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The KISS1 metastasis suppressor: A good night kiss for disseminated cancer cells

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Abstract

Re-expression of KISS1 in tumor cell lines allows all antecedent steps of metastasis, but prevents colonization of secondary sites. Because tumor cells have already disseminated by the time of cancer diagnosis, KISS1 may represent a new opportunity for therapeutic intervention. Moreover, numerous clinical reports demonstrate that a loss or reduction of KISS1 expression in different human cancers inversely correlates with tumor progression, metastasis, and survival. Taken together, these observations compel the hypothesis that KISS1 could be of tremendous utility in controlling metastasis in a therapeutic context. In this review, we highlight some key findings from preclinical and clinical studies and discuss strategies whereby KISS1 may be exploited clinically to treat metastases.

Keywords

KISS1; kisspeptin; GPR54; G-protein coupled receptor; paracrine

1. Introduction

Metastasis hinges upon a stringently orchestrated cascade of events; therefore, interruption of any step effectively halts the process. An attractive group of candidates to treat metastasis are the metastasis suppressors, defined by their abilities to inhibit metastasis without blocking orthotopic tumor growth. This growing family of functionally-defined molecules now exceeds 25 [1, 2]. This number continues to grow since several other inhibitors of the

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steps in metastasis have been identified, but effects on metastasis have not yet been assessed *in vivo*. Although our understanding of the mechanisms of action grows rapidly, collectively, much remains to be learned about these important molecules.

In this short review, we will focus on the KISS1 metastasis suppressor, which affects colonization, the last step of the metastatic cascade. We will take readers through its discovery, preclinical characterization, and theoretical utility and limitations. In short, we will provide data showing that KISS1 expression in neoplastic cells renders them dormant after they have disseminated, effectively giving them what we term a good night kiss. In addition, we refer readers throughout this article to several more comprehensive reviews on KISS1 that have been published previously.

1.1 Discovery of the KISS1 metastasis suppressor

The discovery of *KISS1* began by taking note of early karyotypic analyses of melanomas. Although percentages vary on a case-by-case basis, deletions or rearrangements of chromosome 6, particularly involving the long arm, are involved in >80% of melanomas [3]. For this reason, full-length chromosome 6 was introduced into the human metastatic melanoma cell line C8161 employing microcell-mediated transfer (the hybrids were designated neo6/C8161) [3]. These and subsequent studies revealed that the introduction of a normal copy of chromosome 6 suppressed metastasis without affecting tumorigenicity or local invasion [3].

KISS1 was subsequently identified as a human melanoma metastasis suppressor gene using subtractive hybridization between highly metastatic and nonmetastatic cell lines and respective cell line variants [4-6]. Transfection of full-length KISS1 cDNA into melanoma [4-6] and breast carcinoma [7] cell lines suppressed metastasis in athymic mice using both spontaneous and experimental metastasis assays.

1.2 KISS1 is regulated by genes residing on chromosome 6

Unexpectedly, *KISS1* mapped to chromosome 1q32. Those data were evidence for the existence of a regulatory gene on chromosome 6. Subsequent studies designed to explicitly identify the putative regulatory locus on chromosome 6 identified a 40-cM region between 6q16.3 and q23 as the principle regulatory region of *KISS1* [8]. In addition, complementary studies by Shirasaki and colleagues [9] found that a loss of 6q16.3-q23 was observed in more than 50% of melanoma metastases and importantly, that a loss of heterozygosity (LOH) of this region was strongly associated with a loss of KISS1 (Figure 1).

