Role of Growth Hormone in Breast Cancer

Ramadevi Subramani,1 Sushmita B. Nandy,1 Diego A. Pedroza,2 and Rajkumar Lakshmanaswamy1,2

1Center of Emphasis in Cancer Research, Department of Biomedical Sciences MSB1, Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine, El Paso, Texas 79905; and 2Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center El Paso, El Paso, Texas 79905

Breast cancer is one of the most common cancers diagnosed in women. Approximately two-thirds of all breast cancers diagnosed are classified as hormone dependent, which indicates that hormones are the key factors that drive the growth of these breast cancers. Ovarian and pituitary hormones play a major role in the growth and development of normal mammary glands and breast cancer. In particular, the effect of the ovarian hormone estrogen has received much attention in regard to breast cancer. Pituitary hormones prolactin and growth hormone have also been associated with breast cancer. Although the role of these pituitary hormones in breast cancers has been studied, it has not been investigated extensively. In this review, we attempt to compile basic information from most of the currently available literature to understand and demonstrate the significance of growth hormone in breast cancer. Based on the available literature, it is clear that growth hormone plays a significant role in the development, progression, and metastasis of breast cancer by influencing tumor angiogenesis, stemness, and chemoresistance. (Endocrinology 158: 1543–1555, 2017)

The breast is a multihormone target organ that undergoes changes throughout the reproductive phases under the influence of various hormones (1–5). It is also a well-known fact that hormones influence both the development and growth of breast cancers (1–5). Global breast cancer incidence is on the rise, with nearly 1.7 million women being diagnosed with the disease and 0.5 million women succumbing to the disease annually. One out of eight women is expected to develop breast cancer during their lifetime in the developed countries (6). A majority of the breast cancers develop sporadically. Breast cancer is not a single disease, but it is a group of chronic diseases. Patients diagnosed with breast cancer at an early stage have good prognosis, but these patients still have an increased risk of mortality for the next four decades (7). Currently, there are several methods of classification of breast cancers, which include histopathological, immunohistochemical, and molecular classifications. Various prognostic gene expression–based assays are used to determine subtypes of breast cancer (8, 9), like the Breast Cancer Index, EndoPredict, MammaPrint, Oncotype DX, and PAM50 (10, 11). In general, breast cancers are mainly classified based on the presence or absence of hormone receptors. A very broad classification would be classifying them as hormone receptor–positive (hormone-dependent) breast cancer or hormone receptor–negative (hormone-independent) breast cancer. The hormones that are generally associated with the development and growth of normal breast and breast cancers are estrogen and progesterone. Exhaustive studies have been conducted to investigate the role of estrogen in breast cancer. Estrogen receptor–positive breast cancers have targeted treatments like tamoxifen and aromatase inhibitors (12). Clinical and epidemiological data indicate that a high percentage of women on these treatments develop resistance and also experience undesirable side effects (13). The role of pituitary hormones like prolactin, growth hormone, growth hormone–releasing hormone, and gonadotropin–releasing hormone in breast cancer have been studied to a certain extent but not as exhaustively as estrogen. The pituitary hormones and their receptors could play a
significant therapeutic role in breast cancer by themselves or in combination with the current standard treatment modalities. In the past decade, growth hormone has been gaining a lot of attention in cancer development, progression, and metastasis. Here we try to summarize the role of growth hormone in breast cancer with the available literature.

**Effect of Growth Hormone on Normal Mammary Gland Development**

The mammary gland undergoes major changes postnataally during puberty, pregnancy, lactation, and involution (3–5). Initially at birth, the mammary anlage is made of a primary duct and few secondary branching ducts. Until puberty, development of the mammary gland in females and males is similar. In females, during puberty, a significant ductal development occurs in terms of ductal elongation and branching. The mammary gland undergoes cyclical changes during ovarian cycles. Major differentiation and lobuloalveolar growth of the mammary gland occurs during pregnancy and is maintained throughout lactation. After weaning, the mammary gland undergoes involution, resulting in a gland that mainly has regressed ducts and few lobuloalveolar structures (3–5).

