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The role of kisspeptin system in cancer biology

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ABSTRACT

Kisspeptins are a family of neuropeptides that are known to be critical in puberty initiation and ovulation. Apart from that kisspeptin derived peptides (KPs) are also known for their antimetastatic activities in several malignancies. Herein we report recent evidence of the role of kisspeptins in cancer biology and we examine the prospective of targeting the kisspeptin pathways leading to a better prognosis in patients with malignant diseases.

1. Introduction

Metastasis is a complex process where primary tumors disseminate to secondary organs and it is the most lethal and least effectively treated characteristic of cancer. Tumor metastases can occur hematogenously, by lymphatic spread or by dissemination across body cavities (Paget, 1889; Weiss, 1990; Welch et al., 2000; Chambers et al., 2000; Fidler, 2003; Parker and Sukumar, 2003; Gupta and Massague, 2006; Steeg, 2006; Hurst and Welch, 2011a; Valastyan and Weinberg, 2011). The completion of this process requires coordination of the activation of metastasis-promoting genetic programs and the inhibition of metastasis-suppressing programs in tumors. In addition, tumor microenvironment allowing cancer cells to escape primary sites and grow in secondary organs is also another very important factor that is associated to metastases (Leone et al., 1991; Lee et al., 1996a; Seraj et al., 2000; Muller et al., 2001; Steeg, 2003).

Cancer cells, escaping from the primary tumor site, that complete all the steps of the metastatic cascade, proliferate, and colonize ectopic tissue. A unanimous definition of metastasis is still under debate (Steeg, 2003; Eccles and Welch, 2007a). Despite that it has been advocated that the definition of a “metastasis” be limited to cells that proliferate at the secondary site, rather than just remain as single cells. Once the steps of metastasis were defined cancer research focused on defining the individual biochemical processes allowing tumor cells to migrate from the primary tumor to secondary sites, prior to the development of a therapy. Molecules involved in cellular proliferation, motility, adhesion, invasion, resistance to apoptosis, and angiogenesis were identified and extensively studied (Coussens and Werb, 2002; Folkman, 2006; Friedl et al., 2004; Hehlgans et al., 2007; Jain et al., 2006). As the biochemical basis underlying the individual steps of the metastatic cascade becomes clearer, it has become evident that genes that specifically modify metastasis exist. Since every step in the metastatic cascade is considered rate-limiting, a gene or protein that inhibits any step in the cascade will do so, regardless of the other genes or proteins expressed in a cell.

The existence of tumor suppressors and oncogenes is now accepted as dogma and is well supported by experimental and clinical data. Genes involved in the promotion of metastasis at distinct stages of the disease are also well accepted. However, the hypothesis of the existence of molecules that inhibit the process of metastasis without preventing primary tumor growth was initially met with much skepticism. Since that time, multiple labs, using many different model systems, have demonstrated the existence of a multitude of proteins, coding and noncoding genes that significantly reduce metastasis without preventing primary tumor formation. It is now understood that metastasis, the ultimate step in tumor progression, involves many pathological processes; and, just as there are several hallmarks of primary tumor formation (Hanahan and Weinberg, 2000), there also exist hallmarks of metastatic cells. Inhibition of a single step in the metastatic cascade leads to suppression of metastasis (Bruns et al., 2000; Eccles and Welch, 2007b).

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2. Metastasis suppressors

There are 23 known metastasis suppressor genes that satisfy the definition of metastasis suppressors in vivo. Early metastasis suppressors were identified by comparing loss of heterozygosity (LOH) and karyotypic abnormalities in human cancers. Once these chromosomal abnormalities were defined, microcell-mediated transfer (MMCT) of individual chromosomes thought to encode one or more metastasis suppressors were introduced into cells. Using this method, chromosomes 2, 7, 8, 10, 11, 12, 13, 16, 17, and 20 have been demonstrated to suppress metastasis in multiple tumor cell types.

Since tumor cells encounter numerous different microenvironments from the primary site to the different metastatic foci, it seems obvious that the cell surface would be a key site for critical molecules involved in cancer metastasis. Three lines of evidence have been used to support the involvement of cell-surface molecules in the process of metastasis. The first is that enzymatic modification of cell-surface components can alter adhesion, survival in the circulation, and arrest at secondary sites (Hagmar and Norrby, 1973; Welch et al., 1994ba; Welch, 1997). The second has to do with biosynthetic modification of surface glycoproteins and glycolipids. Alterations in glycosylation appear to not only directly impact cell growth and survival but also facilitate tumor-induced immunomodulation and eventual metastasis (Stowell et al., 2015; Irimura et al., 1981; Shaikh et al., 2008). The third involves the transfer of cell-surface molecules from metastatic to nonmetastatic cells with a corresponding enhancement of metastatic efficiency (Legrue, 1982; Poste and Nicolson, 1980; Poste et al., 1980).

As previously mentioned, metastasis is clearly determined, to a sizable extent, by tumor-host interactions, that is, the microenvironment participates in the induction and selective proliferation of malignant cells. Host physiology can foster or reject neoplastic cells. It stands to reason, then, that some metastasis suppressors might work because they render the ectopic microenvironment less hospitable. The most obvious example of cell-cell signaling relates to inflammatory cells that infiltrate the tissue adjoining a tumor or disseminate cells in response to secreted cytokines, chemokines, or hormones. The immune populations can produce pro- or antitumor molecules that alter the capacity of tumor cells to migrate, invade, or survive (Fridlender et al., 2009; Mantovani et al., 2006). However, it is imperative that other stromal populations not be ignored in the interplay.

The milieu surrounding a tumor cell undoubtedly explains metastatic organotropism. Yet, despite more than a century of attempts, clear-cut biochemical explanations still do not exist. Nonetheless, some clues may be forthcoming from understanding the mechanisms of action of extracellular metastasis suppressors.

High-frequency deletions or rearrangements involving chromosome 6q in late-stage melanoma prompted introduction of full-length chromosome 6 into the human metastatic melanoma cell line C8161 by Microcell Mediated chromosome Transfer (MMCT) (Welch et al., 1994bb). KiSS-1 gene was subsequently identified using subtractive hybridization between metastatic and nonmetastatic cell line variants (Lee and Welch, 1997a; Lee et al., 1996b; Makri et al., 2008). Transfection of full-length KiSS-1 cDNA into melanoma (Lee and Welch, 1997a; Lee et al., 1996b; Makri et al., 2008), breast carcinoma (Lee and Welch, 1997b), ovarian (Jiang et al., 2005a), and pancreatic adenocarcinoma (McNally et al., 2010a) cell lines suppressed metastasis.

