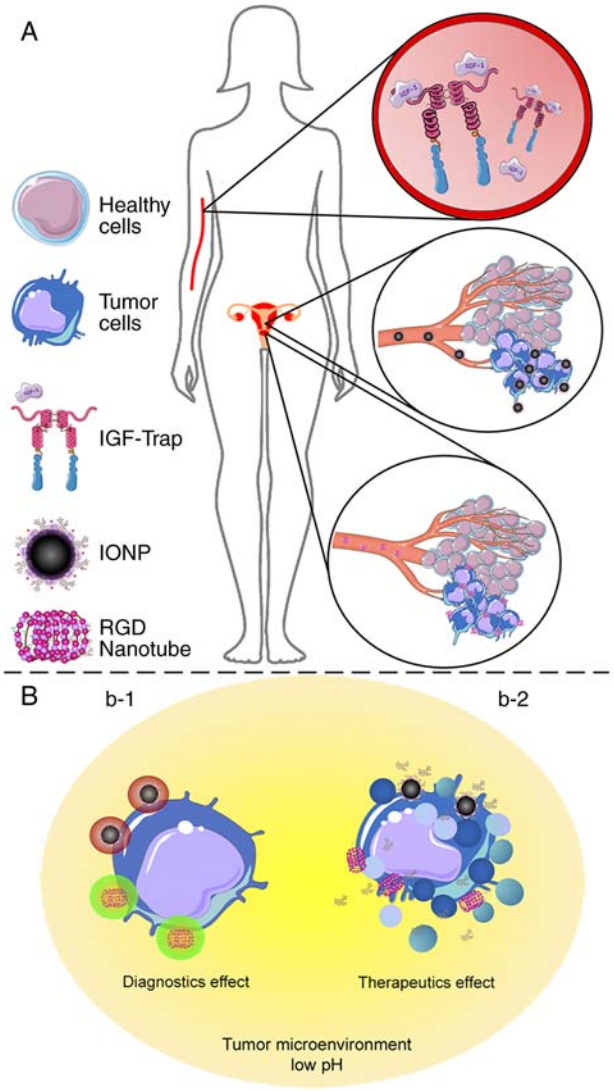

Figure 7. Schematic diagram of the theranostic action of nanotherapy based on elements of the IGF-axis for cervical cancer. (A) IGF-Trap captures the IGF-1 ligand in the bloodstream, limiting its proliferative activity, while the IONPs and RGD nanotubes travel through the circulatory system and access their cellular target guided by IGF-1 or RGD motives, respectively. (B) When IONP or RGD nanotubes bind to tumor cells, the acidic pH of the tumor microenvironment causes a structural change in the nanoparticles. (b-1) Release of transported fluorescent molecules by IONPs as the near-infrared dye (red light) or FITC in the case of RGD nanotubes (green light). (b-2) Release of hydrophobic drugs with a therapeutic function, such as doxorubicin. IGF, insulin-like growth factor; IONPs, magnetic iron oxide nanoparticles; RGD, Arg-Gly-Asp.

Furthermore, the polypeptide fragment contains an RGD motif in its sequence (81,82), and an RGD array is present on the surface of the nanotubes, which serves as a site for the active targeting of cancer cells via integrin binding. RGD is an adhesive peptide widely studied in the field of biomaterials. It has been established that RGD is very effective in promoting the attachment of numerous types of cells to various materials. It constitutes the main binding domain of integrins present in the extracellular matrix, including fibronectin, vitronectin, fibrinogen, osteopontin and bone sialoprotein (83,84).

An interesting application of this protein nanotube system was reported in the study by Asampille *et al* (81). The interior of the nanotubes was loaded with Dox as a representative hydrophobic cytotoxic drug (Fig. 6A) or with the dye fluorescein isothiocyanate as a representative imaging agent (Fig. 6B). In order to determine the ability of the multi-RGD moieties to specifically deliver the nanotubes to cancer cells, integrins were overexpressed on HeLa and MDA-MB-231 cell lines *in vitro*. Confocal microscopy showed that the nanotubes remained attached to the membrane of these cells, while flow cytometry revealed an increase in apoptosis caused by the action of Dox at the cell periphery (Fig. 7b-2). These results demonstrate the theragnostic potential of these nanotubes (28,81) in resistant tumors, including cervical cancer.

