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Mini-review

The role of kinin receptors in cancer and therapeutic opportunities

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ABSTRACT

Kinins are generated within inflammatory tissue microenvironments, where they exert diverse functions, including cell proliferation, leukocyte activation, cell migration, endothelial cell activation and nociception. These pleiotropic functions depend on signaling through two cross talking receptors, the constitutively expressed kinin receptor 2 (B2R) and the inducible kinin receptor 1 (B1R). We have reviewed evidence, which supports the concept that kinin receptors, especially kinin receptor 1, are promising targets for cancer therapy, since (1) many tumor cells express aberrantly high levels of these receptors; (2) some cancers produce kinins and use them as autocrine factors to stimulate their growth; (3) activation of kinin receptors leads to activation of macrophages, dendritic cells and other cells from the tumor microenvironment; (4) kinins have pro-angiogenic properties; (5) kinin receptors have been implicated in cancer migration, invasion and metastasis; and (6) selective antagonists for either B1R or B2R have shown anti-proliferative, anti-inflammatory, anti-angiogenic and anti-migratory properties. The multiple cross talks between kinin receptors and renin–angiotensin system (RAS) as well as its implications for targeting KKS or RAS for the treatment of malignancies are also discussed. It is expected that B1R antagonists would interfere less with housekeeping functions and therefore would be attractive compounds to treat selected types of cancer. Reliable clinical studies are needed to establish the translatability of these data to human settings and the usefulness of kinin receptor antagonists.

1. The kallikrein–kinin system

1.1. Kinins

Bradykinin (BK), an active peptide produced by the kallikrein–kinin system (KKS), was first reported by the Brazilian pharmacologist Mauricio Rocha e Silva and his coworkers in 1949. BK was released when human plasma was mixed with venom of the snake *Bothrops jararaca* or with trypsin. On isolated guinea pig ileum, the substance produced slow delayed contractions when compared to those obtained with histamine and acetylcholine. The name bradykinin was then given to express this slow action (*brady* meaning slow and *kinin* indicating movement in Greek) [140].

The KKS is complex, with several bioactive peptides that are formed in many different compartments. Kinin peptides are implicated in many pathophysiological processes including the regulation of blood pressure and sodium homeostasis, inflammatory processes, renal, cardiac and neurological functions, pain sensation, smooth muscle contraction, and cell proliferation and migration [37].

The KKS represents a metabolic cascade, which upon activation triggers the release of vasoactive kinins (Fig. 1). In humans and in most mammals, the term "kinin" refers to the nonapeptide, BK (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), the decapeptide kallidin (KD: Lys-BK), the methionyl-lysyl-BK, and their carboxy-terminal des-Arg metabolites. BK-(1-7) is an inactive degradation product, whereas BK-(1-5) is involved in the coagulation system. Kinins are released locally from their parental molecules, the kininogens, as a result of limited proteolysis by a class of serine proteases called kallikreins (plasma and tissue kallikreins). Enzymes collectively called kininases metabolize kinins in various site of cleavage; these include angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), carboxypeptidase N, carboxypeptidase M, cathepsin X and aminopeptidase P (APP) [16]. BK is metabolized rapidly by endogenous metalloproteases having a plasma half-life of approximately 15 s and usually low circulating levels. The broad spectrum of their actions is mediated by G protein-coupled receptors (GPCRs), pharmacologically classified as kinin receptor subtype 1 (B1R) and kinin receptor subtype 2 (B2R) [84].

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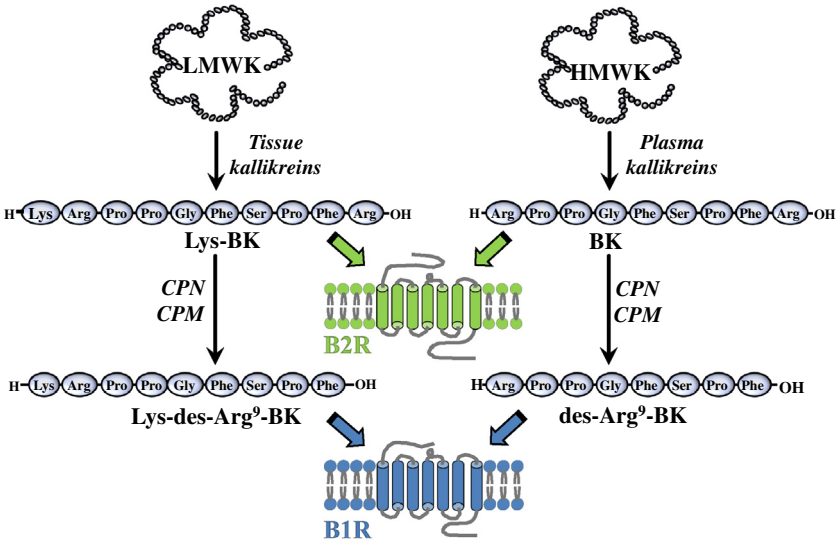

Fig. 1. Schematic representation of the kallikrein–kinin system. The kininogens HMWK and LMWK are cleaved by tissue and plasma kallikreins, respectively, generating the metabolites BK and Lys-BK, respectively, which can be cleaved by the kininases CPN and CPM generating respectively the metabolites des-Arg^9-BK and Lys-des-Arg^9-BK. Lys-BK and BK are agonists of B2R and Lys-des-Arg^9-BK and des-Arg^9-BK are agonists of B1R.

