**Name of Journal: *World Journal of Dermatology***

**ESPS Manuscript NO: 22633**

**Manuscript Type: Review**

P2X7 receptor in skin biology and diseases

Geraghty NJ *et al*. P2X7 in the skin

**Nicholas J Geraghty, Debbie Watson, Sam R Adhikary, Ronald Sluyter**

**Nicholas J Geraghty, Debbie Watson, Sam R Adhikary, Ronald Sluyter,** School of Biological Sciences, University of Wollongong, Wollongong NSW 2252, Australia

**Nicholas J Geraghty, Debbie Watson, Sam R Adhikary, Ronald Sluyter,** Illawarra Health and Medical Research Institute, Wollongong NSW 2252, Australia

**Author contributions:** All the authors contribute to the paper.

**Conflict-of-interest** **statement:** The authors declare no conflicts of interest regarding this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** **Ronald Sluyter, PhD, Associate Professor,** School of Biological Sciences, University of Wollongong, Northfields Avenue, Wollongong NSW 2522, Australia. rsluyter@uow.edu.au

**Telephone:** +61-2-42215508

**Fax:** +61-2-42218130

**Received:** September 9, 2015

**Peer-review started:** September 10, 2015

**First decision:** November 7, 2015

**Revised:** November 23, 2015

**Accepted:** January 27, 2016

**Article in press:**

**Published online:**

# Abstract

The P2X7 receptor is a trimeric ligand-gated cation channel present on immune and other cells. Activation of this receptor by its natural ligand extracellular adenosine triphosphate results in a variety of downstream responses, including the release of pro-inflammatory mediators and cell death. In normal skin, P2X7 is present on keratinocytes, Langerhans cells and fibroblasts, while the presence of this receptor on other cutaneous cells is mainly inferred from studies of equivalent cell types present in other tissues. Mast cells in normal skin however express negligible amounts of P2X7, which can be upregulated in cutaneous disease. This review discusses the potential significance of P2X7 in skin biology, and the role of this receptor in inflammatory skin disorders such as irritant and chronic dermatitis, psoriasis, graft-versus-host disease, as well is in wound healing, transplantation and skin cancer.

**Key words:** P2X7 receptor; Purinergic receptor; Extracellular ATP; CD39; Skin biology; Skin immune system

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The P2X7 receptor is present on immune, stromal and epithelial cells. Activation of this receptor by its natural ligand, extracellular adenosine triphosphate, causes a variety of downstream effects including release of inflammatory mediators and growth factors, as well as cell death. P2X7 has various functions on skin cells, and studies of mouse models of disease and of human cells and tissues highlight emerging roles for this receptor in common skin disorders.

Geraghty NJ, Watson D, Adhikary SR, Sluyter R. P2X7 receptor in skin biology and diseases. *World J Dermatol* 2016; In press

# INTRODUCTION

# *Overview*

The skin fulfils important roles such as barrier protection, thermoregulation, sensation, vitamin D synthesis[1] and immunological protection[2]. Extracellular nucleotides and nucleosides function through a signalling network comprising cell-surface purinergic (P2X, P2Y and adenosine) receptors and ecto-nucleotidases[3]. This network plays important roles in both physiology and pathophysiology, and as such is an emerging therapeutic target to combat many diseases[3]. Evidence indicates that the extracellular nucleotide adenosine triphosphate (ATP) and cell surface purinergic receptors and ecto‑nucleotidases play important roles in skin biology[4,5]. Within this context the P2X7 receptor has a major role. This review aims to describe the cellular distribution of P2X7 in skin, and the potential significance of this receptor in skin biology and disease.

## Purinergic signalling

Purinergic signalling comprises a complex network of cell-surface receptors, where activation is mediated by extracellular signalling molecules such as adenosine triphosphate (ATP), which can act as a danger associated molecular pattern (DAMP) when released into the extracellular milieu after cell stress, damage or death[6]. Extracellular ATP or other nucleotides can subsequently lead to activation of two purinergic P2 receptor subtypes; P2X and P2Y receptors. P2X receptors are a family of seven trimeric ATP‑gated cation channels (P2X1-7); while P2Y receptors are a group of eight G protein-coupled receptors (P2Y1, 2, 4, 6, 11-14). P2 receptors are expressed on numerous cell subtypes, and activation of these receptors by extracellular ATP, or other nucleotides for some receptor subtypes, are important in inflammation and immunity[7]. Activation of P2 receptors by ATP is regulated by the ecto-nucleotidases CD39 and CD73. CD39 degrades ATP into adenosine diphosphate (ADP) and subsequently adenosine monophosphate (AMP) before AMP is converted to adenosine by CD73[8]. Adenosine can then activate P1 receptors; a family of purinergic receptors selective for adenosine[3].