The endocrine system plays a major role in development of the mammary gland. Ovarian hormones estrogen and progesterone play a key role in the development of normal mammary glands (1, 2). In addition to the ovarian hormones, pituitary hormones like growth hormone and prolactin also play a major role in influencing growth of the mammary gland and in the process of lactation (3–5). Earlier it has been shown that in ovariectomized animals, estradiol could restore mammary gland growth, but estrogen replacement was not effective in restoring the development of mammary glands in ovariectomized and hypophysectomized animals (3, 5, 14, 15). Further, using hypophysectomized and ovariectomized mice, it was demonstrated that growth hormone alone was able to induce mammary ductal development, and this effect was greater when growth hormone and estrogen were administered together (16–18). In addition, using pure preparations of growth hormone, prolactin, and placental lactogen, it was demonstrated that growth hormone was effective in promoting mammary growth, whereas prolactin and placental lactogen had no effect (17, 19). Further, knockdown of growth hormone receptor resulted in impaired mammary gland growth, which was evidenced by delayed development of ducts and reduced side branching (20, 21). Particularly, growth hormone has also been shown to impact lobuloalveolar development (22). Administration of growth hormone to growth hormone–deficient rats and mice restored mammary gland growth. On the other hand, inhibition of growth hormone negatively influenced the growth of mammary glands (23). Furthermore, autocrine growth hormone has also been shown to influence the growth of mammary glands (24, 25). Messenger RNA (mRNA) and protein expression of growth hormone is mainly observed in the mammary luminal and myoepithelial cells (26–29). The expression of growth hormone and its receptor is high during puberty, and overexpression of growth hormone leads to precocious mammary gland development (30, 31). Overall, all these findings demonstrate the significance of growth hormone in mammary gland development.

**Mechanism of Action of Growth Hormone**

Growth hormone is mainly synthesized and secreted from the anterior pituitary in response to hypothalamic growth hormone–releasing hormone. Growth hormone along with placental lactogen and prolactin belongs to the family of the evolutionarily related peptide hormones. Among these family members, pituitary prolactin has been studied extensively. Prolactin has been shown to be involved in various physiological and pathological processes, including the development of normal breast and breast cancer (32). Prolactin’s action is mainly mediated through Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, but it also influences other signaling pathways like the Ras-Raf–mitogen-activated protein kinase (MAPK) pathway, phosphoinositide 3-kinase/AKT survival pathway, and Src kinase signaling pathway (33, 34). Human placental lactogen, another member of the growth hormone/prolactin family, is frequently expressed in breast carcinomas (35). The precise role of locally produced placental lactogen in breast cancers is not fully understood, but it is expected to serve as a breast cancer biomarker. Interestingly, human placental lactogen is not detected in the serum of patients with benign breast disease or in serum of normal women, whereas it is frequently detected in serum of some breast cancer patients (36, 37). In contrast, it has been reported that the sera of breast cancer patients did not have detectable levels of human placental lactogen (38). In other species like sheep, rodents, and fish, factors such as decidual prolactin-like protein (39), proliferin (40), proliferin-related peptide (41, 42), and somatolactin (43, 44) are also considered to be members of this family of peptide hormones. Proliferin has been suggested to be an autocrine regulator of angiogenesis because it enhances tube forming and invasive capabilities of the endothelial cells. This proangiogenic effect of proliferin is mediated by STAT5 (45, 46). On the other hand, proliferin-related protein inhibits gastric cell carcinoma proliferation, motility, and tumorigenicity (42). Somatolactin is a
member of the growth hormone/prolactin family, which is synthesized and secreted by the pituitary gland of teleost fish (47). Using in vitro and in vivo experiments, it has been shown that somatolactin plays a role in steroidogenesis (48), gonadal maturation (49), stress responses (50), lipid metabolism (51), and immune functions (52). These findings indicate that growth hormone, prolactin, and the other members of this family play major roles in vital biological processes.