1.2. Kinin receptors and receptor signaling

Kinins exert their pharmacological activities by binding specific receptors: B1R and B2R. BK and KD preferentially bind to B2R, whereas the carboxy-terminally truncated peptides desArg^9-BK and desArg^{10}-KD have a high affinity to B1R. Depending upon the cell type, kinins induce excitability, cell division, permeability, and release of a variety of biologically active agents [17]. Due to the multiple roles of kinins, many signaling pathways have been shown to be activated, notably the mitogen-activated protein kinase (MAPK), PKC and nuclear factor-κB (NF-κB) pathways [66,121].

Kinin receptors are coupled to G proteins leading to the activation of a number of signaling molecules, such as, several isoforms of protein kinase C (PKC) and phospholipases and the generation of second messengers, such as inositol-1,4,5-trisphosphate, diacylglycerol, calcium and arachidonic acid (subsequently converted to prostaglandins). The increase in calcium can also activate the endothelial nitric oxide (NO) synthase (eNOS) and ultimately the production of NO in endothelial vasculature [25,41,148]. Novel signaling molecules continue to be identified in the diverse fields where kinins have a role, such as the Rho-kinases (ROCKs) in the bradykinin-induced increase in murine blood–tumor barrier permeability and the myristoylated alanine-rich C kinase substrate (MARCKS) in bradykinin-induced neurite outgrowth in neuroblastoma cells [90,162]. The remarkable diversity of pathways used by kinin receptors may reflect cell-type specific responses elicited by them.

B1R and B2R activation triggers essentially the same signaling pathways. However, the patterns of signaling are different in terms of cell Ca^{2+} influx (in duration and in intensity) [107]. Kinin-stimulated B2R signaling is often transient, whereas B1R signaling is sustained. Enquist et al. proposed recently that this may be, at least in part, because kinin-stimulated B1R signaling depends on a step in receptor endocytosis, whereas B2R signaling does not [55]. Some studies have reported cross talk between B1R and B2R with evidence that persistent stimulation of B2R may result in up-regulation of B1R [127]. Recently, Rodrigues et al. have provided some evidence that B2R expression is highly upregulated by endothelial overexpression of B1R studying thoracic aorta from transgenic rat overexpressing B1R exclusively in the vascular endothelium [141].

Some indirect mechanisms of kinin receptor activation have been proposed, where the formation of protein complexes on the membrane surface may be a key event. Binding of carboxypeptidase M (CPM) to B1R allosterically enhances B1R affinity for its des-Arg kinin agonist. In addition, kinin substrate (i.e., BK or KD) binding to the CPM active site causes a conformational change in CPM that is transmitted via protein–protein interaction to the B1R, resulting in G protein coupling and activation of calcium, nitric oxide (NO) or ERK signaling [192–194]. Similarly, experimental evidence suggests that the binding of some ACE inhibitors cause a conformational change in ACE that potentiates B2R signaling [56].

Typically, B2Rs are constitutively expressed whereas B1R expression is up-regulated under conditions such as tissue injury, cytokine stimulation and inflammatory insults [136,138], events highly relevant to cancer. However, some tissues such as the spinal cord and some brain regions and cells express B1Rs constitutively [89,129,183]. In addition, B2R expression can be modulated by inflammatory cytokines, such as interleukin (IL)-1, Tumor Necrosis Factor (TNF)-α and Transforming Growth Factor (TGF)-β [11,22,78]. Both receptor subtypes for kinins can be expressed by the same cell type, such as, endothelial cells, fibroblasts and various tumor cells [184].

2. Kinin receptor antagonists

The development of potent and selective kinin receptor modulators has led to the production of a number of peptide and non-peptide agonists and antagonists. However, only one compound, Icatibant (HOE-140) – a hydrophilic decapeptide selective for the B2R – has reached the market for the treatment of hereditary angioedema.

The first family of compounds capable of antagonizing BK and des-Arg^9-BK with specificity was based on the prototype [Leu^8]-des-Arg^9-BK [135]. The first generation of B2R antagonists were based on [D-Phe^7]-BK [172], but these early peptide compounds showed both antagonist and partial agonist activity and low potency. Second generation peptide antagonists of kinin receptors are quite selective and present relatively long-lasting *in vivo* action: these include the highly selective B1R antagonist R-954 and the B2R antagonist HOE-140 [85,114]. Third generation antagonists of kinin receptors, are orally active, and include SSR240612

and MEN16132 (fasitibant) [63,64,158]. For a more comprehensive review see Whalley et al. [182] and Bozo et al. [21].

A certain number of clinical trials have been performed with peptide and non-peptide B1R and B2R ligands (Table 1). however, only two of these developments disregards cancer treatment: the B2R agonist RMP-7 (lobradimil) and the dual B1R and B2R antagonist B9870 (breceptin). In pre-clinical studies of rats with implanted gliomas, intravenous lobradimil significantly increased the uptake of carboplatin into brain tumors [53]. A phase II trial of lobradimil and carboplatin was conducted in pediatric patients with glioma. Unfortunately, the combination of lobradimil and carboplatin was inactive in childhood gliomas [131,179]. Apoplogic Pharmaceuticals has conducted a phase I trial with B9870 in lung cancer, however we were unable to find further information about this development.

The analysis of Table 1 discloses a disappointing scenario. Most clinical studies with kinin antagonists have been halted for undisclosed reasons. It is likely that multiple factors, such as limitations in the predictive power of animal models, poor absorption/distribution/metabolism/excretion profile of some of the compounds, or toxicological problems might be attributable for halting these developments [21,182]. There is a need for improved animal models, particularly with increased use of humanized systems and non-human primates, to improve the translatability from animal models to human disease [61,72].