## The P2X7 receptor

The P2X7 receptor belongs to the family of P2X receptors, which as noted above, are trimeric ATP-gated cation channels. Each P2X7 subunit is composed of intracellular amino and carboxyl termini, as well as two trans-membrane domains connected by a long glycosylated extracellular loop, containing the ATP-binding site[9]. Activation of the P2X7 receptor by extracellular ATP results in K+ efflux, and Na+ and Ca2+ influx, as well as the flux of organic cations and anions including dyes[10]. P2X7 is present on mononuclear leukocytes, but is also found on other cell types including epithelial cells and fibroblasts[7]. P2X7 activation results in the stimulation of numerous pathways including the release of various pro-inflammatory mediators, modulation of various cell-surface receptors, formation of reactive oxygen and nitrogen species, killing of intracellular pathogens and cell death[11] (Table 1). As a result of various studies in humans and animals, P2X7 is emerging as an important molecule in various biological processes[12] and is attracting considerable interest as a therapeutic target in a wide-range of diseases[13]. Due to this, and the increasing knowledge about the expression and function of P2X7 within the skin (Figure 1), there is a growing interest in the role of P2X7 in skin biology and related disorders.

# P2X7 IN SKIN BIOLOGY

## Keratinocytes

Keratinocytes comprise the majority of cells within the epidermis to provide a physical and immunological barrier[14]. It is well established that human and rodent keratinocytes express P2X7. Immunohistochemistry reveals that P2X7 is expressed in the upper layer of human and rat skin[15,16] suggesting that this receptor may be involved in the death of terminally differentiated keratinocytes. Consistent with this concept, human keratinocyte P2X7 co-localises with markers of apoptosis[16], while P2X7 activation induces human keratinocyte death *in vitro*[17] and increases murine keratinocyte death *in vivo*[18]. P2X7 has been reported to be present on human HaCaT keratinocytes[19] and can mediate ATP-induced death of these cells[20], although the presence of P2X7 in these cells has not been confirmed in all studies[21]. Nevertheless over-expression of protein kinase C alpha (PKC) can result in increased expression of P2X7 in these cells[19] indicating that this kinase may be involved in the up-regulation of keratinocyte P2X7 in the upper layers of the epidermis. Despite the apparent localisation of keratinocyte P2X7 to the upper layers of the epidermis, functional studies (using ATP-induced dye uptake measurements) show that the majority of human and murine keratinocytes express P2X7[22,23]. Thus, these immunohistochemistry and functional studies combined suggest P2X7 may be present in all layers of the epidermis, with receptor expression increasing with keratinocyte differentiation and its upregulation resulting in the death of terminally differentiated keratinocytes.

In addition to cell death, P2X7 activation can induce interleukin (IL)-6 release from human keratinocytes[24], and can mediate ultraviolet radiation-induced IL-1 release from both human and murine keratinocytes[25,26]. P2X7 activation on HaCaT keratinocytes has also been implicated in the activation of disintegrin-like metalloprotease-mediated shedding of E-cadherin and transforming growth factor alpha (TGF-) induced by the major bee venom component melittin[27]. Collectively, these results indicate that P2X7 on keratinocytes may also be important in inflammatory and immune functions of these cells.

## Langerhans cells

Langerhans cells (LCs) are professional antigen-presenting cells located in the epidermis, and are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance[28]. P2X7 is present on both human and murine LCs from skin[22,23,29], as well as on migratory LCs (langerin+ dendritic cells (DCs) from human skin explants[30]. Although functional studies of P2X7 on LCs are largely limited to ATP-induced dye uptake measurements[22,23,29], P2X7 activation of migratory LCs causes increased cell-surface expression of the IL-23 receptor and the alarmin receptor for advanced glycation end products (RAGE)[30]. Further, P2X7 is present on human LCs derived from monocytes *in vitro* and activation of this receptor results in the rapid shedding of CD23 (the low affinity IgE receptor) from these cells[22]. Finally, P2X7 is present on the murine LC-like line, XS106, and activation of this receptor results in the release of IL-1 from these cells[31]. Collectively, these studies support a role for P2X7 activation on LCs in promoting inflammation and immunity.

The relative amount of P2X7 activity on LCs appears to be negatively modulated by the ecto-nucleotidase CD39 (Figure 2). It has long been known that LCs express high ecto-ATPase and ecto-ADPase activities[32], which is almost completely due to CD39[33]. Comparison of human monocyte-derived LCs and monocyte-derived DCs generated from the same subjects reveals that the relative P2X7 activity is lower on monocyte-derived LCs compared to monocyte-derived DCs despite similar amounts of cell-surface P2X7 expression[22]. This difference in activity between these two cell types is inversely associated with cell-surface CD39 expression[22]. These observations are consistent with the negative regulation of P2X7 activation by CD39 on murine peritoneal macrophages[34] and murine bone marrow-derived mast cells[35] (Figure 2). Notably, CD39 on LCs has been implicated in facilitating a protective or tolerogenic role for these cells in dermatitis[33,36]. Collectively, variations in CD39 activity may play important roles in the regulation of P2X7 activation on LCs, and in determining the relative contribution of these cells in immunity or peripheral tolerance.