KiSS-1 gene mapped to the long arm of chromosome 1. Using cDNA microarrays and chromosome 6 MMCT donors with defined deletions on the long arm of chromosome 6, Goldberg et al. found that KiSS-1 was regulated by TXNIP and CRSP3 (Goldberg et al., 2003). The KiSS-1 gene encodes a 154 amino acid protein but full-length KiSS-1 is rarely detectable since the nascent protein is proteolytically processed into numerous polypeptides, termed kisspeptins (Kotani et al., 2001a; Ohtaki et al., 2001a). An internal 54-amino acid polypeptide, termed kisspeptin (KP)-54 or metastin, binds to the KiSS-1 receptor (KiSS1R) (Kotani et al., 2001a; Ohtaki et al., 2001a; Muir et al., 2001a). KiSS-1R expression is highest in placenta, pituitary gland, pancreas, brain, and spinal cord (Kotani et al., 2001a; Muir et al., 2001a), while KiSS-1 expression is more restricted, located primarily in the placenta, pancreas, kidney, and the arcuate nucleus of the hypothalamus (Lee et al., 1996b; Ohtaki et al., 2001a; Muir et al., 2001a).

Recently, emerging laboratory findings suggest that *KiSS-1* is transcriptionally controlled by TCF21 that is in turn regulated by miR-21. Therefore, there is an urgent need for further study of how miRNA directly or indirectly influences *KiSS-1* at the posttranscriptional level. There is also a lack of evidence regarding natural agents that mediate upregulation or downregulation of *KiSS-1*. KiSS-1 protein is thought to be cleaved by furins or prohormone convertases based upon the amino acids at the ends of the KP. The preponderance of primary literature on KiSS-1 and KiSS-1R relates to the involvement of these molecules to their potential physiological role in pubertal development (Colledge, 2009; Gianetti and Seminara, 2008; Roa et al., 2008; Tena-Sempere, 2008). Recent evidence suggests the involvement of kispeptins/KiSS-1R system in the repression of trophoblast invasion into the uterine wall, a process of crucial importance for normal fetal and placental development (Hiden et al., 2007). Mechanistically, trophoblast invasion resembles the invasion of tumour cells.

Clinical reports from a variety of tumor types generally support a positive correlation between KiSS-1 expression, and metastasis-free survival and other progression-associated phenotypes (Hurst and Welch, 2011b). The key exception has been a positive correlation with hepatocellular carcinoma progression (Ikeguchi et al., 2003a; Schmid et al., 2007a), but a recent immunohistochemical study suggests that KiSS-1 might be significantly inversely associated with stage and intrahepatic metastasis from HCC (Shengbing et al., 2009a). As described above, many of these studies measured only mRNA expression using 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 KiSS-1 or KiSS-1R. mRNA measurements were required because of difficulties in generating specific antibodies.

Surprisingly, based upon the nature of the experimental studies showing KiSS-1 functionality as a metastasis suppressor, many tumor cells suppressed by KiSS-1 reexpression do not express KiSS-1R (Shengbing et al., 2009a). This has led us to postulate a paracrine feedback loop in which KPs secreted by tumor cells acts upon one or more stromal populations which, in turn, respond with growth-inhibitory factors (Beck and Welch, 2010; Nash and Welch, 2006).

3. The KiSS-1/KiSS-1R system

Kisspeptins are a family of structurally related peptides, encoded by the *KISS-1/KiSS-1* gene, that act through binding and subsequent activation of the G protein-coupled receptor KiSS-1R (Lee and Welch, 1997a). The initial finding was followed by the cloning and chromosomal localization of human *KISS-1* gene (West et al., 1998) and the characterization of the antimetastatic potential of the *KISS-1* transcript (Lee and Welch, 1997a; Lee and Welch, 1997b). Full characterization of the peptide products of the *KISS-1* was obtained in 2001 (Kotani et al., 2001b; Muir et al., 2001b; Ohtaki et al., 2001b). Based on structural similarities and its common origin as KISS-1- derived peptides (KPs), the term *kisspeptins* was given to define this family (Kotani et al., 2001b), replacing the initial terminology of metastin.

KPs are a number of structurally-related amidated peptides, which are derived from the differential proteolytic processing of a common precursor of 145 amino acids encoded by the *KISS1* gene (Fukusumi et al., 2006)

KP posseses, a putative 19-amino acid signal sequence, two potential dibasic cleavage sites (at amino acids 57 and 67), and one site for terminal cleavage and amidation (at amino acids 121–124) (Lee and Welch, 1997b; Kotani et al., 2001b; Muir et al., 2001b), which generates the biologically active kisspeptins (Fig. 1). Proteolysis of prepro-

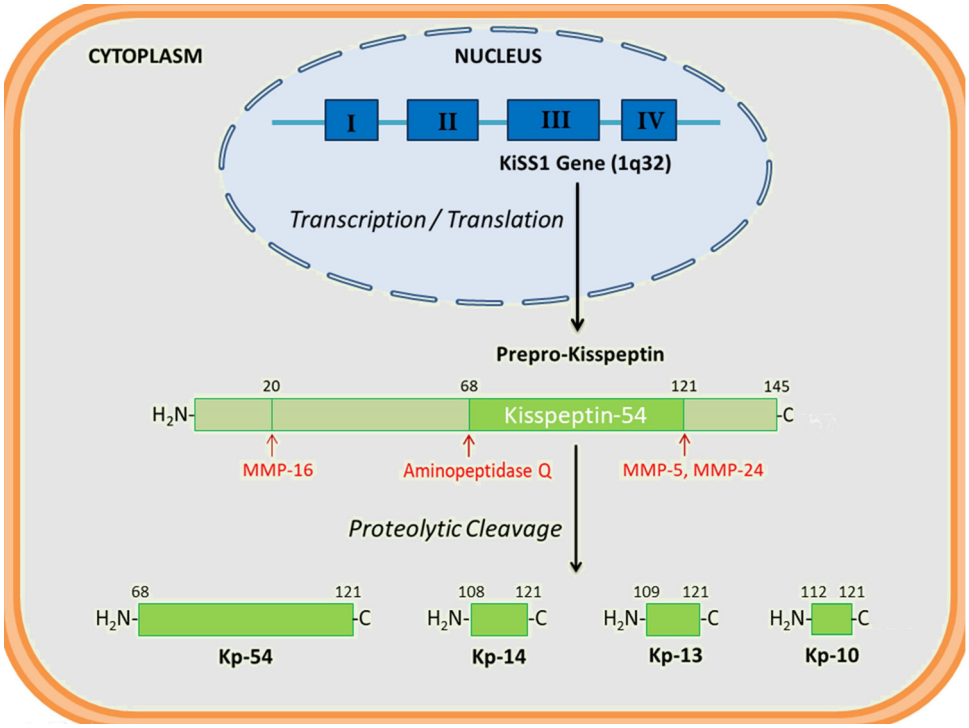

Fig. 1. Kisppeptin processing. KiSS-1 protein is thought to be cleaved by furins or prohormone convertases based upon the aa sequence of the pre pro molecule, leading to the formation of several diferent size kisspeptins all possessing similar C terminal.

