Kinins are bioactive peptides produced by the enzymatic action of two serine proteases (kininogenases), plasma and tissue kallikreins. These kininogenases are proteases that release the kinin molecule from two endogenous and multifunctional protein substrates known as high and low molecular weight kininogens [1]. Plasma
kallikrein participates in surface-dependent activation of blood coagulation, fibrinolysis, and inflammation and is encoded by a single gene (KLKB1) of approximately 31 kb in length that is located on chromosome 4q34–35. KLKB1 was thought traditionally to occur only in the liver, but subsequent studies using quantitative RT-PCR showed that several non-hepatic tissues also synthesized plasma kallikrein [2].

By comparison, tissue kallikrein (KLK1) is the oldest member of a family that comprises a multigene group of 15 serine proteases designated as KLK1 to KLK15 located in tandem within chromosome 19 q13.3-13.4. The other 14 members, referred to as kallikrein-related peptidases, are characterized by their trypsin- or chymotrypsin-like enzymatic activity. In the skin, KLK5 and KLK7 (Figure 1) have been shown to participate in keratinization, hydrolysis of desmosomal adhesion molecules and terminal keratinocyte differentiation [3,4]. So far, tissue kallikrein KLK1 is the only member of the family that exhibits kininogenase activity both in vitro and in vivo. Previous reports have shown that tissue kallikrein, kininogens, and kinin receptors are expressed in normal and pathological human skin suggesting that kinin peptides may be formed in their microenvironments so as to modulate important skin functions that could be of relevance to the pathogenesis of some skin disorders. Actually, kinins are proinflammatory peptides with the capacity to mimic the four clinical signs of inflammation including pain when they are in contact with a denuded epithelial surface.

In this review, we summarize the role of kinins and their receptors in skin homeostasis and how they contribute to keratinocyte differentiation and wound healing.

**THE KININ SYSTEM IN THE HUMAN SKIN**

**Tissue Kallikrein (KLK1)**

The presence of a kinin-releasing enzyme in human sweat was first reported by Fox and Hilton [5]. The occurrence of tissue kallikrein in human sweat was determined in experiments in which a specific immunoblot assay was used [6]. Subsequently, the amount of immunoreactive tissue kallikrein was measured in sweat obtained from different regions of the body; the highest levels of the enzyme were found in samples taken from the trunk and forehead [7]. Additional studies described the major biochemical properties of the tissue kallikrein present in human sweat.
and showed that its relative molecular mass and inhibitor profile were identical to those described previously for KLK1 [8]. Immunocytochemical procedures performed on human skin tissue sections localized tissue kallikrein in the secretory granules of the “dark cells” in the fundus of eccrine sweat glands [9]. Expression of KLK1 mRNA in eccrine sweat glands was later confirmed by in situ hybridization techniques [10]. Interestingly, KLK1 expression was also found in the stratum granulosum of normal epidermis and in appendageal structures such as the inner root sheath of hair follicular epithelium [10]. Immunohistochemical procedures also localized the kinin-forming substrates (kininogens) in the interstitial tissue space and in the space between keratinocytes, making viable the hypothesis that kinins are formed in the skin [11]. High levels of kininogens occur during inflammatory skin disorders when plasma constituents extravasate from venules in response to the different mediators generated in the inflammatory milieu. Thus, the formation of kinins may be favored during some inflammatory skin diseases.

It has also been suggested that tissue kallikrein may promote skin wound healing since the active form of the enzyme induces keratinocyte migration and proliferation by a mechanism that is mediated by protease-activated receptor-1 and epidermal growth factor receptor (EGFR) activation, and independent of kinin receptors activation and nitric oxide (NO) formation [12]. In fact, tissue kallikrein-induced migration of wounded keratinocyte monolayers was associated with increased phosphorylation of EGFR, extracellular signal regulated kinases 1/2 (ERK1/2) mitogen-activated protein kinase (MAPK) and release of heparin-binding EGF-like growth factor (HB-EGF) and amphiregulin, two EGFR ligands [12].

