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THE ONCOLYTIC POTENTIAL OF TARGETING THE KERATINOCYTE GROWTH FACTOR (KGF)/KGF RECEPTOR PATHWAY

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ABSTRACT

Growth factors and cytokines are often directly involved in cancer cell invasion and the cascade of metastatic cancer progression. These growth factors are often produced by stromal tissue, surrounding the primary tumors where they enhance cancer cell proliferation and stimulate progression to a metastatic phenotype. Keratinocyte growth factor (KGF), a member of the fibroblast growth factor (FGF) family, is known to be produced by stromal tissue and to be associated with the growth and progression of many types of cancer. KGF binds to a specific tyrosine kinase receptor which mediates the KGF cellular response via the Erk signaling pathway. Keratinocyte growth factor responsive cancer cells often contain upregulated KGF receptor (KGFR). The KGF/KGFR signaling pathway appears to be an early signal in the progression of many different types of cancer. Thus, selective inhibitors of the KGF/KGFR signaling pathway have the potential to be effective therapeutic agents for the prevention of metastatic cancer development. Furthermore, elements of this signaling pathway may be important biomarkers of cancer progression and/or therapeutic staging.

INTRODUCTION

Cancer metastasis is responsible for most of the morbidity and mortality associated with cancer. Cancer metastatic progression is a multiple-step process which includes enhanced cell proliferation, release of proteolytic enzymes, cell motility and invasion, angiogenesis and establishment of a supportive microenvironment at the sites of metastatic growth (1, 2). The molecular mechanisms that control metastasis are related to alterations in various oncogenes, tumor suppressor genes, metastasis suppressor genes and growth factors and their receptors (3).

Cell motility is another important aspect of the metastatic process which is associated with penetration of cancer cells through the basal lamina and endothelial lining of capillaries and the entry of tumor cells into the blood and lymph vascular system. Entry of the cancer cells into the circulation is responsible for widespread dissemination of highly motile cells throughout the body. Peptide growth factors are known to be involved in cell motility and have a profound effect on metastatic progression (4). For example, the overexpression of epidermal growth factor (EGF), insulin-like growth factor, transforming growth factor and vasoactive epithelial growth factor are clearly involved in progression and metastasis of various cancers (5-9). Accordingly, keratinocyte growth factor (KGF) and/or the KGF receptor (KGFR) have been linked to the invasiveness and progression of many types of cancer. This review focuses on the potential to target the elements of the KGF/KGFR signaling pathway for the diagnosis, treatment or prevention of metastatic cancer progression.

Keratinocyte growth factor

Keratinocyte growth factor (KGF) was first observed in 1989 in a study to identify substances produced in tissue stroma that stimulate the proliferation and motility of epithelial cancer cells (10, 11). This growth factor is a protein comprising 194 amino acids which undergoes post-translational glycosylation which may not be necessary for its full biological activity (10). Originally identified in human embryonic lung fibroblasts, KGF is a member of the fibroblast growth factor (FGF) family and has also been designated FGF-7 (11). The carboxy-terminal region of KGF is 30-40% identical to other members of the FGF family (12, 13). At present, 18 FGFs (FGF1-FGF10 and FGF16-FGF 23) have been identified and grouped into six subfamilies (14). Other FGF homologs (FGF11-FGF14) do not bind to or activate the known FGF receptors and thus are not currently considered part of the FGF family (15).

Reproductive hormones are directly involved in the regulation of KGF expression in reproductive stromal tissue (16-19). For example, in human endometrial tissue, the expression of KGF is progesterone-dependent while the expression of KGFR in epithelial cells is estrogen-dependent (20). Koji et al. reported that KGF transcripts in endometrial tissue of rhesus monkeys were elevated 70- to 100-fold in response to a combination of estradiol and progesterone (18). More recently, Pedchenko and Imagawa reported that prolactin and

progesterone have a direct regulatory role on KGF-induced proliferation of mouse mammary epithelium (21). Furthermore, KGF appears to play a role in development of reproductive tissue (22, 23).