3. Implications of kinin receptor activation in cancer

A role for kinin receptors in cancer has been suggested in a number of studies [36,60,159,191]. The ability of kinins to stimulate cell proliferation, migration and angiogenesis, and increase vascular permeability, probably contributes to the biological behavior of tumors (Fig. 2). In addition, kinin receptors could play an important role in cancer growth and metastasis, since these are critically dependent on the activation of inflammatory pathways. Moreover, kinin receptors have been implicated in cancer pain and kinin receptor antagonists appear to alleviate nociception associated with chemotherapy-induced peripheral neuropathy, a condition that limits treatment of cancer patients [23,62,150].

3.1. Kinin receptor expression in cancers

Several studies reported that the expression of B1R in cancers including renal, esophageal, cervical, gastric, prostate, lung and mammary carcinomas and malignant mesothelioma, as well as cancer cell lines (Table 2) [10,32,33,46,57,62,102,104,116,133,146,175,184]. B2R has also been detected in different cancers, including head and neck squamous cell carcinoma (HNSCC), osteosarcoma, endometrial, prostate, renal, cervical, lung and stomach cancers, lymphoma, hepatoma, mesothelioma and pituitary adenoma (Table 2) [13,33,35,104,111,137,167,176,184,191]. Studies of receptor expression levels have suggested a role for B1R and/or B2R in malignant transformation and tumor progression (Table 2). However, only six studies evaluated the expression of kinin receptors in sample sizes of more than 30 patients. In addition, four of them only evaluated one out of the two receptors. There is a need to expand the knowledge about the expression of these receptors in tumor progression of various cancers, particularly lung and prostate cancer and melanoma.

Previous studies revealed an increased number of B2Rs in cells transformed by the activation of oncogenes. The increase in receptor number is a *ras* specific event (rather than a general effect of transformation) and occurs after overexpression of each of the three normal *ras* gene products (Ha-, K- and N-) as well as after expression of the three activated *ras* gene products [48,126]. In addition, the *dbl* (human diffuse B-cell lymphoma) oncogene is also shown to increase the expression of bradykinin receptors in NIH 3T3 cells to the same extent as *ras* whereas other oncogenes (*v-src*, *v-abl*, *v-mos*, *v-raf*, *v-fos*) did not have this effect [142]. Expression of a mutant *ras* protein in Rat 13 cells increases the expression of the B2R and their sensitivity to ligand stimulation

Table 1
Selected clinical trials with B1R and B2R agonists and antagonists.

Drug	Target	Clinical phase	Indication	Comments	Ref.
HOE-140 (Icatibant, Firazyr)	B2R antagonist	Approved	Hereditary angioedema	Approved for angioedema and in trial for many other conditions	[8,30]
		Phase I/II/III	Ischaemic heart diseases, cardiopulmonary bypass, inflammation, fibrinolysis, surgery, ACE inhibitor-associated angioedema etc.	Decreased intraoperative fibrinolytic capacity in cardiopulmonary bypass	
MEN16132 (fasitibant)	B2R antagonist	Phase II	Knee pain in osteoarthritis	A first phase II study (ALBATROSS) has been completed. A second one is ongoing	[63] NCT0109116
CP-0127 (deltibant)	B2R antagonist	Phase II	Severe traumatic brain injury sepsis	Phase 2 trial was halted due to unexpected preclinical findings. Ineffective for sepsis	[58,96,112]
LF16-0687 (anatibant)	B2R antagonist	Phase II	Severe traumatic brain injury	Inconclusive results, possible safety concerns	[152]
RMP-7 (lobradimil)	B2R agonist	Phase II	Intravenous cereport (RMP-7) and carboplatin in childhood brain tumors	Fail to show improved efficacy	[131,179]
FOV-2304 (safotibant)	B1R antagonist	Phase II	Diabetic macular edema	No results released. It was discontinued in October 2012	NCT01319487
MK-0686	B1R antagonist	Phase II	Postherpetic neuralgia	The development was halted. No specific reason was disclosed	NCT00292763
			Postoperative dental pain		NCT00533403
			Osteoarthritis		NCT00296569
BI-113823	B1R antagonist	Phase I	Osteoarthritis	Phase 1 clinical study was terminated due to unknown reasons	NCT01207973
SSR-240612	B1R antagonist	Reported		The development was halted for an undisclosed reason	No record found
		Phase II			
B9870 (Breceptin)		Phase I	Small cell lung cancer	No information found	

B1R, kinin receptor 1; B2R, kinin receptor 2; ACE, Angiotensin-converting enzyme; NCT, National Clinical Trial (http://www.clinicaltrials.gov).

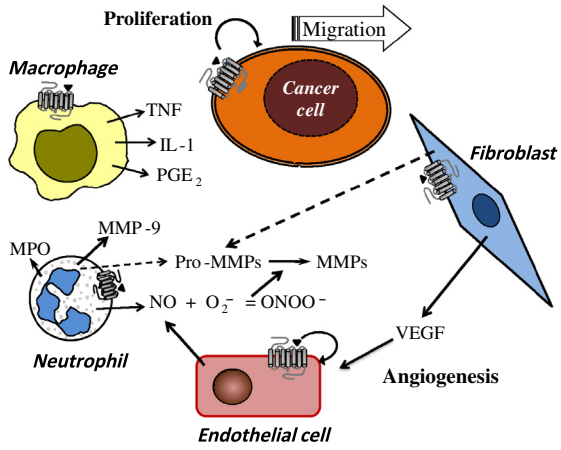

Fig. 2. Schematic drawing of some mechanisms involved on the activation of kinin receptors within tumor microenvironment. It has been suggested, according with *in vitro* and *in vivo* studies, that kinin receptors activation in different cells that compose the tumor microenvironment results in a range of actions, such as the release of MMPs, growth factors and inflammatory mediators, which can promote tumor growth, angiogenesis, invasion and cancer metastases.

of mitogenesis [126,139]. The molecular mechanisms by which *ras* regulates BK expression/actions are still unknown.