kisspeptin, gives rise to a 54-amino acid peptide (KP-54 that is considered to be the major product of the *KISS-1* gene), initially termed metastin because of its capacity to inhibit tumor metastasis. Other peptide fragments of the kisspeptin precursor are: kisspeptin-14, kisspeptin-13, and kisspeptin-10 (Lee and Welch, 1997b; Ohtaki et al., 2001b). These fragments share the C-terminal region of the kisspeptin-54 molecule, where they harbor an Arg-Phe-NH2 motif which is characteristic of the RF-amide peptide family.

This family is composed by a number of neuroactive peptides, which in mammals include also the neuropeptides FF and AF, prolactin- releasing peptide (PrRP), 26/43RFa (also termed QRFP43), and RF-related peptides (RFRP-1 and RFRP-3) (Fukusumi et al., 2006; Bilban et al., 2004; Botia et al., 2011; Clarke et al., 2009). Similarly to kisspeptins, RFRPs, 26RFa, and PrRP have been shown to modulate gonadotropin secretion in various mammalian species (Fukusumi et al., 2006; Bilban et al., 2004; Botia et al., 2011; Clarke et al., 2009; Navarro et al., 2006; Sun et al., 2005).

The KiSS-1 receptor (KiSS-1R, or GPR54) appears to be critical for metastasis suppression in some tumor cells. KiSS-1R is a G-protein-coupled receptor that is ubiquitously expressed at low levels. Despite that KiSS-1R is abundantly present in specialized neurons located within the hypothalamus and pituitary, where it is responsible for regulating pubertal development in the hypothalamic-pituitary-gonadal access (Beck and Welch, 2010; Ohtaki et al., 2001a; Hameed and Dhillo, 2010; Oakley et al., 2009). KiSS-1R was subsequently shown to bind internal fragments derived from the KiSS-1 metastasis suppressor protein, whereas overexpression of KiSS-1R in B16 melanoma cells diminished metastasis when mice were treated with KiSS-1-derived polypeptides (Ohtaki et al., 2001a).

In studies attempting to characterize the *KiSS-1*-derived peptide claiming that its secretion is required for metastasis suppression, a surprising finding was that none of the cell lines that were suppressed for metastasis following transfection and re-expression of KiSS-1 possessed detectable levels of the receptor. That indicates that an autocrine loop was not responsible in the majority of cases. Therefore it was suggested that paracrine signaling to surrounding stroma might be responsible for the metastasis suppressing effects of KiSS-1 (Beck and Welch, 2010; Nash and Welch, 2006). Despite this fact a number of studies suggest that primary cultures derived from skin and lung differentially expressed KiSS-1R.

4. KiSS-1/KiSS-1R signalling

Dissection of the signalling pathways operated by KiSS-1R was obtained using different heterologous cell models (Kotani et al., 2001b; Muir et al., 2001b; Ohtaki et al., 2001b). KiSS-1R is a seven transmembrane domain, Gq/11-coupled receptor. Despite its similarity with galanin receptors, KiSS-1R was shown to be devoid of detectable binding affinity to galanin ligands, (Hameed and Dhillo, 2010). Its activation leads to an increase in intracellular Ca^{2+} ion levels in a pertussis toxin-independent manner, without detectable changes in intracellular cAMP levels, suggesting the lack of association with Gs and/or Gi/o proteins (Kotani et al., 2001b; Ohtaki et al., 2001b). Binding of the ligand to KiSS-1R leads to the activation of phospholipase C (PLC), and to the subsequent stimulation of the hydrolysis of phosphatidylinositol bisphosphate (PIP2) into inositol 1, 4, 5-trisphosphate (IP3), PLC cleavage of PIP_2 to IP_3 and DAG initiates intracellular calcium release. Such an increase in phosphatidylinositol turnover has been demonstrated for both human and mouse KiSS-1R (Kotani et al., 2001b; Stafford et al., 2002). In addition, the rise of diacylglycerol (DAG) formation, leads to protein kinase C (PKC) activation (Ringel et al., 2002a). Activated PKC is thought to cause phosphorylation of mitogen-activated protein kinases (MAPKs), such as ERK1/2 and p38, which have been also involved in this signaling cascade (Kotani et al., 2001b). Activation of KiSS-1R has been also reported to be involved in the increase of arachidonic acid release in CHO-K1 cells stably expressing this receptor (Kotani et al., 2001b).

The above signaling features are the basis for the biological actions of KPs, such as hormone secretion and neuroendocrine function and the control of cell proliferation and migration. The activation of KiSS-1R leads to phosphorylation of different MAPKs, which might contribute to the antimetastatic and/or antiproliferative effects of KPs (Castano et al.,

2009). However, the subset of intracellular kinases activated upon kisspeptin stimulation appears to be, at least partially, dependent on the cellular context. Studies in CHO-K1 cells stably expressing KiSS-1R, demonstrated sustained phosphorylation of ERK1 and ERK2, together with weaker stimulation of p38 MAPK phosphorylation following exposure to kisspeptin (Kotani et al., 2001b). In contrast, in anaplastic thyroid cancer cells that endogenously express KiSS-1R, kisspeptin induced phosphorylation of ERK1/2 but not of p38 MAPK or PKB/Akt (Ringel et al., 2002a). Similarly, studies in pancreatic cancer cell lines revealed that KP stimulated ERK1 phosphorylation in two different cell lines (AsPC-1 and PANC-1 cells), but it only activated p38 in PANC-1 cells (Ringel et al., 2002a).

KPs have been shown to cause phosphorylation of focal adhesion kinase and paxillin, two proteins involved in the cell to cell and cell to matrix adhesion, in mouse melanoma cells stably expressing KiSS-1R, a phenomenon which may contribute to their antimetastatic functions (Muir et al., 2001b). KPs can also interact with specific chemokine signalling routes, such as that of the receptor CXCR4. CXCR4 is a chemokine receptor that was found to be over-expressed in many different human malignant tumors. Stromal derived factor-1 (SDF-1 and CXCL12), is the ligand of CXCR4, It was shown that neutralization of SDF-1 in a mouse xenograft model significantly impairs metastasis. KP-CXCR interaction may also contribute to their function in prevention of tumor spread. kisspeptin partially inhibits CXCR4 signaling, probably by blocking the ability of SDF-1/CXCL12 (ligand of CXCR4) to stimulate (Sousa and Espreafico, 2008).

