Breast cancer is the most common noncutaneous malignancy among women worldwide. In 2018, over 2 million new cases and 627,000 deaths were reported globally with countries such as Belgium, France, Australia, and the United Kingdom having the highest rates. In the United States in 2019, over 268,000 new cases have been reported with over 41,000 deaths. Triple-negative breast cancer (TNBC) represents a particularly deadly form of breast cancer that occurs more commonly in women younger than 50 years, particularly those of African American and Hispanic descent. TNBC patients have poor prognosis and the tumors are typically high grade and metastatic. TNBC tumors are defined by a lack of estrogen receptor-α (ERα), progesterone receptor, and human epidermal growth factor 2 (HER2, also known as ErbB2). TNBC remains the most difficult breast cancer subtype to treat, as TNBC patients do not benefit from the hormone receptor or HER2-targeting drugs used for other breast cancer subtypes. Additionally, these tumors become rapidly resistant to standard chemotherapies. Thus, an urgent need remains to identify new molecular targets for effective treatment of TNBC.

The KISS1 gene is a metastasis-suppressor gene discovered in melanoma cells and its name reflects both its suppressor sequence and its place of discovery in Hershey, PA, the home of Hershey’s Kisses chocolates. The KISS1 gene encodes a 145 amino acid product that is proteolytically cleaved in the blood by furin and matrix metalloproteinases (MMPs) such as MMP-9 and the membrane type I matrix metalloprotease (MT1-MMP), into shorter kisspeptin peptides 10, 13, 14, or 54 amino acid in length. All kisspeptins have an amidated C-terminal end required for binding and activating the kisspeptin receptor (KISS1R), a G protein-coupled receptor, the receptor tyrosine kinase AXL, and transforming growth factor-β to promote cell invasion, metastasis, and drug resistance.
coupled receptor previously known as GPR54. KISS1R is a Gq/11-coupled receptor, and upon ligand binding triggers phospholipase C activation, Ca\(^{2+}\) mobilization, and phosphorylation of mitogen-activated protein kinase (MAPK, ERK1/2) and p38. All KPs exhibit similar affinity for KISS1R; however, KP-10 is the agonist of choice for most studies. KISS1 and KISS1R are expressed in healthy breast tissue and play an essential role in mammary gland formation.

The KISS1/KISS1R signaling pathway has anti-metastasis/anti-tumorigenic roles in many cancers such as melanoma, pancreas, bladder, colorectal, ovary, and prostate, as previously reviewed. Mechanistically, the tumor-suppressive role has been linked to an inhibition of tumor invasion via a repression of MMP-9 expression and activity, and by inhibiting MAPK. Proteases such as MMP-9 promote tumor invasion by degrading the extracellular matrix (ECM). KISS1 expression is lost in certain cancers such as colorectal and bladder cancer, due to epigenetic modifications of the KISS1 promoter and this has been linked to poor patient survival.

In the last decade or so, several studies have shown that in marked contrast to its anti-tumor roles in most cancer, KISS1R signaling can promote cell migration and invasion in ER\(\alpha\)-negative breast cancer such as TNBC. It is important to note that in the human carcinoma, MDA-MB-435 cells which were originally classified as a “breast cancer” line, KISS1 was reported to act as a metastasis suppressor. However, since then MDA-MB-435 cells have been found to express genes resembling melanoma cells and thus are no longer considered a robust breast cancer cell model. Here, we review the underlying mechanisms by which KISS1/KISS1R signal-

Metastasis

Metastasis is the process by which cancer cells detach from the primary tumor, invade through the surrounding ECM, and migrate via the blood stream or lymphatics and colonize at secondary sites. For breast tumors, these sites commonly include the brain, lungs, liver, and bone. When tumors are confined to breast tissue, the 5-year survival rates exceed 90%. However, once metastasis occurs, survival decreases rapidly depending on the extent and sites of tumor colonization. Initial separation and spreading of cancer cells from the primary tumor involves a process known as epithelial-to-mesenchymal transition (EMT). Epithelial cells undergoing EMT lose their cell-to-cell adhesion and cell polarity as well as the expression of epithelial markers such as E-cadherin and gain the expression of mesenchymal markers such as MMP, N-cadherin, vimentin, and \(\beta\)-catenin (Fig. 1). These cells also acquire a spindle-shaped morphology characteristic of fibroblasts and gain the ability to migrate and invade through the basement membrane into the surrounding ECM. Cells which undergo EMT migrate away from primary tumors through cycling of adhesion/de-adhesion molecules regulated by...
integrins and by forming F-actin stress fibers through which myosin cycling initiates cell movement.\(^40\)