3.2. Kinins as growth factor for cancer cells

Some cancers produce BK and use it as an autocrine factor to stimulate their growth, notably small cell lung carcinoma (SCLC), prostate and breast cancer and certain ascites tumors [9,24,160]. Using prostate cancer PC3 cells as a model for the study of androgen-insensitive prostate cancer, Taub and others showed that specific inhibition of B1R signaling attenuates *in vitro* cell growth, migration, and invasion. The activation of B2R also induced proliferation of PC3 cells [9,163] and other cancer cell lines [49,65,81]. BK-induced PC3 cell growth requires activation of the ERK pathway [10]. In normal and cancerous breast cells, BK stimulated cell proliferation through the activation of MAPK pathways [49,65,66,164]. The proliferative effect of BK was higher in tumor cells with respect to nonmalignant epithelium adjacent to the tumor. Greco et al. suggested that BK leads to cell proliferation through B2R activation [67]. Molina and colleagues have shown that stimulation of B1R induced the proliferation of estrogen-sensitive breast cancer cells and ERK1/2 phosphorylation is essential for proliferation [102].

Antagonists for either B1R or B2R have been proposed for the treatment of various cancers, particularly lung, prostate and breast cancers [84,108]. The compound B-9870 (also known as CU-201) inhibits tumor cell growth both *in vitro* and *in vivo* in athymic nude mice [159]. B-9870 was shown to induce apoptosis in various lung, prostate and HNSCC cell lines [28,29,159,164]. B-9870 stimulated apoptosis in lung cancer cells by a novel "biased agonist" mechanism: it inhibited intracellular Ca^{2+} released in response to BK, which indicated blockage of the $G\alpha_q$ signal, and stimulated c-Jun kinases, which suggested stimulation of the $G\alpha_{12,13}$ pathway. This unbalanced action ultimately stimulated caspase-3 activity and led to cell death [28,29,73]. B-9870 also produced increased growth inhibition when combined *in vitro* with chemotherapeutic agents used routinely to treat lung cancer patients [paclitaxel, doxorubicin (DOX), etoposide, and vinorelbine] [29]. However, Morissette and colleagues found that B-9870 is a dual B1R and B2R antagonist with confirmed stimulating effects at the B2R in cells and tissues where B2Rs are overexpressed [108]. Importantly, inhibition of MDA-MB-231 cell growth by B-9870 was not influenced by B1R or B2R antagonists [108]. Thus, the mechanism of action of B-9870 may not be necessarily related to BK antagonist activity. These results should be interpreted with caution.

3.3. Kinins as novel cancer biomarkers

Despite the need to identify clinically useful biomarkers for detection of early disease, there have been only a few examples of circulating molecules that can be used to detect cancers before they are clinically evident. Maeda et al. have identified a new type of BK, 3-hydroxyprolyl (^{3}Hyp)-BK, in ascitic fluid of gastric cancer patient [92]. Subsequently, high amounts of both ^{3}Hyp-BK and BK, and both BK/Hyp–BK were found in ascitic and pleural fluids of human and animal carcinomatosis [97,98].

Recently, Villanueva et al. found that BK and des-Arg^9-BK levels are at higher levels in sera of breast cancer patients and lower in bladder cancer patients when compared with normal subjects, using optimized mass spectrometry [173]. Subsequent studies confirmed that des-Arg^9-BK, was present at increased levels in breast cancer patients and the concentration of this peptide decreased to normal levels after removal of the tumor [170]. Further studies are needed to confirm the potential of BK and, especially, des-Arg^9-BK as biomarkers for the diagnosis and therapeutic management of cancer patients.

3.4. Kinins as pro-inflammatory molecules

There is compelling evidence indicating that kinins are generated rapidly after tissue injury and they seem to modulate most events observed during inflammatory processes including vasodilatation, increase of vascular permeability, plasma extravasation, cell migration, pain, and also synthesis of inflammatory mediators such as eicosanoids, cytokines and nitric oxide (NO) [26]. Several lines of evidence indicate that kinins play a critical role in different inflammatory pathological states such as infections, ischemia–reperfusion injury and cancer [36,94,163,177,178].

One of the first correlations between kinins and inflammation came from the observation that the administration of BK in human or animal tissues reproduced the four cardinal signs of inflammation: redness, local heat, swelling, and pain [53]. Many subsequent studies have established that both B1R and B2R are involved in the onset and maintenance of inflammation [27,39,135].

B1R expression is induced by several different pro-inflammatory cytokines including IL-1β, TNF-α, interferon-γ, EGF, IL-2 and IL-8 [20,42,43,68,101,130,147]. These cytokines activate distinct cytokine receptors and often regulate different pathways, mainly via NFκB signaling, which in turn activates the expression of the very same cytokines and B1R in an amplification cascade [26,115]. Thus, there is a complex interaction between the B1R and pro-inflammatory cytokines that may play an important role in tumor progression and metastasis.

Recently, it was shown that the B1R antagonist R-954 inhibited Ehrlich ascitic tumor (EAT) growth in mice and reduced paw edema after intraplantar injection of EAT cells in rats, resulting in increased survival of animals. In addition, R-954 reduced significantly the extravasation of protein, the production of NO and PGE_2, and release of TNF-α in the mouse peritoneal cavity [59].

Kinins play an important role in the activation of various leukocytes during the inflammatory process, especially by the release of other inflammatory mediators, such as cytokines, prostaglandins, leukotrienes, and reactive oxygen species. B2R on neutrophils is involved in the extravascular migration of these cells at sites of inflammation [119,129,144,145]. Ablation of the B1R gene in mice is associated with a defect in neutrophil accumulation in inflamed tissues [5,129]. Furthermore, activation of B1R in human neutrophils induces chemotaxis and triggers the release of matrix metalloproteinases (MMP)-9 and myeloperoxidase [51,52]. Macrophages

Table 2
B1R and B2R expression in clinical samples from cancer patients and cancer cell lines.