On the other hand, *KISS-1* overexpression interferes with NFκB signaling in HT-1080 cells (Yan et al., 2001a). The resulting reduction of NFκB binding to the matrix metalloproteinase (MMP)-9 promoter and the subsequent decrease of MMP-9 expression may contribute to the prevention of tumor spread (Yan et al., 2001a). Finally, kisspeptins appear to induce apoptosis in certain cell types (Becker et al., 2005; Lee and Welch, 1997b; Navenot et al., 2009a; Navenot et al., 2009b), (Fig. 2) since recent studies suggested that the COOH-terminal of the KiSS-1R is able to interact with the catalytic subunit of the ubiquitous Ser/Thr protein phosphatase PP2A (Pampillo et al., 2009). While the functional relevance of this interaction in terms of signaling is still unclear, it has been proposed that the KiSS-1R/PP2A complex may lead to the dephosphorylation of Akt, explaining some of the antimetastatic function of KPs (Navenot et al., 2009b). KISS-1R signalling is also modulated by arrestins (Pampillo et al., 2009) (Fig. 2).

Nonetheless, the importance of the second intracellular loop for proper KISS-1R signaling had been previously unveiled by the observation that a point L148S mutation in this region causes IHH in humans (Wacker et al., 2008), and severely blunts the ability of KISS-1R to induce PI hydrolysis and to activate ERK1/2 upon Kp-10 stimulation in vitro (Wacker et al., 2008). Indeed, the second intracellular loop was proposed as the site for KiSS-1R binding to Gαq (Wacker et al., 2008).

Summarizing the actions of KPs in cancer, it has been manifested that KP seems to inhibit metastasis of cancer cells in most types of cancer. In fact, KP is low or undetectable in most carcinomas with high metastatic ability, whereas high expression is observed in carcinomas with low metastatic capacity. However, in some cancer types its function is ambiguous. KP antimetastatic actions are associated to the inhibition of some steps in the metastatic cascade such as motility, invasiveness, angiogenesis and proliferation. KISS-1 induces the degradation of NF-κB which interacts with the promoter of matrix metalloproteinase-9 (MMP-9) an enzyme involved in the breakdown of extracellular matrix by degrading type IV and V collagens. In this way, it contributes to reduction of MMP-9 expression which in turn inhibits the ability of tumor cells to form metastases (Ohtaki et al., 2001a; Yan et al., 2001b; Nash et al., 2007). Moreover, KP negatively regulates CXCR4 which is possibly related to motility of cancer cells and thus to metastasis. CXCR4 and its ligand SDF-1 bring about calcium ions mobilization, activation of the MAPK and the Akt pathway. GPR54 blocks calcium ions mobilization and Akt phosphorylation mediated through CXCR4 leading to apoptosis. Consequently, KP inhibits the epithelial-mesenchymal transition which is strongly associated with cancer progression and metastatic activity (Song and Zhao, 2015; Gründker et al., 2015). KISS-1 also inhibits angiogenesis through the inhibition of VEGF expression and so the tumor growth is blocked as was presented in prostate cancer xenografts (Cho et al., 2009a).

5. KiSS-1 and melanoma

KiSS-1 is correlated with both skin and uveal melanoma progression

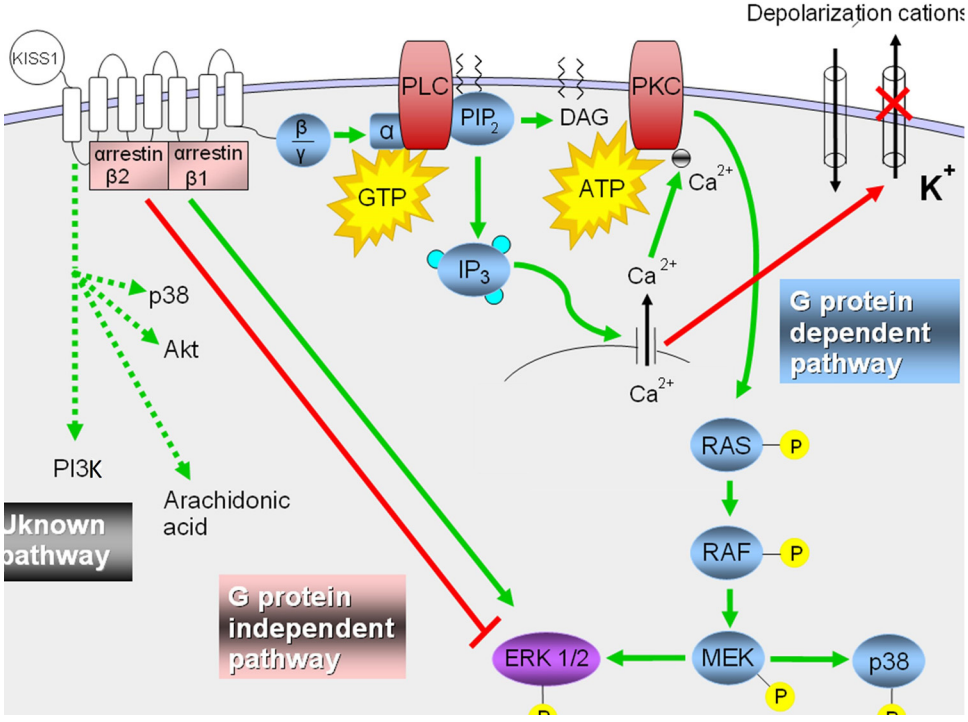

Fig. 2. Schemetic representation of the KPs anticancer mode of action. Activated KiSS-1R recruited arrestin-1 and-2 to the plasma membrane, via interactions with sequences of the second intracellular loop and the cytoplasmic tail, arrestin-2 is required for proper KiSS-1R signalling to ERK1/2, following Kp-10 stimulation. In contrast, arrestin-1 appears to inhibit ERK1/2 signalling. These findings suggest additional, G protein independent signalling pathways for KiSS-1R. Finally recent evidence suggest the involvemt of kisspeptin in a pathway that does not involve arrestins, leading to the inhibition of Akt and the activation of mitogen activated protein kinases (MAPKs) p38 and to the arachidonic acid release.

and metastastic potential. In skin melanoma, loss of *KiSS-1* expression is strongly associated with increase of metastatic ability. KiSS-1 suppresses the potential of melanoma cancer cells to metastasize and so it may be useful in enhancing the staging of melanoma (Lee et al., 1996c; Cvetković et al., 2013; Cho et al., 2009b). In uveal melanoma *KiSS-1* expression was strongly connected with patient survival rate and cancer staging. As a result, it seems to be promising prognostic marker for survival and distinction between metastatic and non-metastatic melanoma cells. KiSS-1 significantly reduces the MMP-9 expression by decreasing the NF-κB binding to the promoter of MMP-9 and in this way inhibits the invasion and motility of cancer cells (Martins et al., 2008).