The ability of tumors to metastasize is dependent on the formation of invasive structures called invadopodia that mediate tumor cell entry into blood vessels (i.e., intravasate) or surrounding tissues (i.e., extravasate).\(^41\) Invadopodia are actin-rich, foot-like, adhesive membrane protrusions that form on tumor cell surfaces (Fig. 2a). These are used to digest components of the ECM to create paths used for invading through tissues via the focal delivery of proteases such as MT1-MMP.\(^42\) Key invadopodia proteins such as coflin and cortactin regulate invadopodia stabilization and maturation and the actin cytoskeleton for invadopodial function.\(^43\) The capacity of tumors to form invadopodia is closely linked with the tumor’s invasive and metastatic potential.\(^44\)–\(^46\) Targeting pathways that regulate invadopodia formation are being tested clinically in many cancers, including TNBC, as a way of blocking metastasis.\(^47\)

**TNBC: Current Treatment**

The subtyping of breast cancers into molecular phenotype based on the expression of ER, progesterone receptor, and HER2 has transformed the way in which breast cancer is treated by permitting the tailoring of treatments specific to each intrinsic subtype.\(^48\) Although the subtypes are defined by microarray-based gene expression, the clinical surrogate for this is immunohistochemical testing of protein expression. In TNBC, the lack of ER, progesterone receptor, and HER2 expression limits therapeutic options to standard cytotoxic anthracycline and taxane-based chemotherapy with higher rates of treatment resistance and metastases. Thus, TNBC is the most challenging to treat and with the worst prognostic outcomes.\(^5\)

With the absence of specific biomarkers in TNBC cells, researchers have been looking to exploit the rich epithelial-like and mesenchymal-like cancer stem cells by targeting pathways upregulated in these cells;\(^49\) however, these findings are in the early discovery phase. The main categories of therapies for TNBC currently being introduced into the clinical realm, albeit with limited data,\(^50\) include (1) poly-ADP-ribosyl polymerase (PARP) inhibitors in the metastatic setting,\(^51\) given in combination therapy with DNA damaging alkylating chemotherapeutics (e.g., platinum) to patients with tumors lacking functional BRCA1 or BRCA2 genes (with resultant impaired ability to repair double-stranded DNA damage); (2) AKT inhibitor (ipatasertib), which has shown modest efficacy in progression-free survival;\(^50\) and (3) immunotherapy agents, for example, checkpoint inhibitors to programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1). PD-1 and PD-L1 bind to sites of DNA damage to target repair pathway activation. Immunotherapy drugs are given as single-agent therapies or combination therapies, with ongoing trials evaluating their efficacy in neoadjuvant, adjuvant, and metastatic settings.\(^52,53\) However, clinical trial results indicate
lower-than-expected impact on survival with checkpoint inhibitors in the metastatic setting and thus combination therapies with targets directed at EMT-related pathways are being explored.\textsuperscript{54} Additionally, TNBC tumors exhibit extensive epigenetic alterations via DNA methylation and novel drug targets aimed at epigenetic re-programming such as BET bromo-domain inhibitors alone or in combination with immunotherapy are targeted for hypermethylated tumors and are also in clinical trials.\textsuperscript{5,55}

Molecular pathways that modulate tumorigenesis are deregulated in the aggressive TNBC phenotype. Although there appears to be some promising new therapies, there is a dire need for prognostic biomarkers and specific protein targets for drug development in TNBC. One significant potential target is KISS1R, and remainder of this review will highlight the role of KISS1R in regulating TNBC metastasis and chemotherapy resistance.