8. Conclusions

Cervical cancer is a public health issue that particularly affects developing countries. The lack of efficiency in screening methods, the prevalence of locally advanced stages and intrinsic resistance to common treatments are the main reasons for the failure to control this neoplasm. The conventional treatment recommended by The International Federation of Gynecology and Obstetrics, which comprises 50-Gy radiotherapy concomitant with CDDP-based chemotherapy and brachytherapy, is applied indiscriminately to the majority of patients (8,9). A prediction system has been proposed that indicates the response to treatment and/or the risk of metastasis via the molecular analysis of transcriptional gene signatures (7,85,86), which are molecular tools that enable oncologists to select the optimum therapeutic strategy for each patient. However, the poor prognosis of cervical cancer to conventional treatment necessitates the development of novel therapeutic alternatives that are more efficient in eliminating resistant tumors. Nanotechnology has been used to prepare dual or theragnostic systems that

Table I. Nanotherapy therapeutics and diagnostics based on elements of the IGF-axis.

Authors	Nanoparticle	IGF-axis target	Theragnostic capacity	Bioactive molecules	Activity	Action mechanism	(Refs.)
Chen *et al*, 2020; Samani *et al*, 2004; Vaniotis *et al*, 2018;	Trap decoys	IGF-1 and IGF-2 ligands	Therapeutic	Chimeric protein	Systemic	Blocks the binding of IGF-1 and -2 with cell receptors	(64,69,71)
Yang *et al*, 2008; Zhou *et al*, 2016	Magnetic iron oxide therapeutic	IGF-1R	Diagnostic and nanoparticles	Magnetic nanoparticles conjugated with IGF-1	Targeted membrane receptors	Nanoparticles loaded with drug or fluorescent molecules, targeting IGF-1R in the cell membrane	(75,76)
Kibbey *et al*, 2006; Binkert *et al*, 1989; Asampille *et al*, 2018; Swain *et al*, 2010;	Protein nanotubes	Tumor cell membrane proteins, i.e., integrins	Diagnostic and therapeutic	IGFBP-2 carboxyl end (repeated RGD motif) conjugated to leader molecule (ligands)	Targeted membrane receptors	Nanotubes loaded with drug or fluorescent molecules, targeting membrane proteins	(79-82)

IGF, insulin-like growth factor; IGF-1R, IGF 1 receptor; IGFBP, IGF binding protein; RGD, Arg-Gly-Asp.

can be manufactured using various materials, including nanogels, polymeric micelles, liposomes and targeting agents such as cell-penetrating peptides (81,87-92), functionalized with drugs and combined with bioactive cellular molecules that increase the specificity and effectiveness of diagnosis and treatment. Furthermore, advances in the manufacture of advanced biological materials such as protein nanomaterials have highlighted their potential in bioengineering and biomedical applications (93) (Fig. 7). The present review emphasizes the participation of three elements of the IGF system (Fig. 7A), which actively participate in tumor survival and resistance mechanisms, summarizing their use as bioactive molecules and/or therapeutic targets of nanocarriers (Table I). It may be concluded that they represent a breakthrough in nano-oncology and have potential in the treatment of resistant cervical tumors.

Acknowledgements

The authors acknowledge Professor Alejandro Ariel García-Arriaga (Division of Health, Biological and Environmental Sciences, Open and Distance University of Mexico, Mexico City, México) and Professor Fernando Ferrara-Suárez (Nanotechnology and Biotechnology Engineering Division, Polytechnic University of the Valley of Mexico. Tultitlán, Mexico State, México) for language editing of the manuscript. Parts of the figures were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Funding

This work was supported by the Research Support of the Polytechnic University of the Valley of Mexico.

Availability of data and materials

Not applicable.

Authors' contributions

JFR and MMR conceived the study, wrote the introduction and conclusions sections, and reviewed and edited the manuscript. LPG, HZM and CCCG wrote the IGF axis, IGF axis in cervical cancer and IGF axis members as therapeutic targets in cervical cancer sections. JN and BMP wrote the extracellular domain of IGF-1R used as a trap nanoparticle and nanoparticles targeting IGF-1R with theragnostic advantages sections. JFR and RVMT wrote the protein nanotubes section. MMR and JAJL participated in the acquisition of data on the IGF axis, extracellular domain of IGF-1R used as a trap nanoparticle, nanoparticles targeting IGF-1R with theragnostic advantages,

and protein nanotubes and worked on the development of all figures. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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