6. KiSS-1 and breast cancer

The role of KP as a metastasis suppressor has also been examined in breast cancer cells (Ji et al., 2013; Ulasov et al., 2012; Teng et al., 2011; Zajac et al., 2011; Xie et al., 2012; Cho et al., 2011). The evidence that rised though is very controversial. A number of studies suggest that kisspeptin mRNA is significantly low in high grade metastatic breast cancer cells (Cvetković et al., 2013; Masui et al., 2004). *KiSS-1* expression has been found to be higher in primary breast cancer cells when compared with brain metastases (Cvetković et al., 2013; Ulasov et al., 2012). In addition, a slight rise of *KiSS-1* mRNA can be observed in low grade breast cancer tissues. A complete loss of KiSS-1 was observed in some cases of breast cancer metastases such as in the paraffin-embedded stage 1 or 2 lymph node-positive breast carcinomas (Ji et al., 2013). Furthermore it has been suggested that KiSS-1 may also be able to deter proliferation of breast cancer tissues (Mooez et al., 2011). This evidence concurs with the notion that kisspeptin is an anti metastatic protein where its down regulation or loss of expression, may add to the formation of metastases.

Mechanistically, kisspeptins' antimetastatic action is through blocking certain oncogenes such as the WASF3 (Cvetković et al., 2013), WASF3 levels are higher in more aggressive breast carcinomas (Teng et al., 2011). Absence of WASF3 in cancer cells is associated with loss of their ability to multiply and invade other tissues (Teng et al., 2011; Teng et al., 2014). When silencing WASF3 in breast cancer cells, the upregulation of *KiSS-1* mRNA is evident (Teng et al., 2011). An upregulation of WASF3 causes a drop on kisspeptin levels (Teng et al., 2011; Xie et al., 2012). When silencing KiSS-1 though, MMP-9, a type 4 collagenase, that correlates with the decomposition of the basement membrane activity, rises and no change in WASF3 levels is evident. As a consequence, it is believed that a loss of KiSS-1 in breast cancer cells might be associated with tumor growth and poor patient prognosis (Ji et al., 2013; Ulasov et al., 2012; Teng et al., 2011; Zajac et al., 2011; Xie et al., 2012; Cho et al., 2011).

The anti-metastatic role of kisspeptin in breast cancer is questioned, since some human breast cancer cell lines, although they present high KP expression levels, they are highly metastatic (Cvetković et al., 2013; Martin et al., 2005; Zajac et al., 2011).

The expression of KiSS-1R in homozygotic tumor cells increased the activity of RhoA GTPases when compared to heterozygotic cells (Zajac et al., 2011; Cho et al., 2011). RhoA GTPases are known to enhance tumor growth and metastasis (Zajac et al., 2011), therefore KiSS-1/KiSS-1R signaling may be able to regulate the initiation, progression and proliferation of breast cancer cells. Additionally introduction of kisspeptin 10 resulted in an increase in MMP-9 activity and it promoted the motility of breast cancer cells by inducing cytoskeletal changes (Zajac et al., 2011).

Triple-negative breast cancer (TNBC) lacks the expression of estrogen receptor α, progesterone receptor and human epidermal growth factor receptor 2 (HER2) and is the most aggressive type of breast cancer. KiSS-1 and KiSS-1R mRNA and KiSS-1R protein are upregulated in TNBC tumors, compared to normal breast tissue. KiSS-1R signaling promotes drug resistance by increasing the expression of efflux drug transporter, breast cancer resistance protein (BCRP) and by inducing the activity and transcription of the receptor tyrosine kinase, AXL. BCRP and AXL transcripts are elevated in TNBC tumors, compared to normal breast, and TNBC tumors expressing KiSS-1R also express AXL and BCRP. However, in TNBC, KiSS-1R promotes tumor invasion. In conclusion, kisspeptin might be directly associated with breast cancer aggressiveness and might be pro-invasive in breast cancer tumors (Cvetković et al., 2013; Martin et al., 2005; Ji et al., 2013; Cho et al., 2011).

7. KiSS-1 and pancreatic cancer

Recent evidence suggests that healthy pancreatic cells express both KiSS-1 and KiSS-1R (Wang et al., 2016; Nagai et al., 2009). A decrease though in the expression of kisspeptin has been observed in human pancreatic cancer cells (Wacker et al., 2008; Yan et al., 2001b; Nash et al., 2007; Song and Zhao, 2015), suggesting that the most lethal aspect of the disease can be predicted and maybe prevented by KiSS-1 (Wang et al., 2016; McNally et al., 2010b; Nagai et al., 2009). This hypothesis is fortified by the fact that *KISS-1* overexpression was able to suppress pulmonary and hepatic metastasis of pancreatic cancer cells in mice (McNally et al., 2010b). KiSS-1 overexpression experiments also used to present evidence of the association of KiSS-1 with a reduction in the invasive and migratory ability of pancreatic cancer cells (Wang et al., 2016), without affecting their proliferation rate (Wacker et al., 2008). In human studies it was determined that tumors with a loss of KISS-1 and/or KiSS-1R are significantly larger than those who express both peptides (Liang and Yang, 2007) whereas pancreatic cancer patients with tumors that expressed high levels of kisspeptin presented significantly higher survival rate and a better prognosis (Nagai et al., 2009). KiSS-1 role as a metastasis inhibitor was fortified by the fact that the majority of pancreatic tumors that are related to metastases present chromosomal abnormalities that are associated with the position of KiSS-1 gene (Chromosome 6q) (Ji et al., 2013; Wang et al., 2016; McNally et al., 2010b; Nagai et al., 2009; Liang and Yang, 2007).