**KISS1R: Metastasis Promoter**

The first landmark study that revealed KISS1R promotes breast cancer metastasis came from Cho et al who used a mouse mammary tumor virus–polyoma virus middle T antigen (MMTV-PyMT) model of breast cancer metastasis.\textsuperscript{56} In this model, the expression of the PyMT oncogene was driven by the MMTV promoter and transformation of the mammary epithelium led to the development of metastatic lesions in the lungs and lymph nodes, in addition to mammary adenocarcinomas.\textsuperscript{57,58} The study showed that Kiss1r haploinsufficiency (Kiss1r \textsuperscript{+/−}) led to delayed breast tumor initiation, growth, and metastasis. To show a direct effect on tumorigenesis, the authors conducted orthotopic injections of isolated mouse primary breast cancer MMTV-PyMT/Kiss1r\textsuperscript{−/−} cells into the mammary fat pads of mice and observed a reduction in primary tumor growth compared with mice injected with MMTV-PyMT/Kiss1r\textsuperscript{+/+} cells. Thus, loss of Kiss1r expression reduced tumor growth. Importantly, the authors verified that there were no pubertal defects of mammary gland development in the Kiss1r heterozygotes that would have resulted in impaired mammary tumor development. The authors also isolated breast tumor cells from primary tumors of PyMT/Kiss1r\textsuperscript{+/+} and PyMT/Kiss1r\textsuperscript{−/−} mice and found that Kiss1r heterozygosity negatively regulated tumor cell proliferation, cell motility, and invasion. Mechanistically, the study found that Kiss1r heterozygous (PyMT/Kiss1r\textsuperscript{+/−}) tumors displayed a significant reduction in MMP-9 mRNA compared with wild-type (PyMT/Kiss1r\textsuperscript{+/+}) tumors. Additionally, KISS1R signaling was found to activate the small G protein, RhoA, a key regulator of the cytoskeleton necessary for cell migration and invasion downstream of Gqα activation, through Gqα-p63RhoGEF-RhoA signaling pathway (\textsuperscript{►}Fig. 3).

**KISS1/KISS1R: Regulation by ERα**

Estrogen signaling via ERα critically regulates the development of the mammary ducts during puberty.\textsuperscript{59} ERα signaling is an important regulator of breast carcinogenesis,\textsuperscript{60} and silencing ERα has been shown to induce EMT.\textsuperscript{61} It is well known that estradiol (E2) directly regulates KISS1 expression in the hypothalamus. Specifically, in the arcuate neurons, ERα negatively regulates KISS1.\textsuperscript{62} Similarly, ERα has been shown to regulate KISS1 and KISS1R in breast carcinoma. Marot and colleagues showed that treatment of ERα-positive luminal breast cancer cells T47D and MCF7 with Tamoxifen, an ERα antagonist, stimulated the expression of KISS1/KISS1R mRNA.\textsuperscript{63} Furthermore, women with ERα-positive breast tumors treated with Tamoxifen had high KISS1 and KISS1R mRNA levels, which is associated with poor prognosis.\textsuperscript{63} Clinically, KISS1 and KISS1R levels are higher in ERα breast tumors compared with ERα+ tumors and this correlates with poor patient outcome.\textsuperscript{37,64} Thus, ERα signaling downregulates the expression of KISS1/KISS1R and when ERα is lacking, this results in an upregulation of KISS1/KISS1R in breast carcinoma. This was also observed to occur in TNBC cells. When ERα was overexpressed in TNBC MDA-MB-231 breast cancer cells, treatment of cells with E2 resulted in a decrease in KISS1/KISS1R mRNA and protein levels, compared with controls.\textsuperscript{19,61} In support of this, KISS1/KISS1R mRNA and protein levels were found to be upregulated in primary tumor biopsies compared with healthy breast tissue and KISS1 and KISS1R protein was found to be immunolocalized in invasive ductal carcinoma in TNBC tumors.\textsuperscript{65} Taken together, the presence of ERα in breast epithelia appears to critically regulate the expression of KISS1/KISS1R.

**KISS1/KISS1R: Malignant Transformation**

The normal (nonmalignant) human MCF10A breast epithelial cells are a widely used model to study breast cell function as well as cell transformation.\textsuperscript{66,67} These cells express mammary gland–specific markers resembling normal human breast and form mammary acini that are capable of secreting milk.\textsuperscript{68} Although MCF10A cells express KISS1R endogenously,\textsuperscript{19} they lack ERα.\textsuperscript{66} This cell model is used commonly to study EMT-like processes in human breast,\textsuperscript{59–71} KP-10 treatment or stable overexpression of KISS1R in MCF10A cells promoted an EMT-like event, resulting in the loss of E-cadherin from cell–cell junctions, the acquisition of mesenchymal markers such as N-cadherin and Snail/Slug and cells become migratory and invasive.\textsuperscript{19} This divulged that KISS1R signaling in breast epithelia lacking ERα can promote malignant transformation (\textsuperscript{►}Fig. 3).