**Kinin Receptors**

Once formed, kinin peptides exert their effects by activating two G protein-coupled receptors characterized by 7-transmembrane spanning helices; these receptors are known as B1 (BDKR1 gene, B1R) and B2 (BDKR2 gene, B2R). The human kinin B2R is preferentially activated by bradykinin and it mediates most of the physiological effects produced by kinins in different tissues/cells throughout the body including the keratinocyte (Figure 1). Bradykinin and its parent molecule Lys-bradykinin have a short half-life (15 to 30 seconds in plasma) because they are rapidly hydrolyzed by several peptidases known as kininases [1]. Two of these kininases, carboxypeptidases N and M, cleave both kinin molecules at the C-terminal Arg converting them into Lys-des[Arg^9]bradykinin or des[Arg^9]bradykinin, both agonists of the kinin B1R [1]. Of the two B1R ligands described so far the human B1R has greater affinity for Lys-des[Arg^9]bradykinin than for des[Arg^9]bradykinin; the opposite occurs with the rodent B1R [13,14].

The kinin B1R is usually expressed at low levels but is rapidly up-regulated during inflammation or after exposure to noxious stimuli such as lipopolysaccharide and proinflammatory cytokines (TNF-α, IL-1β, IL-2, IFN-γ). Kinin B1R up-regulation in different systems is correlated with nuclear translocation of NF-kB, a process that can be blocked by inhibitors of NF-kB stimulation. In addition, glucocorticoids and protein synthesis inhibitors are able to block B1R up-regulation. Up-regulation of the B2R by inflammatory cytokines such as IFN-γ, IL-1, and TNF-α has also been reported (reviewed in [13]). Both kinin B1 and B2 receptor agonists favor nociception and pain, vasodilatation, and vascular permeability [1,15]; B1R has also been shown to facilitate the chronic itching sensation in a diphenylcyclopropenone-induced model of chronic inflammation, an experimental model in which kinin B1R mRNA and protein levels are increased [16].

In general, stimulation of both kinin B1 and B2 receptors trigger a number of common intracellular signaling pathways that include calcium mobilization, phospholipase C, arachidonic acid release, inositol 3-phosphate, MAPK phosphorylation, and EGFR transactivation, among others. Nevertheless, activation of specific intracellular routes depends on both the stimulus and the biological effect that is characteristic for each cell type.

**KERATINOCYTE PROLIFERATION OR DIFFERENTIATION?**

The expression of both kinin B1R and B2R (mRNA, protein and binding sites) has been observed in normal human skin and in tissues obtained from patients suffering various skin disorders. By using in situ hybridization, RT-PCR and immunohistochemistry we and others have shown the expression of both kinin receptors in the human epidermis, in primary cultures of human keratinocytes and in HaCaT cells, an immortalized keratinocytes cell line [17-20].

The first functional studies reported that bradykinin induced phosphoinositide turnover and 1,2-diglyceride formation and tyrosine phosphorylation of several proteins in cultured human keratinocytes [21,22]. Our group later demonstrated that the in vitro stimulation of B2R induced ERK1/2 MAPK phosphorylation, an event that is partially dependent on EGFR transactivation. ERK1/2 MAPK phosphorylation was also dependent on protein kinase C (PKC) activation since the PKC inhibitor GF109203X abolished it [19]. Similar observations were recorded following stimulation of the kinin B1R in human keratinocytes; transactivation of EGFR was visualized as phosphorylation of a band of 170 kDa. Additional experiments showed that EGFR transactivation resulted in phosphorylation of residues Tyr^415, Tyr^992, and Tyr^1068.
The fact that kinin B1R activation does not result in an increase of $[\text{Ca}^{2+}]_i$ mobilization suggests that keratinocyte differentiation may involve a Ca$^{2+}$-independent PKC, a type of activity that represents 95% of total PKC activity [28]. On the other hand, the calcium increase induced by bradykinin is potentiated by a parathyroid hormone-related peptide, a fragment that has been shown to regulate keratinocyte proliferation and differentiation [29]. Whether any of the parathyroid hormone-related peptides can also potentiate the keratinocyte differentiation induced by kinin B2R agonists needs to be investigated.