Study	Clinical specimens	Ref.
Increased levels of B1R was found in colorectal adenomas, which tend to evolve into colonic cancer, and increased levels of B2R was found in hyperplastic polyps (no neoplastic potential)	B1R, *n* = 41 B2R, *n* = 41	[189]
B1R and B2R were detected in human astrocytic tumors	B1R, *n* = 10 B2R, *n* = 12	[133]
B1R and B2R were detected in human gastric carcinoma specimens	B1R, *n* = 17 B2R, *n* = 11	[146]
B1R and B2R were detected in human oesophageal carcinoma, however not highly expressed compared with normal counterpart	B1R, *n* = 10 B2R, *n* = 6	[46]
B1R and B2R were detected in human clear-cell renal carcinoma tissue and adjacent tissue	B1R, *n* = 4 B2R, *n* = 4	[104]
Both B1R and B2R are expressed in human pleural mesothelioma	B1R, *n* = 4 B2R, *n* = 4	[33]
B1R and B2R were detected in five different subtypes of human lung cancer	B1R, *n* = 4–6 B2R, *n* = 3–6	[31]
B1R expression was increased in human bladder cancer samples, while B2R was not. B1R and B2R agonists stimulated the proliferation of grade 3-derived T24 bladder cancer cells and antagonists for both receptors inhibited this proliferation (*in vitro*)	B1R, *n* = 7 B2R, *n* = 7	[151]
B1R mRNA levels were found higher in patients with grade 2 endometrial cancer when compared to the control group and both B1R and B2R presented lower levels in patients with grade 3 endometrial cancer, compared with control, grades 1 and 2	B1R, *n* = 50 B2R, *n* = 50	[117]
B1R and B2R mRNA were detected in human chondrosarcoma tissues at higher expression compared to normal cartilage JJ012 chondrosarcoma cells express both B1R and B2R. Antagonism of any kinin receptor attenuated kinin-induced cell migration (*in vitro*)	B1R, *n* = 3 B2R, *n* = 3	[185]
B2R was found ubiquitously expressed in prostate tissues. B1R was detected only in prostatic intraepithelial neoplasia and malignant lesions and not in benign prostate tissues. Stimulation of B1R on PC3 cells promotes cell growth, migration, and invasion (*in vitro*)	B1R, *n* = 16 B2R, *n* = 16	[163]
Prostate cancer PC3 cells express B1R and B2R. Specific blockade of either B1R or B2R is sufficient to cause inhibition of kinin-mediated cell proliferation. Blockade of B1R also inhibited B2R-mediated cell growth, and, similarly, antagonism of B2R inhibited the B1R-mediated response		[9]
B1R was detected in precursor lesions of gallbladder carcinoma, but showed a low expression in invasive carcinomas. HER-2 receptor was highly expressed in intestinal metaplasia and carcinoma *in situ*, but not in invasive carcinoma (similar to B1R)	B1R, *n* = 92	[166]
B2R was detected in clinical specimens of gastric adenocarcinoma, squamous cell lung carcinoma, duodenal carcinoid, lung papillary adenocarcinoma, hepatoma and Ki-1 lymphoma. B1R expression was not determined	B2R, *n* = 1	[184]
B1R transcripts were detected in invasive breast carcinomas (79/216). In patients with estrogen receptor-negative tumors (*n* = 42), *B1R* mRNA expression correlated with longer disease-free survival. B2R expression was not determined	B1R, *n* = 216	[57]
B1R was found in benign and malignant neoplastic human breast tissues. B1R and B2R agonists induce proliferation of MCF-7 breast cancer cells. B1R antagonist inhibited kinin-induced MCF-7 proliferation, but no B2R antagonists were tested	B1R, *n* = 21	[102]
BK induced the phosphorylation of ERK1/2 in MCF-7, which was inhibited by a B2R antagonist, but not by a B1R antagonist. BK also stimulated the proliferation of MCF-7		[67]
B2R antagonist reduced angiogenesis and tumor weights in rats bearing Walker 256 carcinoma. A B1R antagonist did not change tumor growth. B2R protein was mainly detected in the tumor stromal tissues. B1R was not detected. Angiogenesis and tumor growth were significantly suppressed in B2R knockout mice bearing sarcoma 180		[74]
The growth and angiogenesis of murine sarcoma 180 cells was reduced by a B2R antagonist but not by a B1R antagonist. B2R protein was mainly expressed in vascular endothelial cells in the early phase and in fibroblast-like cells of the stroma in the late phase		[75,76]
A B1R antagonist inhibited Ehrlich ascitic tumor growth *in vivo*. The expression of kinin receptors has not been determined		[59]
Over-expression of B2R was determined in HNSCC human tissues in comparison to normal peritumoral tissue. B1R expression was not determined	B2R, *n* = 180	[13]
In HNSCC samples, B2R levels were 3-fold higher in tumor tissue compared with normal control tissue. B1R was detected in only a small percentage of tumors. The B2R antagonist, but not the B1R antagonist, inhibited bradykinin-induced EGFR and MAPK activation and COX-2 induction in HNSCC cell lines	B2R, *n* = 43	[191]
The expression of B2R in the three grades of glioma was in the order of aggressiveness (WHO I < WHO II < WHO III)	B2R, *n* = 24	[195]
BK, acting via B2R, acts as an important signal directing the invasion of glioma cells toward blood vessels. Most experiments were performed on D54-MG glioma cells, which express high levels of B2R and low levels of B1R		[103]
BK-induced cell migration and COX-2 production were inhibited by a B1R antagonist (*in vitro*) in C6 and U251 glioma cells, which express both B1R and B2R		[88]