8. KiSS-1 and endometrial cancer

KiSS-1R is expressed in endometrial cancer cells and in eutopic and ectopic endometrium of women suffering from endometriosis and its presence has been associated with type and grade (Martins et al., 2008; Kang et al., 2011; Makri et al., 2012). Aggressive endometrial tumors, present low KiSS-1R levels. *KiSS-1* expression is not relevant to the prognosis in this case since it has been suggested that there is no significant difference between healthy and cancer tissue (Gründker et al., 2015). Lack of KiSS-1R expression in endometrial tumors was associated with poor prognosis whereas patients with tumors that over expressed KiSS-1R presented a better prognosis. When exposed to exogenous kisspeptin-10 in vitro, cancer cells lacking the KiSS-1R did not seem to be affected. Conversely, a decrease in the proliferation and the metastatic ability was observed in vitro in KiSS-1R positive tumor cells. The size of the tumors showed no significant alterations. A recent study on a mouse model, revealed that exogenous kisspeptin-10 can inhibit lymph node metastasis from endometrial cancer lacking the KiSS-1R (Ji et al., 2013) suggesting that the mode of action of KiSS-1 may be generated through a different receptor. Despite that the obtained data suggests that KiSS-1/KiSS-1R signaling may be able to inhibit metastasis in endometrial cancer and improve the poor prognosis for patients (Ji et al., 2013; Kang et al., 2011).

9. KiSS-1 and ovarian cancer

In ovarian cancer the role of KiSS-1 remains a mystery since there is some contravercy in respect to its anti cancer activities. Stage 1 ovarian cancer patients presented increased plasma KP concentration when compared with stage 2, 3 or 4 patients (Prentice et al., 2007). In another immunohistochemical study it has been suggested that low KP

expression in ovarian cancirnoma is associated with poor diagnosis (Ji et al., 2013). In contrast, significantly higher expression of KP and its receptor correlates with inhibition of cell migration (Wiiger et al., 2014), sensitization of cancer cells to chemotherapy (Cho et al., 2009a) and suppression of metastases in ovarian cancer (Zhang et al., 2005; Prentice et al., 2007; Jiang et al., 2005b; Jayasena et al., 2012; Gao et al., 2007). Other studies demonstrated that ovarian cancer cells treated with MOC31PE, an immunotoxin that binds to EpCAM, an antigen expressed in epithelial ovarian cancer cells, overexpress KiSS-1 and KiSS-1R (Wiiger et al., 2014). In addition, the overexpression of kisspeptin in ovarian carcinoma suppresses the expression of MMP-9 and NF-κB, factors linked to cancer formation, growth and migration (Ji et al., 2013). It is likely, that the presence of KiSS-1 and KiSS-1R in the tumor are independent markers for a better prognosis. Furthermore the role of KP as a metastasis suppressor has been indicated using an in vivo mouse model (Jiang et al., 2005b). According to this it has been suggested that KiSS-1 and its receptor, function as metastasis suppressors improving the prognosis of ovarian cancer patients (Makri et al., 2012; Jayasena et al., 2012; Gao et al., 2007).

10. KiSS-1 and bladder cancer

High expression of *KiSS-1* is observed in the healthy urothelial epithelium in contrast to bladder tumor cells where kisspeptin expression levels are low or even undetectable (Liang and Yang, 2007; Zhang et al., 2014). It has been proposed that the major reason for *KiSS-1* gene downregulation in several malignancies of the urothelial epithelium, is the alteration in kispeptin's epigenetic signature due to hypermethylation (Takeda et al., 2012; Sanchez-Carbayo et al., 2003). Consequently, the cancer cell is more likely to metastasize leading to poor prognosis.

11. KiSS-1 and gastric cancer

Recent evidence suggests that KiSS-1 inhibits the proliferation and invasion of stomach cancer cells both in vitro and in vivo. This is mediated through the induction of the p38 MAPK signaling pathway which leads to downregulation of MMP-9 and thus to suppression of motility, chemotaxis and invasion. Low KiSS-1 expression levels are connected with frequent vascular invasion, distant metastases and tumor recurrence. Overexpression of the KiSS-1 inhibits cell growth, proliferation and invasion in gastric carcinoma cells, proving the antimetastatic potential of kisspeptin. It has also been suggested that tumor KiSS-1 expression may be used as a prognostic marker to predict survival (Ergen et al., 2012; Li et al., 2012; Lee and Kim, 2009; Kostakis et al., 2018). Furthermore the fact that plasma KP54 levels are increased in patients with gastric cancer at their initial diagnosis suggests that KP54 may have a diagnostic value for gastric cancer (Ergen et al., 2012).

12. KiSS-1 and prostate cancer

KiSS-1 expression levels are significantly higher in benign prostate tissues, in comparison to primary and metastatic prostate carcinomas. Thus it has been suggested that KiSS-1 expression in the tumor may serve as an important prostate cancer marker that can be used to monitor the conversion of a benign condition to malignancy. The KP levels in the circulation are not elevated in prostate cancer and there is no correlation between serum PSA and plasma KP levels (Cho et al., 2009b; Wang et al., 2012; Curtis et al., 2010).

13. KiSS-1 and osteosarcoma

Recent evidence in the role of KiSS-1 as a metastasis suppressor in osteosarcoma patients were initiated after noticing that the more distant the metastasis, the lower the expression of KP in the deceased cells (Wang et al., 2011). Furthermore, the expression of KiSS-1 mRNA was decreased as the invasive ability of the cells increased (Wang et al., 2011). Osteosarcoma cells transfected with KiSS-1, were found not only to have lost part of their ability to invade other tissues (Curtis et al., 2010) but were also found to have suppressed their ability to multiply (Wang et al., 2011). Recently it has been suggested that the cells use the increased expression of KiSS-1 as a defend mechanism (Wang et al., 2011). Last, but not least, the overexpression may be linked to an imbalance of sex steroid (Wang et al., 2011). Oteosarcoma is most frequent in puberty when steroid hormones levels present sudden changes of great magnitude (Wang et al., 2011).

14. KiSS-1 and non-small cell lung carcinoma (NSCLC)

Several studies have investigated the clinical significance of kisspeptin expression in NSCLC with variable results. Karapanagiotou et al reported lack of significant difference -with regard to the serum kisspeptin levels- between NSCLC patients and healthy controls, as well as between early and advanced-stage NSCLC patients (Jakobsen and Sorensen, 2012; Stella et al., 2013; Jemal et al., 2011; Karapanagiotou et al., 2011). In contrast to these findings, Zheng et al concluded that KiSS-1 expression may be significantly lower in advanced-stage NSCLC (III-IV) as compared to early-stage disease (I-II), and may be negatively associated with the presence of lymph node metastasis (Zheng et al., 2010). Furthermore, Sun et al, suggested KiSS-1 protein levels tend to be higher in normal than cancer tissues, while the expression of KiSS-1 and KiSS-1R is reduced during progression from stage IIIB to stage IV NSCLC (Sun and Xu, 2013). Similarly to several previous neoplasms it seems that KiSS-1 levels in the tumor is an important prognostic marker where elevated KP levels are associated with better prognosis.