Thus, by triggering specific intracellular signaling pathways, kinin peptides may produce growth arrest and activation of keratinocyte differentiation to generate a cellular phenotype that can be identified by detecting specific differentiation markers.

**DOES ACTIVATION OF THE KININ B1R FAVOR WOUND HEALING?**

Wound healing is a complex cascade of events, orchestrated by growth factors and proteases; this process involves several phases: *i*) an inflammatory response, *ii*) wound re-epithelialization, angiogenesis and *iii*) granulation tissue formation, wound contraction, scar formation, and tissue remodeling [30] (Figure 2). As a whole, activation and acceleration of healing require the interaction of different cellular types such as leukocytes, fibroblasts, endothelial cells, and keratinocytes.

Diverse *in vitro* and *in vivo* studies have demonstrated the expression of kinin B1R on several cellular players of wound healing. Kinins are important inflammatory...
mediators and can modulate keratinocyte differentiation and proliferation/migration of endothelial cells. However, the role of kinin B1R in wound healing has been scarcely investigated. So far, only three groups have addressed this topic, but have reported contradictory results. The recent study performed by Soley et al. [31] using kinin B1R knockout mice showed a delay of the skin healing process; in fact, wild-type mice showed a complete resolution of wound healing at day 12 whereas kinin B1R knockout mice resolved lesions at day 17, demonstrating that kinin B1R is an important player in this process. The results obtained by this group are in agreement with our results in which topical administration of the kinin B1 receptor agonist, des[Arg9]bradykinin accelerated wound closure, supporting participation of kinin B1R in wound healing [32]. On the contrary, Desposito et al. [33] observed that systemic treatment of mice wounds with the stable B1R agonist SarLys[Hyp1,Lgl4,DPhe8]desArg9-bradykinin had no effect on wound closure. However, the extremely high EC50 (400 ± 46 nM) of this agonist in the mouse when compared with that of the natural agonist des[Arg9]bradykinin (EC50 = 21 ± 3 nM) [34] may explain the lack of effect reported by them in this species. Moreover, Desposito et al. [33] performed 8 mm diameter full-thickness wounds on the dorsal skin of agonist-treated mice and the results obtained were compared with those observed in similar wounds made on untreated mice. This type of comparison is difficult because there are different healing rates in different mice even when they come from the same litter. By comparison, our model considered a topical treatment and two full-thickness 6 mm punch wounds performed on the back of each mouse in such a way that comparison between wounds was performed in the same animal, avoiding animal variability.

THE KININ B1R IN THE INFLAMMATORY, PROLIFERATIVE, AND REMODELING WOUND HEALING PHASES

Inflammatory Phase

In this phase, migration of neutrophils and monocytes from blood compartment to the wound removes blood clot and cell debris from damaged tissue (Figure 2). Leukocytes are recruited by multiple released vasoactive mediators such as kinins, histamine, prostaglandins, leukotrienes, thrombin, IL-8, monocyte chemoattractant protein-1 (MCP-1), or bacterial lipopolysaccharides and chemotactic peptides [30,35]. At the wound site, neutrophils are considered to be primarily bactericidal, killing microorganisms by means of reactive oxygen species and neutrophil extracellular traps [36]. On the other hand, monocytes are recruited by specific chemoattractants such as transforming growth factor-β (TGF-β) and MCP-1, and then differentiate into M1 pro-inflammatory macrophages that later acquire a M2 phenotype (anti-inflammatory and tissue repair activities). Macrophages have an essential role because macrophage-depleted wounds show defective wound repair [30]. M1 macrophages secrete MCP-1 that is crucial for wound healing since MCP-1 deficient mice have an anomalous re-epithelialization [37]. Another important factor is TGF-β1 because knockout animals or inhibition of the major signaling pathways activated by TGF-β1 show an accelerated epithelialization and impaired inflammatory response [38,39]. By comparison, M2 macrophages acquire the capacity to produce platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), two mediators that initiate granulation tissue formation.