Subsequent studies by Goldberg et al. showed that a thioredoxin interacting protein (*TXNIP*, also known as vitamin D up-regulated protein 1, *VDUP1*, or thioredoxin binding protein 2) was expressed more highly in nonmetastatic melanomas and in the neo6/C8161 melanoma cell line [10]. Furthermore, increased *TXNIP* expression by transfection into C8161.9 melanoma cells inhibited metastasis and up-regulated *KISS1.* As unexpectedly, *TXNIP* also mapped to chromosome 1q. Subsequent PCR karyotyping revealed that *CRSP3/DRIP130* (co-factor required for SP1 activity or vitamin D receptor interacting protein) mapped to chromosome 6. *CRSP3* transfected cells up-regulate both *KISS1* and *TXNIP* expression and were suppressed for metastasis [10]. In addition, analyses of clinically derived melanoma samples indicated that a loss of *CRSP3* expression correlates with decreased *KISS1* expression and increased metastasis [10].

In summary, these pivotal studies concluded that *CRSP3* is an upstream regulator of *TXNIP,* which, in turn, regulates KISS1 expression. As a result, a loss or structural abnormality of chromosome 6, as is frequent in late-stage melanoma, results in a loss of *CRSP3* expression,

consequently altering the appropriate regulation of downstream mediators (i.e., *TXNIP* and *KISS1*).

2. The *KISS1* gene produces kisspeptins that bind to GPR54, a G-protein coupled receptor

The *KISS1* gene was predicted to encode a 154-amino acid protein. Yet, despite numerous attempts, our laboratory was unsuccessful in identifying an intact KISS1 protein. The mystery was solved in 2001 when three laboratories independently determined that internal peptides of KISS1 (subsequently termed kisspeptins, KP) bound to a then-orphan G-protein coupled receptor GPR54 (also known as AXOR12 or hOT7T175, but now referred to as the KISS1 receptor, KISS1R; Figure 2). Systematic examination of KISS1R expression reveals high KISS1R expression in placenta, pituitary gland, pancreas, brain, and spinal cord [11, 12]. *KISS1* expression is slightly more restricted, located primarily in the placenta, pancreas, kidney, and the arcuate nucleus of the hypothalamus [4, 12, 13].

Ohtaki and colleagues found that an amidated internal 54-amino acid peptide, which they termed metastin, binds and activates KISS1R [13]. Kotani and colleagues reported the existence of multiple internal peptides, which they termed KP [11]. Some KPs bind KISS1R, whereas others do not. Hereafter, we will retain the nomenclature of KPs (defined based upon the number of amino acids in the peptide) because it defines the gene that originally encoded the peptide.

A precise understanding of the mechanisms by which KPs are processed remains unidentified. Since processing is not the focus of this volume, we refer readers to more comprehensive reviews on the topic [14, 15]. Briefly, however, proteolytic processing of the KISS1 protein is thought to occur by furins or prohormone convertases [11, 13] based upon the amino acids at the ends of the fragments. Specifically, cleavage at the dibasic sites R^{66}-R and K^{123}-R results in production of KP54. Shorter fragments of KP54 have been identified (e.g., KP10, KP13, and KP14). Each represents the C-terminal portion of KP54 and binds to and activates KISS1R [11, 16-19]. The potency of the peptides is enhanced by amidation, although amidation is not required [13].

Transfection of the KISS1R into Chinese hamster ovary (CHO) cells followed by stimulation with KP results in PtdIns(4,5)P_2 hydrolysis, Ca^{2+} mobilization, arachidonic acid release, stress fiber formation, and ERK1/2, p38, and MAP kinase phosphorylation; however, cell proliferation is inhibited [11]. Ohtaki et al. also engineered CHO cells to express KISS1R and found that chemotaxis and invasion were inhibited *in vitro* [13]. Moreover, administration of KP54 to C57BL/6 mice bearing B16 melanomas engineered to express KISS1R attenuated pulmonary metastases [13]. As a result, most inferred that KISS1 exerted anti-metastatic effects via autocrine signaling. In yet another unexpected finding, we showed that none of the cell lines suppressed for metastasis by KISS1 re-expression express KISS1R, suggesting the existence of alternative signaling pathways [15].