Keratinocyte growth factor produced by stromal tissue surrounding the epithelial tumor tissue has been demonstrated to stimulate DNA synthesis, proliferation and migration of epithelial cancer cells (23, 24). In addition to embryonic fibroblasts, KGF has also been identified in stromal tissue from human adult lungs, skin, stomach, kidney, bladder, prostate and mammary tissue (10). Keratinocyte growth factor appears to function as a paracrine mediator of mesenchymal-epithelial interaction in embryonic development, and perhaps, wound healing homeostasis in adult tissue. Evidence of tissue regeneration and wound healing has been demonstrated in cornea, skin, lung and tympanic membrane tissue and hair follicles (15, 23, 25, 26). Furthermore, tissue KGF levels have been shown to increase dramatically following skin, bladder and kidney injury (27-29).

Keratinocyte growth factor also appears to enhance tissue cytoprotection in oral mucosa and tissue along the gastrointestinal tract. These observations have led to the development of palifermin, which is an *N*-terminally truncated derivative of KGF with increased stability, as a cytoprotective agent to prevent or reduce the severity of radiation- or chemotherapy-induced mucositis in bone marrow transplant patients (30). Palifermin has been demonstrated to increase epithelial cell proliferation and the thickness of the oral epithelium for a week (31-33). Furthermore, palifermin and repifermin (a similar FGF10 peptide) are under investigation to improve wound healing, immune function and to treat ulcerative colitis (34-37).

The biological actions of KGF are thought to be involved in normal morphogenesis and tissue repair; however, KGF may contribute to tumor cell progression by enhancing cancer cell proliferation, motility and invasion (26, 38-41). Furthermore, it appears that upregulation or overexpression of KGF and/or KGFR is associated with cancer progression and metastatic development (10, 42). Accordingly, KGF, KGFR and intermediates in the signal transduction pathways may represent valuable therapeutic targets to reduce or prevent metastatic development.

Keratinocyte growth factor receptor

Keratinocyte growth factor receptor (KGFR, also referred to as FGFR2IIIb) is a splice variant of FGFR-2 which is encoded by the *FGFR-2* gene (43, 44). KGFR is a member of the fibroblast growth factor receptor (FGFR) family consisting of four known peptides (FGFR1-FGFR4). The FGF receptors are all membrane-spanning tyrosine kinase receptors with highly conserved amino acid sequences (39). These receptors consist of 3 extracellular immunoglobulin domains, a transmembrane domain and a cytoplasmic tyrosine kinase domain (45). Alternate splicing of the extracellular domain results in several isoforms with distinct binding specificity (46). It is well established that the target epithelial cells contain high-affinity KGFRs (12, 26, 44). In situ hybridization studies confirmed the specific mesenchymal distribution of KGF and the epithelial distribution of KGFR in target tissue. This observation provides further evidence that KGF is a mesenchymally derived mediator of epithelial cell proliferation and migration (10, 47). As with KGF, the KGFR is associated with normal tissue morphogenesis and repair (37, 38, 48-50). However, KGFR is known to be overexpressed in many types of types of cancer and changes in its binding specificity are often associated with cancer progression (51). Accordingly, Jang and coworkers reported gain-of-function mutations with KGFR in gastric and colorectal cancer (52).

KGF/KGFR pathway signaling

Keratinocyte growth factor/KGFR signaling is known to involve either the extracellular signal-regulated kinases 1,2 (Erk 1,2) pathway or the 3-phosphoinositide-dependent protein kinase (PI3K) pathway (25, 53-55). Apparently the primary signaling pathway which mediates KGF-induced cancer cell motility involves the Erk 1,2 kinase pathway (55, 56). Accordingly, the Erk 1,2 signaling pathway mediates both the cell proliferation and cell motility associated with KGF-mediated wound healing (57).