In humans, the growth hormone gene is located on the long arm of chromosome 17 and is approximately 3000 nucleotides in length (53). Growth hormone is obtained from its precursor protein by removal of the amino terminal, which results in a 191–amino acid protein with a molecular weight of 22 kDa. A 20-kDa variable of growth hormone is also present due to alternative splicing, and it accounts for 5% to 10% of total growth hormone secreted (54, 55). Growth hormone receptor is a membrane-bound receptor that belongs to the class I cytokine receptor superfamily (56). Earlier, it was believed that growth hormone binding to its receptor resulted in receptor dimerization, but it has now been demonstrated that growth hormone binds to the preexisting receptor homodimer and exerts its actions. It has been shown that growth hormone binding to the receptor homodimer realigns the orientation of the two receptors above the cell membrane and also changes the orientation of the transmembrane domains (57, 58). Growth hormone also binds with prolactin receptors (59, 60), and in an ovine model, it has been shown to bind placental lactogen receptors, activating its downstream signaling pathways (61, 62). Further, there is exhaustive evidence that growth hormone actions are mediated through various downstream signaling pathways. Binding of growth hormone to the growth hormone receptor results in activation of various signal transduction pathways that are vital for cell growth and survival. Growth hormone binding to its receptor facilitates increased binding of Janus kinase-2 (JAK2). This binding activates tyrosyl phosphorylation of both JAK2 and growth hormone receptor. The activated GHR/JAK2 complex influences several signal transduction pathways through the recruitment of various signaling proteins. The major pathways affected by GHR/JAK2 complex include the STAT signaling pathway, insulin-like growth factor (IGF) signaling pathway, insulin receptor substrate proteins involved in the phosphoinositide 3-kinase/AKT signaling pathway, and the MAPK signaling pathway (63–68). Further, the rapid activation of protein synthesis by growth hormone has been demonstrated to be mediated by mTOR (69).

The gene encoding for all three regions of the growth hormone receptor is present in chromosome 5 (68, 70). The growth hormone receptor gene has alternative first exons and nine coding exons. Exon 2 to 10 encodes the amino acid signal sequence, extracellular hormone-binding domain, hydrophobic transmembrane domain, and the intracellular domain. Polymorphisms of the growth hormone receptor have been demonstrated to impact its downstream processes. Mainly exons 3, 6, and 10 are involved in the polymorphism. Absence of exon 3 results in a shorter form of growth hormone receptor. This leads to changes in growth hormone receptor stability, transport, and processing (68, 70–73). In addition, single-nucleotide polymorphisms have also been observed in the growth hormone receptor gene, and they have been attributed to the development of obesity (74). Overall, growth hormone/growth hormone receptor signaling is mediated through many vital signal transduction pathways that are essential for cell proliferation, survival, metabolism, etc. Alteration of growth hormone signaling results in dysregulation of various pathways, leading to pathologies like cancer.

**Effect of Growth Hormone on Mammary Carcinogenesis**

Mammary carcinogenesis is a multistep process. Initially it starts as mammery hyperplasia where the proliferating mammary epithelial cells fill the ductal or lobular lumen. The next stage of development is the formation of ductal carcinoma in situ or lobular carcinoma in situ. Following further proliferation, migration, and invasion, it becomes locally invasive and finally metastatic. In humans, breast cancer is mainly classified based on the presence or absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 (HER2) (75–77). Breast cancers that are negative for all the above-mentioned receptors are classified as the triple-negative breast cancer. Further, breast cancer is also classified based on gene expressions as luminal type A, luminal type B, HER2 type, and basal type. Luminal type A is a low-grade estrogen receptor–positive cancer, which is a slow-growing cancer with best prognosis. Luminal type B is very similar to luminal type A, but only with the exception that it is somewhat faster growing and does not have good prognosis. HER2 type cancers have extra copies of the HER2 gene and usually are of high grade and have poor prognosis. Finally, the basal type is the most aggressive form of breast cancer with the worst prognosis (78, 79).

Epidemiological data demonstrates that GH/IGF-1 is directly and positively associated with increased risk of breast cancer (80–85). Two meta-analyses have suggested that increased IGF-1 levels are associated with increased risk of breast cancer (84, 86), whereas another meta-analysis found only a marginal association between

---

the levels of IGF-1 and breast cancer risk (87). Experimental data also suggests that reduced GH/IGF-1 signaling negatively impacts the development of mammary gland and mammary tumorigenesis (88). Recently, using next-generation RNA sequencing on 50 mammary gland tumors, it was reported that chronic IGF1R activation led to increased mammary tumor progression, resulting in decreased mammary tumor latency (89).