We note that a preponderance of the primary literature describes the involvement of KISS1 and/or KP in numerous biological processes ranging from pubertal development to pregnancy (reviewed in Colledge[17], Roa et al.[20], Tena-Sempere[21], and Gianetti et al. [22]). For instance, remarkably, in pregnant women, plasma KP54 concentrations increase 900-fold over nonpregnant women in the first trimester of pregnancy, followed by a 7000-fold increase in KP54 during the third trimester [23]. Furthermore, mutations in KISS1R are associated with autosomal recessive idiopathic hypogonadotropic hypogonadism in multiple animals and humans, suggesting that KISS1R is essential in the regulation of puberty [24].

3. Preclinical/Clinical Evidence for KISS1 as a valid anti-metastatic

In animal models, KISS1 expression blocks the ability of melanoma, breast, and ovarian cancer cells to colonize and proliferate at secondary sites in cancer xenograft models [4-7, 25]. Clinical reports compel the prediction that reduction of KISS1 expression would correlate with tumor progression, metastasis, and survival. These data are summarized below and in Figure 1. We emphasize that the majority of the clinical studies have measured mRNA expression by *in situ* hybridization or PCR-based methods. The former are less ambiguous than studies in which stromal cells contaminate the cell preparation, making it impossible to judge the origins of KISS1 or KISS1R. In part, measurement of mRNA was required because of difficulties in generating specific antibodies. Still, many of the commercially available antibodies used have not been validated (or the data are not provided in publications). Likewise, the processing of KISS1 to KP has not been evaluated in clinical samples. While the bulk of data from numerous pilot studies support the role of KISS1 as a metastasis suppressor in clinical settings, technical caveats to the experimental design and some conflicting data can be confusing.

From a patient's perspective, diagnosis of cancer is accompanied by multiple fears. Patients who have undergone apparently successful surgical resection unfortunately experience recurrence locally or at distant sites months or years later. As a result of sometimes subjective pathological criteria coupled with information available to the oncologist, patients often receive therapies to eliminate residual cells or eliminate disseminated cells before *bona fide* metastases develop. Unfortunately, for many cancers, the histology of the primary tumor does not provide unambiguous predictions for whether the tumor has already spread (or not). As a result, a substantial proportion of patients undergo unnecessary treatments as a precaution. We and others hold out hope that biomarkers such as KISS1 could be coupled with traditional pathology to refine a prognosis so that toxic treatments to already cured patients would be minimized. In Figure 1, a comprehensive summary of clinical studies is presented. Selected histotypes are described below.

3.1 Melanoma

The first clinical study implicating KISS1 in a human cancer was performed in cutaneous melanomas. Shirasaki examined KISS1 mRNA expression at various stages of melanoma progression and found that KISS1 expression was found in all nevocellular nevi and eight primary melanomas (<4 mm thickness, i.e., early disease), while in large primary melanomas (>4 mm thickness) and in metastases, KISS1 expression was lost in nearly half of the samples [9].

3.2 Breast and Ovarian cancer

Animal studies examining KISS1 in breast cancer clearly demonstrated suppression of metastases *in vivo*. However, information is limited and somewhat contentious regarding KISS1 in the context of clinical breast cancer. Analyses of KISS1 mRNA from paraffin-embedded stage II or III lymph node positive breast adenocarcinomas shows that only 3% of samples yielded KISS1 mRNA, thus supporting the anti-metastatic role of KISS1 [26]. Likewise, another group showed that KISS1 mRNA expression was lower in breast cancer brain metastases in comparison to KISS1 expression in the primary tumor [27]. In contrast to the studies supporting the anti-metastatic role of KISS1 in breast cancer, Martin et al. found KISS1 messenger elevated in node-positive breast tumors in comparison to node-negative samples, yet no differences were observed in KISS1R [28]. Moreover, in another study, among estrogen receptor-alpha-positive tumor samples from patients treated with tamoxifen, Marot and others found that when both KISS1 and KISS1R expression were high, patients

exhibited shorter disease-free survival [29]. The data in breast are reported here with a cautionary note regarding the technical caveats listed above.