15. KiSS-1 and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the commonest primary malignancy of the liver. Few previous studies have studied the clinical relevance of KiSS-1 expression in HCC. Ikeguchi et al (Ikeguchi et al., 2003b) reported similar levels of KiSS-1 mRNA in normal and cancerous livers, but also a statistically significant association between overexpression of *KiSS-1* gene and tumor progression in HCC, suggesting that KISS-1 expression may promote acquisition of a more aggressive tumour phenotype. Schmid et al (Schmid et al., 2007b) found that high KiSS-1 expression may represent an independent predictor of disease-free and overall survival in HCC patients. Shengbing et al (Shengbing et al., 2009b) reported downregulation of *KiSS-1* gene in HCC and a potential involvement of this gene in regulation of the transcription of MMP-9 transcription, a matrix metalloproteinase with a crucial role in cell motility and metastasis, and further suggested that KiSS-1 expression may be used to predict the development of intrahepatic and distant metastasis.

16. KiSS-1 and esophageal cancer

Previous data on kisspeptin expression in esophageal cancer are extremely limited. Ikeguchi et al (Ikeguchi et al., 2004) found similar mRNA levels of kisspeptin and kisspeptin receptor in esophageal squamous cell carcinomas (ESCC) and non-cancerous esophageal tissue. Loss of KiSS-1 and KiSS-1R mRNA was nevertheless associated with the occurrence of lymph node metastasis and a reduced survival among ESCC patients, independently of the depth of tumor invasion; more specifically, disease-specific 5-year survival rates were significantly higher among ESCC patients with preserved expression of both KiSS-1 and KiSS-1R mRNA mRNA levels in the tumor tissue as compared to those with loss of KiSS-1 or KiSS-1R mRNA mRNA as well as those with loss of kisspeptin and kisspeptin receptor mRNA (68% versus 31 and 32%, respectively). These findings suggest that loss of *KiSS-1* and *KiSS-1R mRNA* gene expression may represent a clinically valuable

Table 1
Effect of KiSS-1/KiSS1R expression in cancerous tissues and in patient prognosis.

Malignancy	KiSS1 mRNA	KiSS1R mRNA	Effect	Prognosis	References
Melanoma	↑		-Tumor suppressor -Induces dormancy state in melanoma cells	Better	(Martins et al., 2008; Lee et al., 1996c; Cvetković et al., 2013; 93)
	↓		Metastases occurrence	Bad	
Breast Cancer	↑	↑	-Tumor suppressor -Inhibits EMT -Induces -metastasis -Invasion -drug resistance in triple negative tumors	Contraversial	(Cvetković et al., 2013; Cho et al., 2009b; Mooez et al., 2011; Martin et al., 2005; Ji et al., 2013; Ulasov et al., 2012; Teng et al., 2011; Zajac et al., 2011; Xie et al., 2012; Cho et al., 2011)
	↓	↓		Bad	
Pancreatic Cancer	↑		Metastasis inhibition	Better	(Yan et al., 2001b; Nash et al., 2007; Song and Zhao, 2015; Wang et al., 2016; McNally et al., 2010b; Nagai et al., 2009; Liang and Yang, 2007)
	↓	↑	Metastases occurrence	Bad	
Endometrial Cancer	↑		NS	N.S	(Gründker et al., 2015; Ji et al., 2013; Kang et al., 2011)
	↓	↓	NS	N.S Tumors with: -High KiSS1R good prognosis. -Low KiSS1R bad prognosis.	
Ovarian Cancer	↑		-inhibition of cell migration -sensitization of cancer cells to -chemotherapy -suppression of Metastases -suppresses the expression of NF-κB and MMP- 9 induces: -metastases -tumor growth	Contraversial	(Cho et al., 2009a; Makri et al., 2012; Prentice et al., 2007; Wiiger et al., 2014; Zhang et al., 2005; Jiang et al., 2005bJayasena et al., 2012; Gao et al., 2007)
	↓				
Bladder Cancer	↑		-Tumor suppressor	Better	(Zhang et al., 2014; Takeda et al., 2012; Sanchez-Carbayo et al., 2003)
	↓	↑		Poor	
Gastric Cancer	↑		-Tumor suppressor -inhibits cell growth, proliferation and invasion	Better	(Ergen et al., 2012; Li et al., 2012; Lee and Kim, 2009; Kostakis et al., 2018)
	↓		-Metastasis occurrence	Poor	
Prostate Cancer	↑		In benign tumors Inhibition of Angiogenesis in xenografts	Good	(Cho et al., 2009a; Wang et al., 2012; Curtis et al., 2010)
	↓	↓	In advanced tumors	Poor	
Osteosarcoma	↑		-Tumor suppressor -inhibits cell growth, proliferation and invasion	Better	(Wang et al., 2011)
	↓		-More aggressive tumors	Poor	
NSCLC	↑		-Tumor suppressor	Better	(Jakobsen and Sorensen, 2012; Stella et al., 2013; Jemal et al., 2011; Karapanagiotou et al., 2011)
	↓		-Metastasis occurrence	Poor	
HCC	↑	↑	-Tumor progression -Induces metastases	Poor	(Hurst and Welch, 2011b; Ikeguchi et al., 2003a; Schmid et al., 2007b; Shengbing et al., 2009b)
	↓			Better	
Esophageal cancer	↑		Metastasis inhibition	Better	(Ikeguchi et al., 2004)
	↓	↓	-Metastasis occurrence	Poor	(Ikeguchi et al., 2004)
Colorectal cancer	↑		-Tumor suppressor -Metastasis Inhibition	Better	(Kostakis et al., 2015; Ji et al., 2014; Okugawa et al., 2013Stathaki et al., 2014)
	↓		-Metastasis occurrence	Poor	
Thyroid Cancer	↑	↑	Tumor suppressor	Better	(Ringel et al., 2002b; Savvidis et al., 2015)
	↓			Poor	

biomarker for the prediction of lymph node metastases in ESCC. Further prospective studies are of course needed to validate these preliminary observations.

17. KiSS-1 and colorectal cancer

The role of KiSS-1 as a potential metastasis suppressor in CRC has been previously investigated in a limited number of studies. Ji et al studied the expression of KiSS-1 mRNA and KiSS-1R protein –using real-time PCR and immunohistochemistry, respectively- in CRC and found a negative association between KiSS-1 mRNA levels and Dukes stage, TNM stage, tumour size and development of lymph node metastases. Reduced expression of KiSS-1 receptor was also significantly associated with reduced disease-free survival, suggesting that KiSS-1 may be a

useful prognostic biomarker in CRC (Kostakis et al., 2015; Ji et al., 2014). Okugawa et al found a significant correlation between reduced KiSS-1 expression and the progression of lymph node metastases in CRC tissues, concluding that loss of KiSS-1 may represent an independent predictor of disease progression (Ji et al., 2014).