Earlier, it was observed that about 40% of breast cancer patients had increased levels of serum growth hormone (90), whereas another study did not observe any change in serum levels of growth hormone in premenopausal breast cancer patients (91). This difference could be due to the method of sample collection and analysis. But the observed increase in growth hormone in breast cancer patients could be a consequence of breast cancer formation or could be a driving force for the development of breast cancer. Normal human mammary epithelial cells express the human growth hormone gene, whereas in proliferative disorders of the mammary gland, it is also expressed in the mammary stroma. Moreover, increased human growth hormone gene expression is positively associated with metastatic mammary cancer cells (27). Human growth hormone expression has been positively correlated with lymph node metastasis, tumor stage, human epidermal growth factor receptor-2 status, and proliferative index in breast cancer (85). It has also been demonstrated using immunohistochemistry that 90% of ductal carcinoma in situ lesions express growth hormone receptor (92).

Altered level of growth hormone is associated with height of an individual. Height is considered as a risk factor for cancer in humans. It has been observed that tall women have a higher risk of developing breast cancer (93–95). A direct association between increasing adult height and increasing cancer risk has been implicated in various organs like the breast, ovary, prostate, colorectal, and melanoma (96–102). A prospective study conducted in the United Kingdom demonstrated a clear association between increasing height and cancer risk for every 10 cm of height gained over “normal” height. This height-associated cancer risk was not influenced by any of the confounding factors, such as women from different socioeconomic groups, alcohol intake, body mass index, physical activity, age at menarche, parity, age at first birth, menopausal status, and use of oral contraceptives or hormone replacement therapy (95). A meta-analysis of data obtained from 159 prospective cohorts using 5,216,302 women including 113,178 events strongly suggested that adult height is a risk factor for breast cancer. It was also suggested that genetic factors and biological pathways impacting adult height played an important role in the etiology of breast cancer (103). In general, an overrepresentation of malignant disorders has been observed in acromegalics (104). Further, a few studies indicate that malignancy occurs only in specific organs like the breast and colon (105, 106). The findings of the U.K. 1946 birth cohort study demonstrated that girls who were tall at 7 years of age had a higher risk of breast cancer later in life (107). Faster growth during adolescence increased the risk of premenopausal breast cancer by 30% and postmenopausal breast cancer by 40% (108). On contrary, some studies have also observed no difference in cancer incidence among acromegalics compared with normal populations (109). Increased birth weight is considered as an independent risk factor that can be associated with increased risk of breast cancer in women (110, 111). Moreover, risk of developing breast cancer is also positively associated with height at different stages of development (97, 107, 111). The velocity at which a girl grows between 4 to 7 years of age and the height at 8 years of age is positively correlated with the risk of breast cancer (107). In patients with Laron syndrome, where the growth hormone receptor is nonfunctional, no incidence of breast cancer is observed (112).

Animal models have been used extensively to study the effect of growth hormone in various cellular processes involved in the development of mammary cancer. In general, three main approaches are used to determine the role of hormones in mammary carcinogenesis. To study the role of growth hormone in mammary carcinogenesis, the three following approaches have been used. The first approach is to investigate the effect of exogenous growth hormone administration on mammary carcinogenesis (113). The second approach is studying the effect of growth hormone suppression in mammary carcinogenesis by using specific inhibitors of growth hormone (23, 114), and the third approach is using transgenic mouse models to understand the significance of growth hormone in mammary carcinogenesis (115–117). We (113) and others (118, 119) have demonstrated the significance of growth hormone in mammary carcinogenesis using the spontaneously dwarf rats, which have a point mutation in the growth hormone gene rendering it nonfunctional and resulting in undetectable levels of growth hormone in circulation. Administration of the chemical carcinogen N-methyl-N-nitrosourea to spontaneously dwarf rats did not result in mammary tumor formation, whereas exogenous administration of growth hormone to the carcinogen-exposed dwarf rats resulted in very high incidence of mammary tumors (22, 113). These findings have also been confirmed using another chemical carcinogen (dimethylbenzanthracene)-induced mammary carcinogenesis model (118). Further, even the well-established mammary tumors in these rats regressed...
after withdrawal of exogenous growth hormone treatment (118). Using other animal models, where growth hormone signaling was disrupted, it was further demonstrated that the mammary carcinogenesis is influenced by growth hormone (65, 66). On contrary, it has been observed that growth hormone administration to hypopituitary patients did not increase cancer risk. This finding could be due to the short follow-up period of only 3.7 years, whereas a longer-term follow-up study would provide more convincing evidence (120).