The role of KISS1 in ovarian cancer appears less ambiguous. Immunohistochemistry (IHC) of numerous ovarian cancer samples employing antibodies directed against the various KP and KISS1R found that positivity for both individually correlated with favorable prognosis and superior overall survival [30]. Similarly, at approximately the same time, another study reported that high simultaneous KISS1R and KP54 expression was significantly associated with improved survival [31].

3.3 Gastrointestinal cancers

Several studies have implicated KISS1 in various gastrointestinal cancers. In gastric cancer, Dhar et al. found low KISS1 expression in patients with distant metastases and worsened overall and disease-free survival [32]. In another gastric cancer study, analysis of KISS1 protein expression in tissue microarrays found that KISS1 was reduced in lymph node and liver metastases compared with primary gastric tumors [33].

Pancreatic cancer is especially difficult to manage as early detection is rare and metastatic disease is common. Consequently, five-year survival is typically only 5%. Pancreaticoduodenectomy (Whipple procedure) is the only potentially curative approach, yet the majority of patients have incurable disease at diagnosis, and few patients are candidates for surgery. Normal pancreas expresses detectable KISS1 and pancreatic tumor tissues show significantly lower expression of KISS1 mRNA, yet curiously exhibit heightened KISS1R expression [34]. Furthermore, exogenous KP54 does not affect proliferation of the pancreatic cancer cell line PANC-1, but reduces *in vitro* migration [34]. IHC analysis showed $KP54^{neg}$ and $KISS1R^{neg}$ tumors were significantly larger than tumors that expressed either KP54 or KISS1R [35]. Strong expression of KP54 or KISS1R in samples was significantly correlated with improved survival. In fact, KP54 expression alone was found to be an independent prognostic factor for the survival of pancreatic cancer patients [35]. In some patients, before surgical resection, plasma KP54 levels were measured by ELISA and patients were classified as having either high or low plasma KP54 [35]. While survival was not significantly different, unlike those patients with low plasma KP54, none of the patients with high KP54 levels died following surgery (up to 22.1 months) [35]. In another study comparing plasma KP54 levels, the most significant relationship identified was that pancreatic cancer patients simply had higher plasma KP54 levels [36]. Collectively, these findings are intriguing in that they establish KISS1 as an important prognostic indicator in pancreatic cancer, and for the first time, demonstrate the potential significance of plasma KP levels within patients.

The responsiveness of pancreatic tumors to KISS1 and/or KP suggested that KP could perhaps be used in a therapeutic setting. While not tested as a therapeutic, re-expression of KISS1 in a xenograft model of pancreatic cancer resulted in significantly reduced orthotopic tumor growth and metastases to lung and liver (L. McNally, D.R. Welch, D. Buchsbaum, submitted for publication).

The loss of KISS1 and KISS1R gene expression was not associated with tumor size or invasion in esophageal squamous cell carcinoma, but was found to be a significant predictor of lymph node metastasis [37]. The same group, using RT-PCR, reported that over-expression of both KISS1 and KISS1R was *positively* correlated with HCC progression [38]. These findings were corroborated by another study using immunohistochemistry [39].

4. Can KISS1 be exploited clinically?

Perhaps the most intriguing property of KISS1 derives from data in which re-expression of KISS1 still allows all antecedent steps of metastasis, including seeding at a secondary site without *colonization* of ectopic tissues. Briefly, KISS1 maintains disseminated tumor cells in a dormant state after they have seeded other tissues. While it has long been recognized that blocking any step of the metastatic cascade effectively prevents metastasis, it had been under-appreciated how critical the last step (colonization) in the process is. Since tumor cells have already disseminated by the time most cancers are diagnosed, even for a portion of the smallest tumors, interventions that target colonization afford new opportunities for cancer therapy [40]. While dormancy *per se* would not be a cure, maintenance of tumors in an asymptomatic state would represent a significant advance.