Metastatic breast cancer cells such as TNBC cells, MDA-MB-231, and Hs578T exhibit high expression of KISS1 and KISS1R in contrast to weakly invasive, ERα-positive breast cancer cells (T47D, MCF7) or nonmalignant breast MCF10A cells.\textsuperscript{65} Depletion of KISS1R in TNBC cells using RNA interference reduced the expression of mesenchymal markers and stress-fiber formation and impaired invadopodia formation concurrent with their ability to migrate or invade.\textsuperscript{72} Normal cells, in contrast to transformed cells, depend on cell to ECM contact to be able to grow and divide. In the absence of a substrate to attach to, normal cells undergo apoptosis.\textsuperscript{73} In contrast, transformed cells such as tumors have the capability to grow and divide without the need of a substrate and this is a hallmark of carcinogenesis.\textsuperscript{74} Thus,
tumor cells can form colonies in an anchorage-independent manner and this ability can be evaluated using an anchorage-independent growth assay, also known as soft agar colony formation assay. Loss of KISS1R expression in TNBC cells reduced the ability of TNBC cells to form colonies on soft agar, further implicating a role for KISS1R in malignant transformation of breast epithelia.

KISS1/KISS1R: Tumor Cell Invasion

Using several TNBC cell lines (MDA-MB-231, Hs578t, SCP2, and SUM159) and ERα-negative cells (MCF10A, SKBR3), KISS1R signaling has been shown to promote cell migration and invasion, vital processes for metastasis. These have been observed in response to stimulating cells with KP-10. Using a gain-of-function model, the overexpression of human KISS1R in ERα-negative cells, normal MCF10A cells, and SKBR3 breast cancer cells (which have low levels of endogenous KISS1R) also induced cell migration and invasion. Furthermore, KISS1R overexpression in SKBR3 cells triggered tumor cells extravasation using the chick chorioallantoic membrane assay. KP-10 treatment of cells further increased the number of tumor cells that extravasated into the stroma, whereas a KISS1R antagonist (P-234) blocked the KP-10-mediated effect. This provided the first evidence that human KISS1R signaling regulates breast cancer invasion in an in vivo context.

In human TNBC cells, KISS1R signaling promotes cell invasion by several mechanisms (Figs. 2 and 3). First, KISS1R stimulates invadopodia formation and by activating key invadopodia proteins, cortactin, coflin, and MT1-MMP, through a β-arrestin2 and ERK/MMP-9-dependent mechanisms. Second, KISS1R activates the tyrosine kinase receptor epidermal growth factor receptor (EGFR or ErbB1) and stimulates TNBC invasion via β-arrestin2 and MMP-9-dependent mechanisms. In fact, KISS1R directly binds EGFR in TNBC cells and KP-10 enhances this interaction. Treatment of TNBC cells with the KISS1R antagonist, P-234, blocked the KP-10-mediated effect. This overexpression correlates with a loss of estrogen responsiveness and a poor patient prognosis. EGFR expression itself is negatively...
regulated by ERα. Unfortunately, anti-EGFR therapies alone have not been effective in treating TNBC. KISS1R is localized to the leading edge in lamellipodia of migratory breast cancer cells, co-localizing the actin-scaffolding protein, IQGAP1. KISS1R binding to IQGAP1 is necessary for EGFR activation that promotes TNBC invasion. However, KP-10 failed to activate EGFR or stimulate cell invasion of ERα-positive MCF7 and T47D cells, or upon expression of ERα in TNBC cells. This implies that ERα signaling keeps KISS1/KISS1R function in check, in addition to negatively regulating their expression.