COX, cyclooxygenase; EGFR, epidermal growth factor receptor; ERK, extracellular-signal-regulated kinase; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; WHO, World Health Organization.

express both B2R and B1R and their stimulation results in the generation of various inflammatory mediators, such as TNF, IL-1 and PGE_2 [18,143,165]. T lymphocytes appear to express only the B1R, the activation of which could alter their migration in selected tissues during inflammation, including in central nervous system [99,118,149]. Immature human monocyte-derived dendritic cells constitutively express B1R and B2R, and BK increased the *in vitro* migration of these cells [14]. All these results suggest that kinin receptors might play a pivotal role in the recruitment of pro-inflammatory cells within the tumor microenvironment.

Our group has provided some insights into the relevance of B1R in leukocyte infiltration within tumors and its consequences in tumor engraftment and growth in response to apoptotic cells. Previously, we have shown that the co-injection of dying cells along with sub-tumorigenic doses of melanoma cells favored melanoma growth. The presence of apoptotic cells causes a transient inflammatory infiltrate, composed mainly of neutrophils and macrophages. This effect was suppressed in B1R–deficient mice, which have impaired transmigration of neutrophils to inflamed tissues [36]. On the basis of these results, we suggest that disrupting the balance between apoptotic cells and leukocyte infiltration may provide insights for understanding and interfering with tumor cell viability during treatment with apoptosis-inducing drugs. Accordingly, we observed increased infiltration of B1R-positive cells within the tumor microenvironment of dacarbazine-treated melanoma-bearing mice.

3.5. Kinins as pro-angiogenic molecules

The relevance of angiogenesis for tumor growth and metastasis has been long recognized. Kinins can promote angiogenesis in different experimental models of normal and cancer cells/tissues, through B1R, B2R or both.

BK induced angiogenesis in rabbit corneas and on postcapillary venular endothelial cells through B1R and Fibroblast Growth Factor (FGF)-2 up-regulation [105,125]. Loiola and colleagues presented evidence that the targeted deletion of B1R or B2R impairs endothelium mediated vasodilation by reducing NO bioavailability in mesenteric arterioles [87]. Indeed, evidences indicate that B2R and B1R activation in endothelial cells leads to the generation of NO via activation of different eNOS and iNOS (reviewed by Kuhr et al. [83]).

Studying mice bearing sarcoma 180 cells, Ishihara and colleagues suggested that BK would promote angiogenesis by increasing vascular permeability in the early phase of tumor development via B2R expressed in the endothelial cells and not via B1R, and by promoting the up-regulation of Vascular Endothelial Growth Factor (VEGF) via B2R in the stromal fibroblasts in the late phase [74–76]. Tumor-associated angiogenesis and tumor growth were markedly attenuated in B2R knockout mice and in mice treated with B2R antagonists in two rodent models of mice genetically deficient in the kallikrein–kinin system and in Walker 256 carcinoma [74]. Recently, Yu and co-workers found that exogenous BK increased VEGF expression in prostate cancer cells (PC3 and DU145 cells) and further promoted tube formation in endothelial cells. The B2R antagonist HOE140 or small interfering RNA (siRNA) reduced BK-mediated VEGF production by the cancer cells. In addition, BK knockdown reduced VEGF expression and abolished prostate cancer cell conditional medium-mediated angiogenesis [187].

Anti-cancer drugs access solid tumors via blood vessels, and must penetrate tumor tissue to reach all cancer cells. Previous studies conducted in Dr. Tannock's laboratory have demonstrated steep gradients of decreasing doxorubicin fluorescence with increasing distance from blood vessels, which suggested that many tumor cells may not be exposed to sufficient concentration of the drug [128,132]. Our results show that treatment of mice bearing EMT6 sarcoma with the B1R antagonists R-954 and R-715 resulted in enhanced doxorubicin penetration after 2 h of treatment (Fig. 3). These results suggested that B1R antagonists might be used in combination to increase the delivery of certain chemotherapeutic agents. Intravenous infusions of the B2R agonist RMP-7 enhanced the delivery of hydrophilic chemotherapeutic agents (carboplatin and doxorubicin) into brain tumors, through increases in the permeability of the blood–brain tumor barrier [54]. The enhanced delivery increased the efficacy of chemotherapy, suppressed tumor growth and increased survival in tumor-bearing rats. However, a randomized phase 2 trial in patients with glioma receiving carboplatin with or without RMP-7 suggests that RMP-7 did not improve the efficacy of carboplatin. This negative clinical result may be due to sub-optimal dosing of RMP-7 [131]. More recently, it was demonstrated that dual B1R and B2R activation provides enhanced blood–brain barrier permeability and carboplatin drug delivery in the malignant F98 glioma rat model, which also translated into increased survival of glioma-bearing rats [38].

3.6. Implication of kinins in cancer migration, invasion and metastasis

Activated MMPs play critical roles for degradation and remodeling of extracellular matrix at the site of cancerous lesions facilitating angiogenesis, tumor invasion and metastasis [110,157]. It has been shown that BK induces eNOS and cyclooxygenase (COX), generating NO and PGs respectively, via B2R [19,93,120,122]. NO and PGs are involved in angiogenesis stimulated by VEGF and in tumor vascular permeability [109,124]. Furthermore, NO reacts with superoxide anion radical (O_2^-) and forms peroxynitrite ($ONOO^-$), which can activate neutrophil- and fibroblast-derived pro-MMPs leading to the release of MMPs and therefore they may up-regulate tumor metastasis and angiogenesis [51,93].