## Dermal dendritic cells

Dermal DCs are a heterogeneous population of professional antigen-presenting cells, and like LCs are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance[37]. It is well documented that P2X7 is present on human and murine DCs derived from monocytes[38-41] or within lymphoid tissues[42,43], but direct evidence for P2X7 on dermal DCs is limited. P2X7 is present on foetal skin-derived DCs, where it may be involved in T cell stimulation[44], however direct evidence for DC P2X7 in this process is not well established. Interpretation of these results is complicated by subsequent findings that extracellular ATP can induce human and murine T cell proliferation *via* P2X7 in an autocrine fashion[45]. Thus, the role of P2X7 in T cell stimulation by dermal DCs remains to be elucidated.

P2X7 is also expressed on migratory DCs from human skin explants[30]. Activation of P2X7 on skin migratory DCs resulted in the release of IL-1 and IL-6, as well as the up-regulation of IL-23 and vascular endothelial growth factor (VEGF) mRNA and cell-surface expression of HLA-DR, and the co-stimulation molecule CD86[30]. Finally, P2X7 activation on these cells promotes the development of T helper 17 (Th17) cell responses[30].

## Dermal macrophages

Dermal macrophages are a heterogeneous population of cells important in innate and adaptive immunity, as well as in tissue homeostasis and wound healing[37]. Direct evidence for P2X7 on dermal macrophages is lacking, but it is well established that this receptor is present on human and murine macrophages derived from monocytes[46-48] or isolated from tissues[49,50]. P2X7 activation on human and murine macrophages results in the release of pro-inflammatory mediators such as IL-1 and prostaglandin E2[51], as well as the production of reactive oxygen species[52], and killing of intracellular mycobacteria[53], chlamydia[54] and toxoplasma[55]. Of note, P2X7 activation eliminates *Leishmania amazonensis*, the causative agent of human cutaneous leishmaniasis[56], within murine peritoneal macrophages[57], supporting the potential importance of macrophage P2X7 in skin biology.

## Mast cells

Mast cells are present in the dermis, and play important roles during inflammation and immunity[58]. In contrast to other tissues, mast cells in normal human and murine skin express negligible amounts of P2X7[59,60], and ATP incubation of these cells fails to cause IL-1 release despite inducing IL-1 release from murine bone marrow-derived mast cells[61]. This negligible P2X7 expression on skin mast cells is due to fibroblasts expressing the retinoic acid-degrading enzyme Cyp26b1[61]. Although the exact mechanism by which these fibroblasts prevent P2X7 expression on skin mast cells is not known, exogenous retinoic acid upregulates P2X7 expression on bone marrow-derived mast cells[61]. This suggests that Cyp26b1-expressing fibroblasts in mice regulate retinoic acid concentrations to suppress P2X7 expression on skin mast cells. Whether this same inhibitory mechanism operates for human skin mast cells or limits P2X7 expression on other dermal cell populations remains to be determined.

## Granulocytes

Granulocytes (neutrophils, eosinophils and basophils) are circulating innate immune cells that infiltrate the skin to promote inflammation and immunity[62]. Small numbers of neutrophils also circulate through normal skin, where they are presumed to function as sentinels[63]. Direct evidence for P2X7 on granulocytes within the skin is lacking, but P2X7 is present on human blood eosinophils[64,65] and murine bone marrow-derived basophils[66]. P2X7 activation on human eosinophils results in cation fluxes, increased expression of the integrin CD11b and reactive oxygen species formation, as well as chemotaxis of these granulocytes[64,65]. P2X7 activation is involved in the IgE-dependent activation of murine bone marrow-derived basophils[66], which may have implications for cutaneous allergic inflammation. Collectively, these results suggest P2X7 may play important roles in the pro-inflammatory actions of these granulocytes.

In contrast to eosinophils and basophils, P2X7 appears to be absent on neutrophils. Repeated evidence demonstrates that P2X7 is not present in human blood neutrophils[67,68]. Neutrophil infiltration however is reduced by P2X7 deficiency in murine models of skin inflammation[69] suggesting that P2X7 may be present on murine neutrophils or that P2X7 activation on other skin cells indirectly promotes neutrophil infiltration. Nonetheless future studies are required to determine if P2X7 is present on murine neutrophils or on neutrophils within skin.