Another way by which KISS1R signaling stimulates cell invasion is via the secreted ECM protein, fibulin-3, also known as epidermal growth factor (EGF)-containing fibulin-like extracellular matrix protein 1 (EFEMP1). Fibulin-3 is a secreted glycoprotein found in the ECM, known to regulate cell–matrix interactions, tissue remodeling, cell morphology, cell adhesion, and motility. A recent study found using transcriptome analysis that fibulin-3 was expressed in cancer exosomes, which are extracellular vesicles released by cancer cells known to regulate organ-specific metastasis. The fibulin-3 gene, EFEMP1, was found to be amplified in TNBC in contrast to other breast subtypes and plasma fibulin-3 levels were found to be elevated in TNBC patients compared with healthy subjects. Furthermore, KISS1R signaling was found to induce fibulin-3 mRNA and protein expression as well as fibulin-3 secretion by TNBC cells. Downregulation of fibulin-3 in TNBC cells impaired KP-10-induced cell migration and invasion. Mechanistically, fibulin-3 was found to regulate TNBC cell invasion via ERK1/2 and MMP-9-dependent pathway, downstream of KISS1R activation (Fig. 3).

It is well known that KISS1 mRNA levels are highly expressed in the placenta and plasma kisspeptin levels soar during pregnancy and remain elevated until parturition. Rasouzlzadeh and colleagues examined the effect of placental-derived kisspeptin on breast cancer cell adhesion and invasion. They collected conditioned media from human placental cells obtained from 11 placenta from healthy women with term pregnancy and undergoing Cesarean delivery. They found that placental-derived kisspeptins had a differential effect on TNBC (MDA-MB-231) cells compared with ERα-positive breast cancer (MCF-7) cells. In MDA-MB-231 cells, placental kisspeptins selectively reduced cell adhesion and promoted cell migration and invasion, which was inhibited upon treatment of cells with the KISS1R antagonist, P-234. In contrast, treatment of MCF-7 cells with placental kisspeptins had no effect on cell adhesion or invasion. Mechanistically, the study showed that placental kisspeptins increased MMP-9 expression and activity in MDA-MB-231 cells to thereby regulate cell invasion. This corroborates findings from previous studies that kisspeptins can differentially modulate invasiveness of breast cancer cells, depending on the ERα status.

Interestingly, KISS1 has been shown to function downstream of TGF-β to promote cell invasion in TNBC^- (Fig. 4). Tian et al showed that TGF-β signaling via Smad2/p21 induced high expression of KISS1 in TNBC cells (MDA-MB-231 and SCP2) in contrast to ERα-positive (MCF-7) breast cancer cells. Downregulation of KISS1 blocked TGF-β-induced TNBC invasion by stimulating MMP-9 expression and activity. The authors examined KISS1 gene expression in 1,215 human breast tumors classified by ER status using the Cancer Genome Atlas (TCGA) database and observed higher KISS1 expression in the aggressive basal-type, ERα-negative tumors versus the less aggressive ERα-positive tumors. Furthermore, using immunohistochemical analysis of KISS1 protein expression in a tumor microarray composed of normal breast tissue and breast carcinoma tissue from 48 patients, the study reported that positive lymph node status is associated with a higher KISS1 levels. Further studies are required to determine how this links with survival outcome and by what mechanisms TGF-β regulates KISS1 expression and whether KISS1R is involved in this pathway.

**KISS1/KISS1R: Drug Resistance**

TNBC patients have a lower survival rate following initial response to chemotherapy because tumors tend to develop chemoresistance and this limits the available options for previously treated patients. KISS1R signaling has been...
shown to induce chemoresistance in TNBC cells and multiple ERα-negative breast cancer cells by two mechanisms.65 First, KISS1R modulates the expression of the ATP-binding cassette drug efflux transporter, breast cancer resistance protein (BCRP), a major multidrug-resistant transporter in TNBC.92,93 Second, KP-10 treatment of cells activates the tyrosine kinase, AXL,65 a binding partner of EGFR that is highly expressed in TNBC.94,95 AXL signaling is known to induce EMT as well as drug resistance,96,97 and AXL inhibitors are currently in clinical trial in various cancers.98–100 KISS1R induces AXL transcription via enhanced binding of Sp1 to the AXL promoter. Knockdown of AXL using siRNA decreased the expression of EMT markers, but did not decrease BCRP expression, suggesting that KISS1R promotes drug resistance via two independent mechanisms. KISS1R overexpressing cells displayed reduced accumulation of the chemotherapeutic drug, doxorubicin, and displayed resistance to apoptosis as evidenced by a reduction of cleaved PARP, which occurs in the onset of apoptosis. In fact, KISS1R signaling promoted tumor cell survival by enhancing the expression of cell survival molecules such as AKT, ERK, and the antiapoptotic protein, survivin.65 Depletion of AXL or antagonizing KISS1R signaling resensitized tumor cells to chemotherapy. Although the mechanisms by which KISS1R activates AXL are to be determined, this study revealed that KISS1R is a key regulator of TNBC drug resistance.