An analysis of gene expression in MCF-7 breast cancer cells revealed that KGF treatment produces an increase in the mRNA levels of growth factor receptor bound protein-2 (Grb2) and other Erk signaling intermediates (58). The *Grb2* gene is very highly conserved among species. Moreover, the Grb2 protein is a ubiquitously expressed adaptor protein. Growth factor receptor bound protein-2 is also known to activate tyrosine kinase signaling via Ras (59), which could in turn activate the Raf/MEK/Erk1,2 pathway (60). Tari et al. demonstrated that downregulation of Grb2 protein expression by with Grb2 antisense oligonucleotides can inhibit the proliferation of breast cancer cells in an Erk 1,2-dependent manner (61). Grb2 is also known to be associated with FGF receptors (62) and has been shown to be involved in cell motility (63). The Grb2 protein was observed to be overexpressed in breast cancer cells and in specimen breast cancer tissue (64, 65). Furthermore, it has been observed that KGF treatment doubles the expression of phospho-Erk 1,2, while downregulation of Grb2 expression inhibits KGF-mediated breast cancer cell motility (56). Accordingly, Erk 1,2 activity is known to be involved in the proliferation of endometrial carcinoma cells and associated with KGF-mediated invasiveness of stomach cancer cells (53, 55).

It has also been suggested that signal transduction associated with the FGFR involves the binding of heparin sulfate, an abundant cell surface molecule, to form a ternary signaling complex (66). It has been further suggested that heparin proteoglycans on the surface of cancer cells may attract KGF to cell surface receptors. In addition, the proteoglycans may serve as a reservoir for KGF on the cell membrane, thus making this growth factor available for KGFR activation and enhanced signaling (67).

Involvement of the KGF/KGFR pathway in cancer

Enhanced cancer cell motility is usually observed during the metastatic dissemination of tumor cells to secondary sites (68). This stimulation of motile cell behavior is known to be regulated by specific cytokines and growth factors (69, 70). In many cases, the stromal tissue which surrounds the primary tumor cells produces growth factors, which stimulate tumor cell motility and proliferation; hence progression to a more metastatic phenotype (71, 72).

Recently, Zang et al. used a cancer cDNA profiling assay to examine the expression of KGFR in 154 tumor samples and paired normal samples representing 19 types of human cancer (73). The researchers observed that KGFR was upregulated in many reproduc-

tive and other types of cancer tissue at an early stage of cancer development (i.e., uterus, cervix, vulva, prostate, testes and lung). These results support the concept that that KGFR upregulation may be an early event in the progression of these cancers and that KGFR expression levels may be a useful prognostic biomarker. However, it was found that KGFR was upregulated in more advanced tumors in other types of cancer (i.e., ovary, stomach, small intestine, rectum, bladder, trachea and pancreas), while it was downregulated in some other types of cancer on the array (i.e., skin, liver, colon and kidney). As highlighted in the various examples above, KGF signaling appears to be involved in the progression of many types of cancer and, therefore, has the potential to serve as a useful oncolytic biomarker.

A summary of the literature on the involvement of the KGF/KGFR pathway in various common cancers follows.