How could properties of KISS1 be exploited in clinical settings? Lost KISS1 or KISS1R expression in tumor cells could be replaced using gene therapy strategies. Indeed, both non-viral and viral-mediated transfer of metastasis suppressor genes has shown promise in animal models of various cancers (reviewed in Smith and Theodorescu [41]). At this time, a stand-alone therapy employing KISS1 is not especially feasible with current technologies. Nonetheless, it remains theoretically possible.

Defects in metastasis suppressor expression appear to be caused by lack of expression rather than loss-of-function mutations in the coding regions [40, 41]. In a paradigm first advanced by Patricia Steeg and colleagues for *Nm23* [42], strategies to re-express *KISS1* could represent a viable strategy. In the case of *KISS1*, upstream mediators were found to be responsible for reduced *KISS1* expression. Replacement of the upstream regulators or mimetics (i.e., a peptidic or non-peptidic agonist that is not identical to the natural ligand) could be used. This strategy is complicated because systemic administration of agents that could up-regulate KISS1 or KISS1R could affect the biology of other tissues. Given its important endocrine roles and pleiotropic distribution *in vivo*, generalized re-expression may introduce unexpected off-target effects.

The third, and in our opinion most attractive, therapeutic option is treatment with KP (mimetics). This strategy is feasible because KPs are secreted. Moreover, systemic administration of KPs could access tumor cells throughout the body, unless they are in pharmacological sanctuaries. With our previous data showing that metastases to all sites were inhibited by KISS1 expression, the utilization of KPs would be predicted to block metastases to all tissues. Fortunately, the safety of KISS1/KP administration is already proven in humans! Subcutaneous administration of KP54 did not cause any reportable side effects; however, these treatments result in a robust release of gonadotropins [43, 44], as expected based upon the endocrine roles of these molecules. Further supporting a potential therapeutic window are data showing the extremely high KP levels present in plasma during pregnancy. The levels achieved during late pregnancy are higher than the doses currently considered. As above, however, manipulation of either KISS1 or KISS1R may affect normal physiological processes.

KISS1-based treatments would be theoretically straightforward as long as the metastatic tumor cells express the KISS1R. Unfortunately, data from our laboratory introduced another challenge to the KP therapy strategy — many of the tumor cells do not express KISS1R [15]. We previously postulated that stromal cells, which differ in each tissue, might express KISS1R and that paracrine feedback to the tumor cell might be involved in the differential growth of tumor cells in various sites [14]. Like many other labs, we found KISS1R to be expressed in selected stromal populations. However, a paracrine feedback loop has yet to be established, but is the subject of ongoing studies. If the paracrine hypothesis were to prove

correct, it is possible that the relative genetic stability in stromal cells, compared with tumor cells, could be taken advantage of, since development of resistance to KISS1-based therapies would be less likely.

Although the biology and mechanism of action of KISS1-mediated metastasis suppression has been a challenge, this metastasis suppressor function offers great hope for future roles in predicting cancer outcome and, perhaps the effective treatment of cancer's most deadly attribute.

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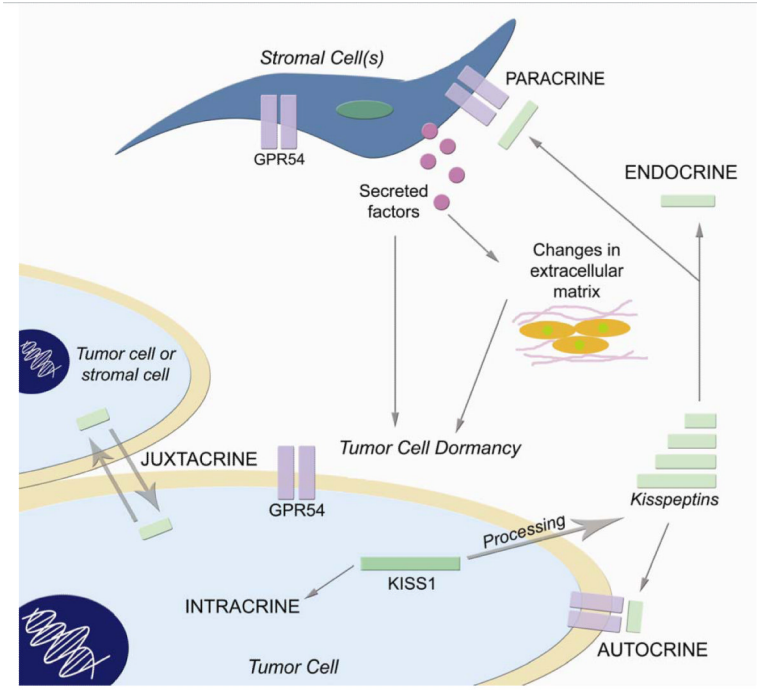