Schremmer-Danninger et al. [35] showed that B1R is increased in human skin biopsies obtained following surgery whereas kinin B2R expression did not change in the traumatized skin. Furthermore, using a murine model of thermal injury Rawlingson et al. [40] reported an early involvement of both kinin B1 and B2 receptors in plasma extravasation into the burn wound suggesting an important regulatory role for kinin receptors at the beginning of the wound healing process. Actually, kinin B1R agonists increase venular permeability by inducing contraction of endothelial cells and hence producing intercellular gaps through which plasma diffuse freely. Further, B1R agonists activate phospholipase C and NO generation in endothelial cells of precapillary vessels producing arteriolar dilatation [41]. On the other hand, the kinin B1R is an important player for recruitment of both neutrophils and macrophages at the site of injury and the high level of cytokines (TNF-α, IL-1β, IL-2, and IL-4), present in the inflammatory milieu up-regulate the expression of B1R in these leukocytes [41,42] (Figure 3). Stimulation of kinin B1R in human neutrophils results in chemotaxis, release of several proteases and up-regulation of CD11b/CD18 integrins [42-44]. Interestingly, kinin B1R agonists also induce the expression of intercellular adhesion molecule, ICAM-1 in endothelial cells [44]. The interaction between both neutrophils and endothelial cells facilitates neutrophil migration into the injury site. In addition, kinin B1R activation modulates the release of prostaglandins, TNF-α, IL-1β and chemokines [41]. Importance of kinin B1R on leukocytes recruitment is supported by studies showing that kinin B1R knockout mice exhibit lower numbers of neutrophils and mononuclear cells than wild-type animals at the wound site [31]. Moreover, our results show that topical application of a kinin B1R agonist onto the wounds increases recruitment of CD68 immunoreactive macrophages (unpublished results). Only a few studies have focused on the consequence of kinin B1R activation in macrophages, but early studies showed that stimulation of macrophages with a kinin B1R agonist induces TNF-α and IL-1 release, and increases NO levels
factor receptors and some of their ligands (TGF-α, TGF-β, amphiregulin, epiregulin, HB-EGF, neuregulins 1 and 2 and keratinocyte growth factor). When receptors are activated, they trigger a number of signaling cascades that lead to reorganization of the cytoskeleton and phosphorylation of transcription factors involved in the expression of proteins/proteases required for keratinocyte migration, proliferation, and differentiation [47]. Wound healing experiments performed on TGF-α deficient-mice show that the early phase of re-epithelialization is delayed [48] whereas a lack of HB-EGF produces a marked setback in wound closure as a consequence of severe delay in keratinocyte migration [49]. As mentioned before TGF-β is an important factor for re-epithelialization because it initiates keratinocyte migration.

The activation of kinin B1R regulates positively keratinocyte differentiation, but does not increase keratinocyte proliferation in vitro or in the margin of mice wounds treated with a B1R agonist [19,20,32]. Apparently, kinin B1R stimulation produces opposite effects on cell migration depending on the cell type involved; our in vitro approach showed that kinin B1R agonists produce a
weak keratinocyte migration whereas its topical application onto wounds in an in vivo mouse model significantly reduced the wound area, probably by augmenting keratinocyte migration [32]. The in vivo microenvironment is much more complex than the in vitro situation and possibly the topical application of a kinin B1R agonist induces the release of cytokines (IL-4) and growth factors (HB-EGF) [32,50] or activates metalloproteases like MMP-2 and MMP-9, key players of keratinocyte migration [51] (Figure 3). Coincidently, stimulation of kinin B1R produces a transient c-JunN-terminal kinase phosphorylation and JunB nuclear translocation, transcription factor, which is known to regulate IL-4 expression [50]. Using a mouse model of wound healing, we observed that immunoreactivity for both MMP-2 and MMP-9 gelatinases was concentrated around wound borders and that cells expressed both MMPs in a cytoplasm area that was in close contact with the extracellular matrix [32] suggesting an association with extracellular matrix degradation or cleavage of growth factors/cytokines sited throughout the matrix.