Administration of somatostatin, an inhibitor of growth hormone, reduced mammary carcinogenesis by lowering the levels of growth hormone (121). Growth hormone inhibitor pegvisomant administration blocks growth hormone receptor and insulin-like growth factor-I receptor signaling in the mammary gland. It delays mammary ductal growth and decreases its branching. Further, administration of pegvisomant to athymic nude mice carrying MCF-7 xenografts resulted in inhibition of xenograft growth. Molecular analysis revealed that pegvisomant inhibited growth of the MCF-7 xenograft by reducing proliferation and insulin receptor substrate phosphorylation and increasing apoptosis (23). In addition, it has also been shown that suppression of GH signaling inhibited the growth of patient-derived breast cancer xenografts in immunodeficient mice (92). Furthermore, it has been demonstrated that the human growth hormone receptor antagonist B2036 strongly inhibits the proliferative and morphological effects of autocrine human growth hormone (122). These results emphasize the significance of growth hormone and its downstream signaling in breast cancer (123).

Using the litt/litt mice, which have a point mutation of the growth hormone–releasing hormone gene, it was clearly demonstrated that growth hormone is essential for the development of mammary cancer (124). Genetically engineered transgenic mouse models have tremendously helped us to understand the significance of various factors involved in mammary cancer development, including the importance of growth hormone. Female C3 (1)/Tag mice develop spontaneous estrogen receptor-negative mammary cancers (125). When these mice were crossed with the Laron mice in which the growth hormone receptor is disrupted, it significantly delayed mammary tumor formation. In addition, it has also been demonstrated that inhibition of growth hormone signaling could be a potential treatment strategy for estrogen receptor-negative mammary cancers (115). Transgenic mice overexpressing a growth hormone gene exhibit high incidence of spontaneous mammary cancers (126), whereas transgenic mice overexpressing a growth hormone antagonist are refractory to dimethylbenzanthracene-induced mammary carcinogenesis (117). All these findings clearly demonstrate the key role that growth hormone plays in the development of breast cancer.

Role of Growth Hormone in Angiogenesis

Preclinical and clinical research has demonstrated that angiogenesis is a fundamental step required for cancer growth and metastasis (127). The process of angiogenesis is still not fully understood. One of the most accepted theories is that cancer cells secrete certain soluble factors that attract neighboring blood vessels to form branches toward the cancer, eventually supplying the cancer cells with required nutrients and also impacting metastasis (128). Autocrine growth hormone enhances angiogenesis in mammary tumorigenesis (129). The chick chorioallantoic membrane assay indicated a proangiogenic role for growth hormone (130). Growth hormone administration has also been shown to improve cardiac function (131–133). Further, recombinant adeno-associated, virus-mediated gene transfer of human growth hormone into cardiac tissue of rats resulted in improved cardiac function (134). In growth hormone–deficient patients, administration of growth hormone rescued microvascular abnormalities (135). Growth hormone influences various angiogenic factors like vascular endothelial growth factors, thrombospondin 1, fibroblast growth factors, and endothelial nitrous oxide synthase (134). It also promotes endothelial cell migration and tube formation. Further, it has been reported that growth hormone increases endothelial cell tube-forming capabilities. Further, using the mouse xenograft model, it was also shown that autocrine/paracrine growth hormone secreted by the mammary cancer cells enhances angiogenesis during mammary tumorigenesis (129). In addition, VEGF-A levels were increased by autocrine/paracrine human growth hormone expression in mammary carcinoma cells. This increase in VEGF-A is believed to promote tumor angiogenesis and lymphangiogenesis, resulting in increased microvasculature density (129). Based on the available data, it is clear that growth hormone could play a major role in mammary cancer development by supporting and/or enhancing tumor angiogenesis.