Fig. 1. Clinical studies examining KISS1, KISS1R, and KP in various cancers

The majority of reports cited in this figure provide evidence in support of KISS1 as an anti-metastatic. Studies finding negative observations or correlations regarding KISS1 are designated negative associations. Numbers in brackets correspond to the reference.

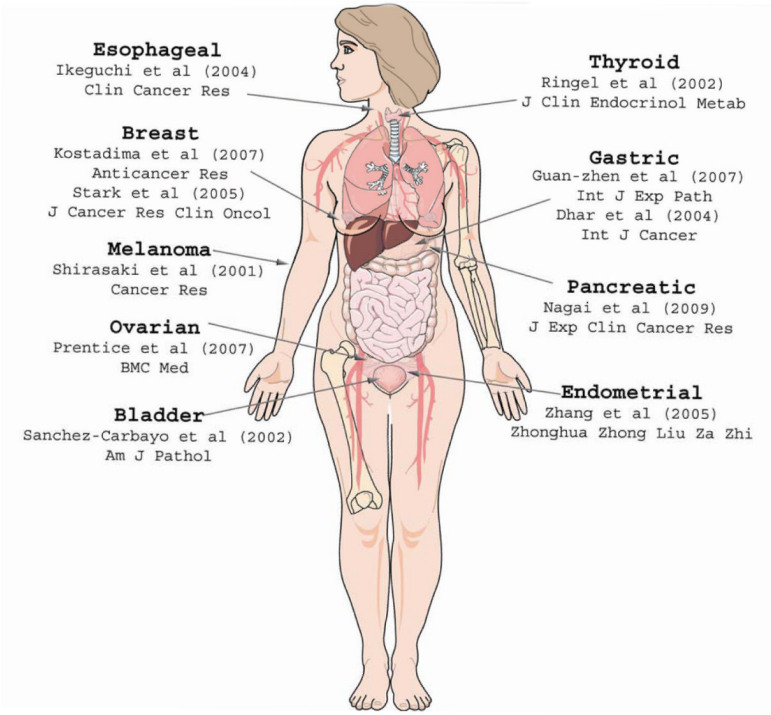

Fig. 2. Possible mechanisms by which KISS1 may cause dormancy in disseminated tumor cells at secondary sites

Intracrine signaling: (un)processed KISS1 protein may interact with other intracellular proteins to initiate anti-proliferative signals. ***Juxtacrine signaling***: unprocessed (KISS1) or processed KISS1 (KP) may be exchanged between adjacent tumor cells or stromal cells. ***Autocrine signaling***: despite the lack of KISS1R expression on many tumor cell lines that are suppressed for metastasis by engineering them to express KISS1, KP could signal through KISS1R or an as-yet unidentified alternative receptor in an autocrine fashion to induce dormancy. ***Endocrine signaling***: as potent mediators of various endocrine processes, KP may influence the endocrine system to produce dormancy-inducing factors or cause deviations from endocrine homeostasis that may bring about metastasis suppression. ***Paracrine signaling***: KP may activate or induce stromal cells to produce secreted factors that may (in)directly elicit dormancy in metastatic cells or manipulate structural changes in the surrounding extracellular milieu that may also be capable of inducing dormancy. At the time of submission, all of these mechanisms are, for the most part, still speculative. However, experimental data support non-autocrine mechanisms [15].