An essential requirement for keratinocyte adhesion and migration is to change the integrin profile to allow its release from tight and adherens junctions. Integrins mediate cell-matrix interactions (cell polarity and migration) and act as signaling molecules across the plasma membrane that transduce both “inside-out” and “outside-in”. The integrin repertoire in basal keratinocytes is restricted to α2β1, α3β1, α9β1, and α6β4, whereas during wound healing α3β1 and α9β1 are up-regulated. Integrins can also regulate the balance between cell proliferation and differentiation to produce an effective re-epithelialization and a firm attachment of the new epithelial layer [47]. Thus, lack of integrins α3, α6, β4, β1, and β6 results in a disorganized basement membrane and abnormal cell adhesion, proliferation and differentiation [52]. There are few studies concerning the role of kinin B2R on integrin expression/activation [53,54], but there are no studies that analyze the effect of kinin B1R agonists on the expression/activation of integrins in keratinocytes and during wound healing.

When formation of new stroma or granulation tissue begins macrophages, fibroblast and blood vessels move into the wound at the same time. In this phase, macrophages provide a continuing source of growth factors, like PDGF and TGF-β1, necessary to stimulate fibroplasia and angiogenesis. In the wound, and influenced by the local microenvironment, macrophages undergo phenotypic switching from M1 to M2 phenotype, an event that depends on down-regulation of IL-10 and up-regulation of IL-4 and IL-13 [30]. Likewise, fibroblasts, activated by PDGF and TGF-β1 in concert with extracellular matrix molecules, proliferate, migrate, and produce the new matrix necessary to support cell ingrowth. Studies on the effect of kinin B1R agonists on fibroblasts are contradictory; in human embryonic lung fibroblasts they stimulate type I collagen synthesis, whereas in rat cardiac myofibroblast they decrease collagen secretion [55,56]. Further, kinin B1R agonists have been reported to have no effect on mouse fibroblast migration and proliferation [33]. In alliance with macrophages and fibroblasts, the new vessels move into the wound to initiate formation of granulation tissue. Endothelial cells initiate angiogenesis in response to growth factors like FGF-2 and VEGF, which are partially secreted by macrophages. The importance of VEGF-A for an adequate wound healing (Figure 3) has been demonstrated by using neutralizing VEGF-A antibodies onto porcine wounds, treatment that strongly impaired angiogenesis and formation of granulation tissue [57,58]. Several reports deal with participation of kinin peptides in angiogenesis; they produce an angiogenic effect on endothelial cells, by up-regulating FGF-2 expression, potentiating migration and cell growth or by stimulating VEGF synthesis and release [59]. We have shown that B1R stimulation produced significant endothelial cell migration and release of both MMP-2 and MMP-9, but did not increase endothelial cell proliferation [50]. Our in vitro studies so far indicate that kinin B1R agonists stimulate keratinocytes to release VEGF and IL-4, growth factors that promote endothelial cell migration and release of MMP-2 and MMP-9, two crucial events during angiogenesis (Figure 3).

PARTICIPATION OF KININS AND THEIR RECEPTORS IN OTHER SKIN DISORDERS

Psoriasis

Early studies showed that human biopsies obtained from patients suffering basal cell carcinoma, lichenificated atopic eczema, and psoriasis have expression levels of tissue kallikrein (KLK1) and kinin receptors that are similar to those observed in normal skin [18,35]. On the other hand, several reports have indicated that angiotensin-converting enzyme inhibitors (ACEI) may induce and/or exacerbate psoriasis, an effect that may be due to inhibition of kinins degradation by ACEI; then, the increased levels of kinins in the skin might increase inflammation and make psoriasis worse [60]. Interestingly, presence of ACE insertion polymorphism has been associated to occurrence of psoriasis. This allele has been associated to low ACE activity, a quality that results in reduced kinin degradation [61]. In agreement with this idea is the fact that psoriasis patients have elevated plasma levels of kininogens, the substrates required for kinin release [62]. However, the vascular response to kinins when they are injected intradermally into psoriasis patients is not altered when compared to normal volunteers [63]. Another source of kinins in psoriasis patients may come...
from circulating neutrophils, which infiltrate the lesional epidermis in these patients. It is important to mention that human neutrophils contain the components, which are needed to form kinins, tissue kallikrein (KLK1) and kininogens [1,42,44]. Moreover, elevated levels of all KLKs have been found in serum and in the lesional stratum corneum of patients with psoriasis [64].