In a study of human head and neck squamous cell carcinoma (HNSCC), KISS1 has been shown to regulate drug resistance to the chemotherapeutic agent, cisplatin.101 In this cancer, KISS1 functions as a metastasis suppressor and thus, KISS1 expression is lost in patients with metastatic tumors compared with nonmetastatic tumors. The authors observed a profound decrease in KISS1 mRNA expression in the cisplatin-resistant cell lines compared with the parental cells, but there was no change in KISS1R expression. Depletion of KISS1 by siRNA in the parental HNSCC cells induced resistance to cisplatin. Conversely, overexpression of KISS1 in HNSCC cells increased sensitivity of cisplatin-resistant cells to the chemotherapeutic in addition to inhibiting cell migration and proliferation. Importantly, using two preclinical xenograft models where human cells were injected into immunocompromised mice, the study showed that reexpression of KISS1 in human cisplatin-resistant HNSCC cells decreased metastasis. Although the authors do not address the mechanism regulating the loss of KISS1 in HNSCC, this study clearly revealed a role for KISS1 in inhibiting cisplatin drug resistance as well as metastasis in HNSCC.

Conclusions and Future Perspective

Metastasis, the leading cause of cancer-related death, remains a major impediment for the treatment of cancer102 and several new therapeutic approaches are being investigated including targeting the tumor microenvironment, mitophagy, and immune therapy.103–105 In contrast to its original classification as a metastasis-suppressor gene in melanoma, this review provides information as to the state of our current knowledge on the proinvasive roles of KISS1 in breast cancer.

Understanding the role of the KISS1/KISS1R pathway in regulating TNBC metastasis and drug resistance is still in its early period. Studies using preclinical xenograft models as well as patient-derived xenografts are required for a better understanding of the underlying molecular mechanisms by which KISS1R regulates cell invasion and whether targeting this pathway inhibits TNBC metastasis and drug resistance in vivo. Questions that remain to be answered include how does KISS1R communicate with other receptors such as growth factor receptors (e.g., TGF-β and AXL) and what role does KISS1R signaling play in other ERα-negative breast cancer subtypes (e.g., HER2-positive tumors).

Traditionally, the epigenetic regulation of gene expression in cancer is considered to be mediated via the inactivation of expression of tumor suppressor genes. Indeed, in colorectal and bladder cancer where KISS1 functions as a tumor suppressor, KISS1 expression is decreased in primary tumors due to epigenetic modifications.16 Recently, it is surfacing that epigenetic de-repression mechanisms such as DNA and histone demethylation are at play resulting in the overexpression of some oncogenes or cancer promoting genes in cancer and these can initiate cancer development and make tumors more aggressive and resistant to treatment.106–108 KISS1 expression is elevated in patient TNBC primary tumors; however, whether KISS1 is epigenetically regulated or undergoes miRNA regulation that results in changes in regulatory elements in TNBC needs further investigation.

In summary, biomarker identification to guide treatment decisions in TNBC is an unmet need, and an improved understanding of the molecular pathways that are deregulated in the early stages of TNBC can provide opportunities for targeted drug therapeutic intervention. TNBC cells overexpress KISS1 and secrete kisspeptin; however, it is yet to be determined whether plasma kisspeptin levels are altered in TNBC patients and whether this could serve as a potential biomarker for monitoring metastasis and disease recurrence. Despite the need for further investigations, it remains abundantly clear that KISS1/KISS1R plays important roles in TNBC invasion, metastasis, and drug resistance and this pathway represents a novel drug target.

Conflict of Interest
The authors declare no potential conflict of interest.

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