TARGETS

Breast cancer

Mammary glands of adult female animals are remarkably sensitive to KGF (74). For example, systemic administration of KGF in nulliparous female rats for 3 days was found to produce massive mammary ductal hyperplasia and an elevation of mitotic figures (74). Similarly, administration of KGF to adult male and pregnant female rats produced ductal hyperplasia and acinar proliferation. Accordingly, intraductal hyperplasia is well known to be characteristic of premalignant breast lesions which leads to neoplasia (10). Kitsberg and Leder created a strain of transgenic mice that carry a constitutively upregulated KGF transgene (75). They observed that female mice with this transgene develop very dramatic mammary epithelial hyperplasia and eventually all animals developed metastatic mammary carcinomas. Consistent with these results, KGFR gene upregulation was observed in human primary breast tumor samples (76). It was reported that expression of KGFR occurs in malignant and nonmalignant breast cancer cell lines; however, it was also observed that highly malignant, metastatic breast cancer tissue expressed relatively little KGFR (77). These findings suggest that KGF-mediated stimulation of breast epithelial proliferation and migration may be an early event in the molecular cascade that leads to breast cancer progression and metastasis (78). Thus, KGF may stimulate the motility of well-differentiated breast cancer cells (e.g., ER positive breast cancer) and have little or no effect on less differentiated, highly malignant tumor cells that have escaped normal regulatory mechanisms. Furthermore, KGF may not stimulate highly malignant tumor cells because KGFR-associated signal transduction is constitutively upregulated, and thus these cells would be unresponsive to additional KGF stimulation. In agreement with these statements, Zang et al. observed that treatment of ER-positive human breast cancer cells with recombinant human KGF produced a profound stimulation of cell motility and an upregulation of the *KGFR* gene. Researchers also found that this effect did not occur in ER-negative cell lines (79). In another study, KGF motility response in breast cancer cells proved to be dose-dependent and characterized by an immediate increase in ruffling of the plasma membrane and cell scattering which continued for up to 48 hours following KGF treatment (80). Furthermore, transfection of MCF-7 cells with a KGF-producing vector was observed to enhance cell motility and to produce a characteristic motile morphology (81). Such changes in cell morphology, associated with membrane ruffling and motility, are believed to be associated with cytoskeletal reorganization and necessary for adhesion foci, cell surface ligand-receptor binding and regulation of gene transduction (82, 83). Accordingly, a significant alteration in the distribution of f-actin, an indicator of cytoskeletal reorganization, was observed in the cytoplasm of KGF-stimulated MCF-7 cells (84).

Both KGF and KGFR have been reported to enhance the progression of breast cancer by inhibiting normal apoptosis via the overexpression of Bcl-2 (85). Furthermore, results of a recent study indicate that KGF-mediated signaling involves the *Wilms' Tumor 1* (*WT1*) and *focal adhesion kinase* (*FAK*) genes (86). Interestingly, both *WT1* and *FAK* are involved in the regulation of Grb2 and signaling via the Erk pathway (87-89).

Taken together these observations suggest that KGF-mediated stimulation of breast epithelial proliferation and migration may be an important step in breast cancer progression and metastasis (90). Furthermore, KGF expression correlates closely with estrogen receptor (ER)-α expression in human breast cancer tissue, and the promoter region of the *KGF* gene is known to contain a semi-palindromic sequence of the estrogen response element (91). It has been demonstrated that selective inhibition of ER-alpha using a selective RNAi reduced KGF-mediated stimulation of breast cancer cells (92, 93). These findings illustrate the potential value of KGF/KGFR expression levels to serve as biomarkers for breast cancer progression and/or responsiveness to chemotherapy.

Prostate cancer

The expression of both KGF and KGFR were found to be elevated in benign prostatic hypertrophy (BPH) and in prostate cancer where KGF appears to act in a paracrine manner in cancer progression (94-96). It has been proposed that KGF acts together with androgens in the stimulation of cell proliferation in BPH (97, 98). Using immunolocalization techniques, Planaz and coworkers detected KGF in epithelial cells from both BPH and prostate cancer tissue and suggested that KGF stimulates cell proliferation in an autocrine manner during cancer development (99). In clinical prostate cancer the expression of KGF and KGFR increases with disease progression. Furthermore, the switching from stromal to epithelial regulation, which permits the cancer cells to escape normal stromal regulation, occurs during metastatic progression (100, 101). Accordingly, switching of the KGFR from the FGFR2-IIIb (androgen-regulated receptor isoform) to the FGFR2-IIIc isoform, which recognizes other FGF peptides, occurs during tumor progression and enhances unregulated tumor growth and invasion (71, 100, 102-104). Thus, monitoring these receptor isoforms may serve as an early biomarker for progression of prostate cancer (105).