Role of Growth Hormone in Stemness

The widely accepted cancer stem cell theory proposes that cancer originates in progenitor cells or stem cells. There are several theories that have been proposed to explain
the origin of cancer stem cells. The “misplacement somatic cell” theory states that cancer stem cells could originate from misplacement of somatic stem cell de novo (138). Another theory proposes that improper regulation and/or mutations may transform normal stem cells to cancer stem cells (139). Additionally, data also indicate that differentiation of common progenitor cells leads to the formation of different intratumoral lineages (140, 141). Growth hormone has been demonstrated to influence mammary stem cell number and increase the risk of breast cancer (142, 143). The level of growth hormone receptor is high in human mammary epithelial cells cultured as mammospheres when compared with these cells grown on adherent cultures, suggesting that growth hormone receptor could be a potential stem cell factor (24, 143–145). It has been demonstrated that stem cells and early progenitor cells express growth hormone receptor. Further, growth hormone/growth hormone receptor signaling enhances stemness by increasing proliferation of mammary stem cells (143). The GH/IGF-1 axis has been suggested to be a master regulator of stem cell number in various organs including the breast (143). Growth hormone promotes stemness by stabilizing the hTERT mRNA and enhancing telomerase activity (2, 146). Growth hormone signaling regulates the miR-96-182-183 cluster and enhances the processes of the epithelial-to-mesenchymal transition and invasion, resulting in increased stemness (147). Based on the limited data that is available, it is clear that growth hormone promotes stemness of breast cancer stem cells.

Role of Growth Hormone in Chemoresistance

One of the standard methods of treatment of various cancers is chemotherapy. It is well known that several cancer patients initially respond to chemotherapy but later on develop chemoresistance (148). Development of chemoresistance leads to recurrence of cancer and results in death due to the failure of chemotherapy (149–151). Cancer patients exhibit intrinsic or acquired resistance to chemotherapeutic drugs. Chemoresistance usually follows exposure to cytotoxic drugs and results in the development of aggressive cancers, which do not respond to any treatment. There are several factors that influence the development of chemoresistance, which include drug efflux mechanisms, altered signaling transduction pathways, genetic factors, altered capacity to metabolize drugs, etc. (152, 153). In this regard, growth hormone that has the ability to stimulate mammary carcinogenesis by influencing cancer cell proliferation, survival, and stemness has also been associated with promoting chemoresistance. Growth hormone influences chemoresistance by altering various processes like drug efflux, oxidative stress response, and apoptosis. Autocrine growth hormone contributes to the development of chemoresistance by altering various proteins that are involved in growth arrest and DNA damage (GADD 153/CHOP) (154). Growth hormone also influences chemoresistance by regulating catalase, glutamylcysteine synthetase, glutathione peroxidase, and superoxide dismutase 1, which are all involved in oxidative stress-induced apoptosis (155). Overall, growth hormone/growth hormone receptor signaling plays a major role in inducing chemoresistance, favoring metastatic growth (114, 156, 157).

Role of Growth Hormone in Metastasis

The process by which cancer cells spread from the site of origin to different organs through blood and lymphatic vessels and form a new colony is called metastasis. A majority of breast cancers express growth hormone and growth hormone receptors, but metastatic breast cancers have the highest expression (27). The epithelial-to-mesenchymal transition is considered an essential step for metastasis (158, 159). Acquiring the mesenchymal features enhances the cancer cells’ ability to migrate and invade (159–161). The epithelial-to-mesenchymal transition also helps cancer cells to develop resistance to anoikis and acquire anchorage-independent growth. Autocrine human growth hormone has been demonstrated to facilitate the epithelial-to-mesenchymal transition in epithelioid breast cancer cells, which results in an invasive phenotype (147, 162). Growth hormone signaling promotes the epithelial-to-mesenchymal transition by influencing several genes involved in this process and also plays a major role in promoting anchorage-independent growth of breast cancer cells (163, 164). Autocrine human growth hormone has been established as an oncogenic factor promoting breast cancer stem cells, which have been implicated to play a major role in metastasis. Human growth hormone has been demonstrated to enhance tumor-initiating capacity, migration, and invasion of breast cancer cells. Thus, inhibition of growth hormone is a potential therapeutic strategy to prevent initiation, progression, and metastasis of breast cancer.