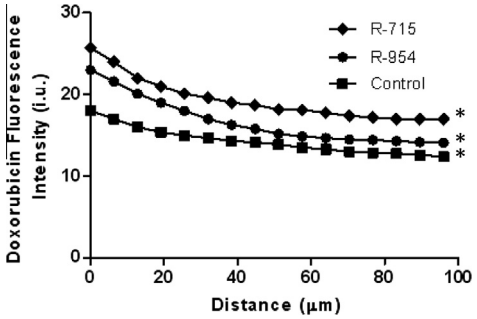

Fig. 3. The gradient of doxorubicin fluorescence intensity in relation to distance from the nearest blood vessel. Mice bearing EMT6 tumors ($n = 6$ tumors) were treated with saline (control) and the B1R antagonists R-715 (0.5 mg/kg) or R-954 (3 mg/kg s.c.) followed by doxorubicin intravenous injection 2 h later and their tumors were resected, sectioned and imaged. Image analysis was undertaken using customized algorithms. The graph shows the mean absolute (background-subtracted) values of fluorescence intensity of doxorubicin for the three different treatments, as a function of distance to the nearest tumor vessel. $^*p < 0.001$.

Several studies have shown that activation of kinin receptors results in the transactivation of EGFR and production of MMPs in cancer cells. B2R activation stimulated the *in vitro* invasion of HNSCC via EGFR [164,191]. In addition, *in vitro* activation of B1R in breast cancer cells induced the accumulation of MMP-2 and MMP-9 in the extracellular medium, through the activation of the ERK1/2 pathway and EGFR transactivation [50]. BK also induces MMP-9 expression via reactive oxygen species (ROS) dependent pathways in brain astrocytes [86].

Cancer cells must be able to migrate in order to metastasize. BK was found to enhance the migration of chondrosarcoma cells by increasing α2β1 integrin expression through the B1R and B2R/PLC/PKCδ/NF-κB signal transduction pathway [185]. BK, acting via B2R, stimulates the migration of glioma and bladder cancer cells *in vitro* [7,103]. Furthermore, Vassou et al. reported that opioids increase bladder cancer cell migration through their interaction with B2Rs (in the absence of opioid receptors), although this interaction is of low affinity [171]. BK also promotes migration of human prostate cancer cells by increasing adhesion molecule intercellular adhesion molecule-1 (ICAM-1) expression via B2R [188].

Using simultaneous intracellular calcium concentration ($[Ca^{2+}]_i$) measurements and electrophysiological recordings, Cuddapah et al. have elegantly demonstrated that $K_{Ca}3.1$ channel and ClC-3, a voltage-gated Cl^- channel/transporter, are activated as a result of bradykinin-dependent $[Ca^{2+}]i$ increases. In addition, inhibition of $K_{Ca}3.1$ or ClC-3 channels decreased bradykinin-induced migration through murine cerebral parenchyma *in situ* [40].

The above results suggest that tumor cells may bear a BK autocrine/paracrine mechanism which could promote the action of kinins, leading to signal amplification for tumor growth involving enhanced tumor vascular permeability, angiogenesis, inflammation and MMP activation. It is indeed noteworthy that tumors are not only composed of genetically transformed cells (tumor cells), but also of host cells such as endothelial cells, leukocytes and fibroblasts [69], which express the kinin receptors and probably interact in this network. Ikeda and colleagues suggested that BK generated from host cells may facilitate tumor-associated angiogenesis and tumor growth by stimulating stromal B2R signaling to up-regulate VEGF production mainly in fibroblasts [74].

Surprisingly, it was recently reported that melanoma cells (Tm5) which express B1R, but not B2R, when pre-treated with B1R agonist produce less aggressive tumors, characterized by decreased proliferation and vascularization *in vivo* [44]. Besides that, these tumors exhibited a decrease of inflammatory cells infiltration and upregulation of the cytokines IL-6 and IFN-γ, which may have a role in host anti-tumor immune response. These animals also presented no signs of metastasis and increased animal survival [44]. The authors suggest that activation of the B1R has a host protective role during murine melanoma progression. According with these results, B1R is having an anti-tumor role. The authors point that the pro-tumor role for the B1R, found in most publications, is likely due to the cross talking effect with the B2R. To reinforce this idea, they have elegantly shown that introduction of B2R in Tm5 cells completely abrogated the B1R-mediated effect of decreasing cell migration.

Indeed, most studies relating the kinin receptors to cancer were performed in models were tumor cells express both B1R and B2R (Table 2). A better understanding of the relative functional roles of the B1R and B2R, both temporally and spatially, as well as its cross talk, emerges as an essential part of good preclinical and clinical studies. At the same time, in order to evaluate the relevance of a cancer model where B2R is absent, more studies with larger clinical sample are urgently needed. Meanwhile, B1R antagonists still show great potential at least for the treatment of tumors that express both kinin receptors. It is also likely that the therapeutic window for the use of these antagonists or agonists will need to be carefully defined.

4. Implication of other components of the KKS in cancer: The kallikreins

The human tissue kallikrein (KLK) family has fundamental roles in cancer. Individual members of the KLK family such as prostate cancer-specific marker KLK3, which is also termed prostate-specific antigen (PSA), have been identified as cancer biomarkers [180]. Many studies have reported the overexpression of various kallikreins such as KLK4, KLK5, KLK7, KLK 10 and KLK14 in prostate, ovarian, breast, colorectal cancer and others, as well as its correlation with patients' diagnosis, outcome and in predicting chemotherapy response [4,79,80,123,190]. As an example, KLK1 has been implicated in the growth and invasiveness of many cancers [6,45,47]. The mechanisms may involve their intrinsic activity as proteases promoting the degradation of extracellular matrix [6,100,168] and the activation of kinin receptors either directly [15] or through the generation of kinins [91]. Moreover, KLK1 gene silencing reduced endothelial progenitor cells migratory, invasive, and pro-angiogenic activities. HK1-induced effects are mediated by a B2R-dependent mechanism involving iNOS and MMP-2 [156].