Colon cancer

Overexpression of KGFR has been observed in colorectal cancer cells (106) and KGF was found to produce a dose-dependent stimulation of well-differentiated colorectal cancer cells, but not metastatic cancer cells or poorly differentiated colorectal cancer cells (107, 108). Yoshino and coworkers reported that KGFR is overexpressed in

tumor samples from approximately two-thirds of colorectal cancer patients (109). Since the receptor was localized at the center of cancer nests and co-localized with cytokeratin-20, which is known to be a diagnostic marker for colorectal cancer, this co-localization of both may improve the predictive therapeutic accuracy of these biomarkers (110). Keratinocyte growth factor receptor expression was associated with a well-differentiated histology, suggesting that KGFR signaling occurs early in the development of colorectal cancer (109). Wantanabe and coworkers who examined KGF and KGFR expression in colorectal cancer tissue from 12 patients, proposed that KGF acts in a paracrine and autocrine manner to induce cell growth in this cancer (111).

Lung cancer

Keratinocyte growth factor is involved in embryonic lung development and in the adult lung it appears to be involved in the homeostasis and repair of alveolar and bronchial epithelial cells (50, 74, 112). However, in a study of KGF and KGFR expression in tissue from human lung cancer patients, Yamayoshi and coworkers (113) observed that co-expression of KGF and KGFR was associated with greater differentiation in squamous cell carcinomas, while in lung carcinomas KGF co-expression was associated with poor differentiation, metastatic involvement and a shorter duration of patient survival. These investigators speculated that KGF/KGFR expression and signaling may be useful biomarkers for the grading of lung carcinoma. Furthermore, Baumann et al. have proposed the use of KGF as a molecular target for radiotherapy of lung cancer (114).

Ovarian, uterine and cervical cancers

Steele and coworkers reported that KGFR is undetectable in normal ovarian epithelial cells, while 80% of the ovarian cancer samples expressed KGFR (115). It was suggested that KGFR overexpression is involved in the progression of ovarian cancer by making the premalignant tissue more responsive to paracrine KGF stimulation (115, 116). This argument is supported by research by Parrott et al., who reported that KGF produced in the ovarian tumor microenvironment may be involved in the progression of this cancer (117). Similarly, KGFR was detected in carcinomas from 86% of cervical cancer patients, suggesting that KGFR mediates the progression of reserve and squamous metaplastic cells in cervical cancer tissue (118). Furthermore, several groups have reported that the KGF signaling pathway enhances the proliferation of human endometrial cancer and may be a useful progression biomarker (55, 119). Accordingly, KGF expression appears to be regulated by estradiol, progesterone and gonadotropins (hormones that are known to regulate the normal growth and cycling of ovarian, uterine and cervical tissues; 19, 117).

Pancreatic cancer

Carcinoma of the pancreas is one of the most deadly forms of cancer, with a death rate approaching the incidence rate, largely because most patients have advanced, metastatic disease at the time of diagnosis (120). Keratinocyte growth factor expression and KGFR signaling appear to be associated with enhanced proliferation and the progression of human pancreatic cancer. For example, Siddiqi and coworkers observed that KGF expression was enhanced in 7 of 16 human pancreatic cancer samples and that 5 of 7 pancreatic cancer cell lines expressed KGFR (121). Similarly, overexpression of KGFR in 7 of 10 pancreatic cancer samples was observed using a cDNA cancer profiling array comparing tumor and patient matched normal tissue (73). Interestingly, it was reported that KGF and KGFR expression levels were increased 5-fold within 28 days in a rat model of pancreatitis in vivo (122). In addition, overexpression and co-localization of KGF and KGFR in pancreatic cancer and adjacent parenchyma has been observed, indicating that KGF may enhance the progression of pancreatic cancer in either an autocrine or paracrine manner (123). Similarly, during disease progression other FGFs and FGF receptors are overexpressed and appear to be involved in the invasiveness of pancreatic cancer (124-126). In a recent study of human pancreatic cancer cells it was reported that KGF treatment significantly enhanced the proliferation and motility of the pancreatic cancer cells within a period of 24-48 hours (127).

