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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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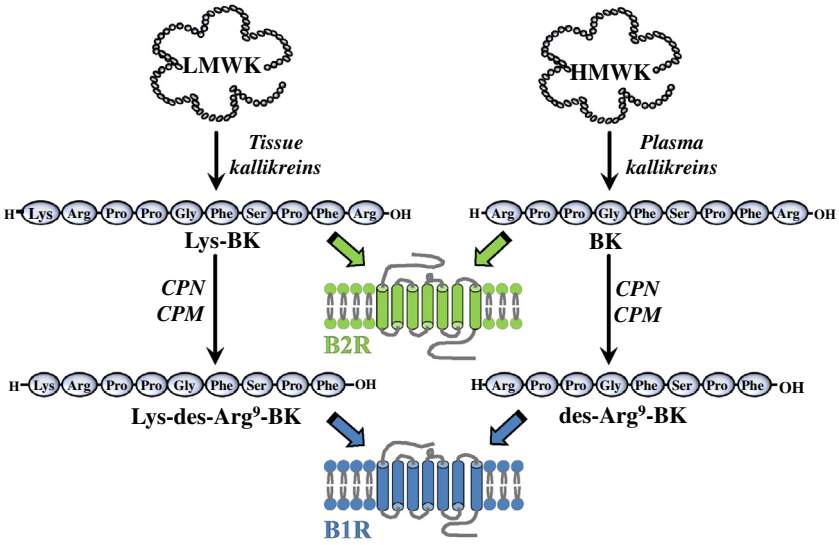

Fig. 1. Schematic representation of the kallikrein–kinin system. The kininogens HMWK and LMWK are cleaved by tissue and plasma kallikreins, respectively, generating the metabolites BK and Lys-BK, respectively, which can be cleaved by the kininases CPN and CPM generating respectively the metabolites des-Arg^9-BK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