In addition to their actions as proinflammatory peptides, kinins have also been associated to keratinocyte differentiation. Actually, kinin B2R agonists do not increase cell proliferation, but they induce keratinocyte differentiation as established by the expression of the differentiation markers cytokeratin 10, involucrin, and profilaggrin [19,20]. Coincidentally, experiments performed on B2 knockout mice show that these animals have epidermal cellular hyperproliferation and acanthosis when compared with wild type mice [64]. Whether the increased proliferation of keratinocytes, which speeds up their cell cycle, results from B2R malfunction in the microenvironment of lesional skin in psoriasis patients remains to be investigated.

**Atopic Dermatitis**

Bradykinin has been described as a potent histamine-independent pruritogen in lesional skin of atopic dermatitis. This peptide induces intense itch and pain in lesional skin and the increase in pain does not suppress itch feeling [65]. Notably, bradykinin produced weak itch and pain, of almost identical strength, in non-lesional skin of patients with atopic dermatitis and in healthy volunteers.

Experimental studies using animal models of itch-related scratching show that pretreatment of mice with a kinin B1R antagonist reduces this response when inflammation is induced with complete Freund’s adjuvant [66]. Another mouse model, which uses oxazolone to induce atopic dermatitis, results in up-regulation of B1 and B2 receptors in the skin. Both B1 and B2 receptor antagonists partially reduced the pruritus produced by oxazolone suggesting that participation of kinins and their receptors may have an important role in this model of atopic dermatitis. In fact, knockout mice, which are deficient in kinin B1 or B2 receptors display reduced pruritus following intradermal injection of trypsin, a situation that is also observed when mice are intraperitoneally injected with B1 or B2 receptor antagonists prior challenge [67].

It is important to consider that in addition to their direct effects on pain and pruritus, kinins can increase the release of substance P, calcitonin gene-related peptide, and prostaglandin E₂, three major mediators of pruritus and key players of atopic dermatitis and psoriasis. In the skin, neuropeptides are located in nerve fibers of the papillary layer, around skin appendages and blood vessels. Future interdisciplinary studies should focus on the intricate network of interactions that exist between different mediators, their receptors and the cells which are responsible for their production.

**CONCLUSION**

Biological actions of kinins range from increase in vascular permeability to angiogenesis and keratinocyte differentiation. In the skin, kinins and other members of the kallikrein system have been investigated for their participation in several physiological and pathological processes. Kinins, and in particular kallikrein-related peptidases (KLK5 and KLK7), modulate keratinocyte differentiation and precise steps of wound healing such as plasma extravasation, leukocytes chemotaxis, keratinocyte migration, and angiogenesis. In addition, kinins can enhance their effects by inducing the release of angiogenic molecules (IL-4 and VEGF) from keratinocytes, endothelial cells, neutrophils, and macrophages.

The complexity of wound healing is amplified by local factors, such as ischemia and infection, also by systemic factors such as age, nutritional status, and pathologies such as diabetes mellitus. The final result is the formation of a scar, which is sufficiently functional. However, in some cases, the repair process is disorganized or insufficient resulting in hypertrophic scars, keloids, or chronic wounds that do not heal. Therefore, new studies could help us to establish the role of kinin peptides and especially of kinin B1R agonists in wound healing, allowing us in the future to identify new molecular targets that contribute to re-epithelialization and wound closure during chronic wound healing as it occurs in diabetic patients.

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