The above research suggest that upregulation of KGF secretion and/or KGFR overexpression may be important biomarkers and, therefore, signals in the progression of pancreatic cancer (121, 123, 128). Consequently, inhibition of KGFR signaling and/or inhibition of genes and proteins regulated by KGF/KGFR signaling may impede the progression of pancreatic cancer cells to a more metastatic phenotype (126, 129).

Stomach cancer

As early as 1990, researchers observed that *KATO-III cell-derived stomach cancer amplified* gene, which is 88% homologous to *KGFR*, was upregulated in poorly differentiated stomach cancer tissue (130). An upregulation of the KGFR gene of as much as 30- to 40-fold in gastric cancer compared to normal tissue has also been reported (73, 131). Keratinocyte growth factor from gastric fibroblasts or added to the culture media was found to stimulate the proliferation of scirrhous gastric carcinoma cell lines (132). Furthermore, KGF treatment enhanced the production of matrix metalloprotease-9 and urokinasetype plasminogen activator (both associated with cancer cell invasion) in these human stomach cancer cells (53). Matsunobu and coworkers reported that KGFR expression was associated with expansive growth and shallow gastric wall invasion at an early stage of stomach cancer (133). These studies suggest that KGFR expression may be used as a tool to identify stomach cancer progression.

Targeting the KGF/KGFR pathway

It appears that an upregulation of KGF/KGFR signaling at an early stage of cancer development is involved in the progression of a number of common cancers as described above and as a result, selective inhibitors of this signaling pathway may be effective oncolytic therapeutic agents.

KGF antagonists

Fibroblast growth factors are a family of peptides which share unique binding affinity for heparin. Accordingly, it appears that binding to heparin and other cell surface proteoglycans enhances the activity of these FGF peptides (134). Heparin proteoglycans on the cell surface may act to bind the FGF growth factors, increasing their availability to cell surface receptors and serving as a reservoir for the

FGF growth factors on the cell membrane (135). However, heparin is reported to inhibit the action of KGF, unlike other members of the FGF family (135, 136).

It has been known for decades that anticoagulant treatment with heparin reduces the growth and metastatic development of various cancers (134). Retrospective meta-analysis of clinical studies for the prevention of venous thromboembolism, employing heparin and/or low-molecular-weight heparin (LMWH), has indicated that their therapeutic use is associated with a reduction in cancer-associated mortality (137). Low-molecular-weight heparin is more stable and has better pharmacokinetic properties than heparin and, accordingly, most of these studies found greater anticancer activity with LMWH therapy (134, 138). The mechanism for this oncolytic effect has not been established, but it has been suggested that inhibition of FGF-mediated tumor angiogenesis may be responsible for this activity (26, 134). However, in light of the fact that heparin inhibits KGF, the reduction in KGF activity may also be involved in the beneficial effects of heparin treatment in improving cancer patient survival.

The KGFR2β(IIIb)/Fc chimera is a soluble extracellular fragment of KGFR which acts as a highly selective KGF inhibitor (139). Accordingly, KGF binds to this KGFR fragment with much greater selectively than to the heparin-related compounds (140). The results of a study which compared the influence of heparin, LMWH and KGFR2β(IIIb)/Fc on KGF induced breast cancer cell motility and proliferation demonstrated that all three were equally effective KGF antagonists during the first several hours of treatment. However, after 2 hours the heparin-mediated inhibition of KGF activity diminished, while LMWH and KGFR2β(IIIb)/Fc produced a more prolonged inhibitory effect lasting up to 48 hours (139).