Growth Hormone as a Therapeutic Target

Experimental and clinical data clearly demonstrate the involvement of growth hormone and growth hormone receptor signaling in breast cancer initiation, progression, and metastasis. Several decades back, hypophysectomy was performed to treat metastatic breast cancers, which led to drastic regression of metastatic breast cancers (165). Based on these observations, pituitary growth
hormone and prolactin were thought to be involved in the pathogenesis of breast cancer (166, 167). It has been reported that human growth hormone expression in mammary carcinoma efficiently predicts the survival outcome of breast cancer patients (85). Autocrine human growth hormone promotes neovascularization and also regulates various signaling pathways and miRNAs (147). Animal experiments have demonstrated a vital role for pituitary growth hormone in mammary tumor initiation and progression. These findings suggest that systemic and/or local inhibition of growth hormone could result in better survival outcomes and be useful in treating breast cancer. Pegvisomant, a growth hormone receptor inhibitor, has been shown to possess anticancer properties against breast cancer models. There are also several somatostatin receptor ligands, such as octreotide, lanreotide, pasireotide,
somatotropin, etc., that inhibit growth hormone secretion (168). These drugs are used to treat acromegaly and could potentially have a significant impact on breast cancers. Growth hormone inhibitors along with standard therapies might help to reduce the burden of breast cancer.

Studie suggest that growth hormone and its down-stream signaling molecules could act as therapeutic targets for breast cancer. To develop such strategies, one needs to understand several aspects of growth hormone’s influence on breast cancer, such as when in the process of breast cancer development is growth hormone involved. If inhibition of growth hormone after the establishment of breast cancer reduces the growth, one should determine the optimum time, length, and dose of treatment. First, it is important to know how growth hormone specifically impacts breast cancer development and metastasis. Next, it is also equally important to know the specific time point at which growth hormone impacts breast cancer. Both these aspects need to be clearly understood before considering growth hormone as a therapeutic target. Hopefully, these questions will be answered using the currently available technology and advanced animal models to develop growth hormone as a potential therapeutic target.

**Conclusion**

Epidemiological, preclinical, and clinical data indicate the significance of growth hormone and its signaling in breast cancer development, progression, and metastasis by promoting breast cancer cell proliferation, survival, angiogenesis, migration, invasion, chemoresistance, and stemness (Fig. 1). Given this level of influence of growth hormone on breast cancer, it presents itself as a potential target for breast cancer treatment. In conclusion, growth hormone inhibition individually or in combination with standard treatments could prove beneficial to breast cancer patients who currently do not have any targeted treatment option.

**Acknowledgments**

Address all correspondence and requests for reprints to: Rajkumar Lakshmanaswamy, PhD, Center of Emphasis in Cancer Research, Department of Biomedical Sciences, Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine El Paso, El Paso, Texas 79905. E-mail: rajarun. lakshmanaswamy@ttuhsc.edu.

Disclosure Summary: The authors have nothing to disclose.

**References**


18. Nagasawa H, Noguchi Y, Mori T, Niki K, Namiki H. Suppression of normal and preneoplastic mammary growth and uterine adenomyosis with reduced growth hormone level in SHN mice given...


57. Xu J, Sun D, Jiang J, Deng L, Zhang Y, Yu H, Bahl D, Langenheim JF, Chen WY, Fuchs SY, Frank SJ. The role of prolactin receptor in


113. Kaulsay KK, Zhu T, Bennett W, Lee KO, Lobie PE. The effects of autocrine human growth hormone (hGH) on human mammary...
carcinoma cell behavior are mediated via the hGH receptor. 


123. Yin D, Vreeland F, Schaff IJ, Millham R, Duncan BA, Sharma A. Clinical pharmacodynamic effects of the growth hormone receptor antagonist pegvisomant: implications for cancer therapy. 

Cancer Res. 2007;73(3):1000–1009.


125. Maroulakou IG, Anwer M, Garrett L, Green JE. Prostate and mammary adenocarcinoma in transgenic mice carrying a rat C3(1) simian virus 40 large tumor antigen fusion gene. 


127. Schneider BP, Miller KD. Angiogenesis of breast cancer. 


139. Hartwig FP, Nedel F, Collares T, Tarquinio SB, Nor JE, Demarco FF. Oncogenic somatic events in tissue-specific stem cells: a role in cancer recurrence? 