Overexpression of KiSS-1 suppressed the invasiveness of CRC cells, and the gene exerted its function by reducing the expression of MMP-9 via blocking of the PI3K/Akt/NF-κB pathway.

Hypermethylation of *KISS-1* occurred frequently in CRC samples (83.1%,) (105/126), but was infrequent in normal colorectal tissues (6.34%, 9/142). Moreover, *KISS-1* methylation was associated with tumor differentiation, the depth of invasion, lymph node metastasis and distant metastasis (Okugawa et al., 2013).

Finally it has been suggested that the antimetastatic effect of tumor-elevated kisspeptin in colon cancer patients may be mediated by the effect of kisspeptin on EMAP-II expression in colon cancer tumors. EMAPII is a cytokine that is specifically induced by apoptosis, and it is involved in the control of angiogenesis, inflammation, and wound healing. The release of this cytokine renders the tumor-associated vasculature sensitive to tumor necrosis factor. Exogenous, synthetic and naturally produced, kisspeptin seems to induce, through the KiSS-1R, the EMAP-II expression and secretion in colon cancer cell lines whereas elevated kisspeptin and EMAP-II expression in colon cancer tissues was associated with lack of metastases in colon cancer patients (Stathaki et al., 2014).

18. KISS-1 and thyroid cancer

Published data on the biological role of kisspeptin in thyroid cancer are sparse. Ringel et al (Ringel et al., 2002b) found increased expression of kisspeptin receptor in papillary thyroid cancer, as compared to the adjacent normal tissue, suggesting a potential involvement of kisspeptin in modulating the biological behavior of thyroid cancer. Savvidis et al (Savvidis et al., 2015) reported higher expression of KISS-1 in differentiated thyroid cancer tissues with extrathyroidal invasion, as compared to localized tumors, while increased KP expression was also correlated with advanced disease stage as well as reduced tumor size. Additional studies are needed to clarify the exact role of kisspeptin in the development, progression and prognosis of thyroid neoplasia.

19. Discussion

Kisspeptin or metastin is a 54 amino acid peptide (KP54) which exerts its function through the KiSS-1R (Welch et al., 2000; Fidler, 2003). Recent findings suggest that KP54 can be cleaved to many different isoforms that share the same COO- terminal all possessing the ability to bind and activate KiSS-1R. KPs are essential in reproduction in *in utero* sexual development as well as determining the onset of puberty and sexual behavior, by signaling GnRH secretion. While recent evidence suggests that KPs could be the link between energy homeostasis and the reproductive system (Ikeguchi et al., 2003b). Apart from their roles in reproduction, KPs seem to be involved in tumor progression and metastases. In the majority of cancers, kisspeptins seem to be a good prognostic factor and they have been associated with the inhibition of metastases (Table 1). These facts render them as one of the metastases suppressor factors, part of the hosts defense system to tumor spread.

Binding of the KPs to their receptor can lead to activation of ERK 1/2 either by activating the G-protein dependent pathway through PLC activation that leads to Ca^{2+} efflux or by activating the G-protein independent pathway through arrestin β2. ERK 1/2 activation leads to the reduction of expression of MMP-9, a factor that plays an important role in angiogenesis and metastases in cancer. Furthermore kisspeptins seem to inhibit Akt activation, a kinase with many functions that is involved in the inhibition of apoptosis and in cell migration. In colorectal cancer kiss-54 seems to induce EMAP-II expression, a factor that inhibits angiogenesis and induces apoptosis. KP was also demonstrated to activate EIF2AK2 via RhoA-mediated pathways in many cancer cell lines in vitro. Results obtained from nude mice bearing LoVo cells-derived colon cancer xenograft tumors, suggested that KPs inhibited tumor growth and metastases through an EIF2AK2-dependent mechanism. From the above it can be understood that KiSS-1 presents dual roles: one in human physiology affecting the onset of puberty by signaling GnRH secretion and the other in cancer biology, inhibiting the metastatic capacity of malignant tumors, in most cases, through the degradation of MMP-9 the inhibition of Akt and the activation of EIF2AK2.

KP agonists and antagonists have potential diagnostic and therapeutic applications. Kisspeptin agonists can be used to evaluate the gonadotrophic potential of infertile individuals. They may also be used to treat subjects with sub-fertility through the stimulation of LH to result in ovulation. They can also be used to define the role of kisspeptins in various physiological and pathological states of the HPG axis. As they reduce LH pulse frequency and amplitude without affecting basal LH secretion, kisspeptin antagonists may be useful as contraceptives in women or in the treatment of sex steroid-dependent diseases, such as prostate and breast cancer, endometriosis and uterine fibroids. Finally there is also the possibility for the use of, KiSS-1 in the treatment of metastatic cancers. The fact that the active peptides of KPs are secreted proteins and their mode of action is generated after secretion (endocrine/paracrine/autocrine) through its receptor, suggests that kisspeptin antimetastatic effects may be generated accordingly. Therefore kisspeptin analogues could be used through the bloodstream aiming KiSS-1R expressing tumors prior to reduce their metastatic ability in KiSS-1R expressing tumors (Blake et al., 2017).

Furthermore, the continuous administration of KP agonist analogues in male rats, monkeys and dogs was associated with the rapid significant testosterone suppression therefore allowing treatment of hormone-dependent diseases such as prostate cancer (Matsui and Asami, 2014). The major limitation is the fact that the majority of the human tumors do not express the KiSS-1R and that there are several lines of evidence suggesting that continuous KP administration can results in desensitization/tachyphylaxis of KiSS-1R in rats, monkeys and women with hypothalamic amenorrhea (Matsui and Asami, 2014). A future perspective in this field would be to determine the role of kisspetin peptides in the tumor microenvironment where KPs could be the trigger to induce such changes to lead to metastasis inhibition and to determine the role of KiSS-1 on tumors that lack the KiSS-1R. In addition recent evidence indicated that KP expression is affected by miR-199 that leads to KiSS-1 signalling inhibition and is associated with metastases in colorectal cancer (Shen et al., 2016). Thus the role of kisspeptins as novel potential antimetastatic agents as well as the factors that affect the expression of KPs, at least in some tumors, should be further examined.

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Declaration of Competing Interest

None.

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