In addition, there are a number of other heparin-like compounds or heparinoids which may be useful in the treatment of cancer (141-143). Suramin, a polysulfated naphthylurea which produces heparin-like inhibition of FGF signaling, has been shown to be effective in the treatment of bladder, kidney and prostate cancers (144-146). Furthermore, suramin treatment may enhance the effectiveness of other chemotherapeutic agents in prostate cancer (147). Similarly, Rotolo et al. reported that silencing the expression of KGFR restored the responsiveness of breast cancer cells to 5-fluorouracil and speculated that selective inhibition of the KGF/KGFR pathway may prevent resistance to chemotherapy (148). Other promising heparinoids include PI-88, which acts as a heparinase inhibitor (149), and BXL-628, a vitamin D analogue, which is a KGF inhibitor that has been demonstrated to inhibit the proliferation and invasiveness of prostate cancer cells (150).

These compounds have the potential to be useful in the treatment or prevention of cancer progression associated with KGF signaling. However, the anticoagulant activity and poor oral bioavailability for most heparin-related compounds may limit their long-term use in cancer therapy.

KGFR tyrosine kinase antagonists

Changes in the regulation of growth factor receptor tyrosine kinase (TK) activity and the related signal transduction is known to be involved in the development and progression cancer (66, 151, 152). As an example, it is well known that EGF receptor overexpression is predictive of aggressive and metastatic cancer development (153-155) and selective EGF receptor TK inhibitors have been demonstrated to be therapeutically effective in the treatment of various cancers (153, 156, 157).

In 1993, Yan and coworkers established that a transition in the KGFR occurs from the initial (FGFR IIIb) isoform found in primary tumors, which is KGF responsive, to the FGFR IIIc isoform found in more advanced cancer, which is unresponsive to KGFR (100). This transition of KGFR isoforms during cancer progression suggests that KGFR activation is an important early step in the initiation metastatic cancer progression. Therefore, selective inhibition of the FGFR-IIIb isoform would provide an opportunity to prevent or reduce cancer progression to a more malignant phenotype.

Nonselective inhibitors of mitogen-activated protein kinase signaling have been demonstrated to inhibit KGF stimulation of breast and endometrial cancer cells (55, 56, 158). These nonselective inhibitors alter the signaling activity of numerous growth factors which would likely result in unacceptable adverse side effects. However, selective KGFR TK antagonists may be relatively nontoxic and therapeutically effective oncolytic agents. Since KGFR is a growth factor TK receptor; the design of small-molecule, selective inhibitors of KGFR that compete with adenosine triphosphate (ATP) for the catalytic site in the receptor is a viable approach that has been employed (159, 160).

In efforts to design novel KGFR-selective ATP site-directed ligands, Hackett et al. employed in silico site-directed mutagenesis to generate a homology model of the KGFR TK domain. The compounds identified with this modeling algorithm were found to inhibit KGF-mediated breast cancer cell proliferation and motility in a culture wounding model. Furthermore, the researchers observed that the most potent KGF inhibitor produced a reduction in the density of KGFR on breast cancer cells, suggesting that receptor targeting downregulates the expression of KGFR (161). Therefore, these selective KGFR TK antagonists may be useful therapeutically to target the KGFR signaling pathway and prevent or significantly reduce cancer progression.

CONCLUSIONS

It is clear that the progression of cancer to a metastatic phenotype is largely responsible for cancer mortality. Today very few therapeutic modalities with the ability to selectively inhibit or reduce metastatic progression are available. We know that upregulation of KGF and KGFR appears to be involved in cancer cell proliferation, motility and enhanced survival. Because KGF/KGFR signaling appears to be associated with the progression of many types of cancer at an early stage, the measurement of tissue or circulating levels of KGF/KGFR or related signaling may serve as important biomarkers of cancer progression and/or therapeutic monitoring. Moreover, agents which are selective and potent inhibitors of the KGF/KGFR signaling pathway may have considerable oncolytic potential.

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