5. Interactions between the KKS and the Renin Angiotensin System (RAS): Cancer implications

There are links between the KKS and the RAS, which result from interactions of their multiple components (Fig. 4). ACE represents a central physiological bridge connecting the RAS and the KKS. By degrading BK and converting angiotensin (Ang) I to Ang II, ACE regulates the circulating and tissue levels of endogenous Ang II and kinins [154,155]. Indeed, BK is much more readily hydrolyzed by ACE than Ang I [196]. Several studies have revealed that ACE inhibitors (ACEi) reduce growth and angiogenesis of experimental tumors [3,113,174,181,186]. Although the mechanisms of ACEi effects are complex and relate to their specific pharmacological properties (for a review see [70]), it needs to be determined whether the accumulation of kinins generated by ACEi would be

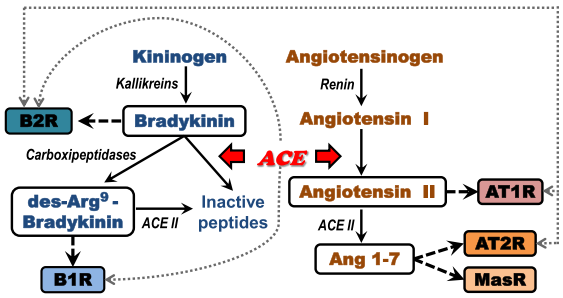

Fig. 4. Interactions between the KKS and the Renin Angiotensin System (RAS). ACE represents a central physiological bridge connecting the KKS (left side) and the RAS (classical RAS on the right side). ACE regulates the levels of endogenous Ang II and kinins by degrading BK and converting Ang I to Ang II. A crosstalk between ACE, B1R and/or B2R is also postulated in some systems and increases the complexity of these interactions. Similarly, cross talks between AT1R and AT2R with B2R have also been described.

part of ACEi's anti-tumor effect or if, in fact, it attenuates its overall effect. The evidences presented here strongly suggest that kinins are pro-tumor peptides, supporting the notion that ACEi's anti-tumor effects may be blunted by the secondary effects of increased levels of kinins and subsequent activation of B1R and/or B2R. Therefore, it is likely that combination of ACE inhibition and kinin antagonists may augment anti-tumor responses. In this regards, the B2R antagonist Icatibant was suggested to augment the effects of current cytotoxic chemotherapy for the treatment of epithelial ovarian cancer (EOC) in combination with other eight drugs, including the ACE inhibitor captopril. The rational is that Icatibant would ameliorate BK-induced EOC ascites and also control the increased levels of BK that result from ACE inhibition [77].

However, the multiple cross talks between the RAS and the KKS seem to be much more complex (Fig. 4, dotted lines). There is evidence that B1R expression is triggered by chronic ($\geqslant$7 days) ACE inhibition in healthy subjects [12,95,106]. B2R expression was increased by enalapril (ACEi) treatment in diabetic, but not healthy mice [134]. Furthermore, it has been recognized that the beneficial effects of ACEis in cardiovascular diseases extend beyond the inhibition of ACE to alter Ang II and kinin levels. It is been proposed that ACEis enhance activity of B1R and B2R, functioning as direct allosteric agonists of B1Rs and as indirect allosteric enhancers of kinin activity on B2Rs via interactions with ACE, probably by formation of heterodimers [34,56,82]. Endogenous peptides of the RAS, such as Ang derivatives Ang_{1-7} and Ang_{1-9}, can augment orthosteric BK effect on B2R. In addition, it has been reported that AT1R and B2R form constitutive heterodimers [2]. The AT1R/B2R heterodimers display increased sensitivity toward angiotensin II and are found in platelets and in omental vessels of preeclamptic women [1]. However, in cultured COS-7, HEK293, and NIH3T3 cells, although both receptors were functional, no AT1R/B2R heterodimers were detected [71]. On the other side, AT2R overexpression in transgenic mice stimulated kallikrein activity, kinin generation and B2R activation [169]. Other potential interactions between the RAS and the KKS have been described and may have important consequences in human diseases such as cancer [153,161]. Very little is known about these potential cross talks in the context of malignancies, particularly the existence of such interactions in cancer cells and its consequence for the use of RAS and KKS targeting agents for cancer treatment.

6. Conclusion

Studies with selective antagonists have provided support for the role of kinin receptors as potential therapeutic targets in many cancers. However, there has been limited experience with kinin

antagonists in clinical trials for cancer. Furthermore, in spite of good supporting preclinical data, most kinin antagonists have failed clinically for various conditions. This highlights the need to reassess the drug discovery and development process for kinin antagonists. There are various B1R and B2R antagonists available, therefore preclinical and clinical studies utilizing the existing molecules should be considered. These molecules will likely have a role alone or in combination with other treatment modalities. Meanwhile, the current results also represent a potent driver force for the discovery of new kinin receptors antagonists with improved pharmacokinetic. Importantly, a better understanding of the relative functional roles of the B1R and B2R as well as its cross talk with each other and with other systems/receptors, such as the RAS and GPCRs, is likely to avoid disappointing clinical trials. It is worth mentioning that the blockade of B2R for prolonged periods of time may produce undesired side-effects. In contrast, the inducible expression of B1R suggests that its inhibition would interfere less with housekeeping functions, and B1R antagonists would be attractive compounds to treat selected types of cancer.

Conflict of interest

The authors declare that there is no conflict of interest.

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