## T cells

Both human and murine skin contains populations of tissue-resident and recirculating T cells, which are key cellular mediators of adaptive immunity[70]. Direct evidence for P2X7 on these skin T cells is lacking, however it is well known that human and murine T cell subsets from blood and lymphoid tissue express P2X7[71]. P2X7 activation induces the rapid shedding of CD62L (L-selectin) from both human and murine CD4+ and CD8+ T cells[72,73]. This cell adhesion molecule can regulate the migration of certain T cell subsets to sites of skin inflammation[74]. Thus, the possibility remains that P2X7-induced CD62L shedding may regulate T cell migration within the skin. There is also evidence that P2X7 activation promotes Th17 cell development in humans[75] and mice[76]. Thus, a further possible role for P2X7 on skin T cells is in the generation of cutaneous Th17 responses.

Dendritic epidermal T cells (DETCs) are resident T cells found in the epidermis of mice, but not humans, and have important roles in inflammation, immunity and wound healing[77]. Murine DETCs express low amounts of P2X7 mRNA[26] but an earlier study, using an anti-P2X7 monoclonal antibody and ATP-induced dye uptake measurements, failed to observe P2X7 on DETCs, despite the presence of P2X7 on keratinocytes and LCs[23]. Nevertheless ATP, released from keratinocytes, can enhance IL-17 release from CD3-activated DETCs[26]. A direct role for P2X7 activation on DETCs in this process was not established, and these cells express high amounts of mRNA for P2X1, P2X2, P2X3 and P2X5[26], thus it remains to be established if DETCs express functional P2X7. It also remains to be established if P2X7 is present on resident T cells in human skin, which are considered to be the equivalent cell type to murine DETCs[77].

## B cells

B cells are key cellular mediators of adaptive immunity, but their role in the skin immune system is poorly understood. Emerging evidence indicates the presence of B cells in normal skin, although it is unknown if they are skin-resident or circulating B cells[78]. Further evidence indicates roles for B cells in cutaneous immunity and inflammation, and skin cancer[78]. As for T cells, evidence for P2X7 on skin B cells is lacking, but P2X7 is present on human and murine B cells from blood and spleen[79,80]. P2X7 activation results in the rapid shedding of CD62L from human B cells[79] suggesting that this mechanism may regulate B cell migration within the skin. P2X7 activation also results in the rapid shedding of CD23 from human and murine B cells[80]. Although the functional significance of this process is yet to be established, soluble CD23 can regulate IgE production[81]. Thus, P2X7-mediated release of soluble CD23 may regulate the development or severity of atopic dermatitis.

## Fibroblasts

Fibroblasts are a heterogeneous population of cells located in the dermis with a variety of functions including tissue homeostasis, wound healing and inflammation[82]. Human skin fibroblasts express P2X7[83,84]. In addition to cation fluxes, dye uptake and membrane depolarisation, P2X7 activation in these cells results in microvesiculation, process elongation, IL-6 release and apoptosis[84]. High concentrations of glucose potentiate these P2X7-mediated responses[84]. This effect of glucose is attributed to a redistribution of P2X7 on the cell surface rather than increased expression of this receptor[84]. Of note, skin fibroblasts from Type 2 diabetic subjects demonstrate enhanced P2X7-mediated responses compared to skin fibroblasts from normal subjects[85]. This enhanced P2X7 activity is suggested to be an important mechanism in the pathogenesis of vascular damage in diabetic subjects[85], but this concept is yet to be developed. P2X7 may also be expressed on murine skin fibroblasts, but observations are limited to the subcutaneous fibroblast cell line L929[86]. This study demonstrated that P2X7 activation mediates cation fluxes, membrane depolarisation and cytotoxicity in these cells.

# P2X7 IN SKIN DISORDERS

## Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a type IV delayed-type hypersensitivity (DTH) reaction characterised by a T cell-mediated response to allergens[87]. A role for P2X7 in ACD in humans is supported by the up-regulation of this receptor in the epidermal basal layer of inflamed skin of atopic dermatitis patients compared to normal human skin[88], while other experimental evidence supports a role for P2X7 in murine models of ACD. ACD is commonly studied using animal models of contact hypersensitivity (CHS)[87]. Both pharmacological blockade and genetic deficiency of P2X7 impairs CHS responses in mice[89]. This impaired CHS response is due to the absence of P2X7-mediated IL-1 release from DCs abrogating the sensitising capacity of these cells[89]. Intradermal injection of the hydrolysis-resistant nucleotide, adenosine gamma-thiotriphosphate (ATPS), can also enhance the CHS response in mice[31] indirectly supporting a role for P2X7 in ACD. However, ATPS cannot activate murine P2X7 *in vitro*[90] despite activating other mammalian P2X7[90,91]. This raises the possibility that ATPS acts on other P2 receptors in this model of murine CHS[31]. Notably, non-metal haptens can induce ATP release from primary human and HaCaT keratinocytes[92] providing a possible source for extracellular ATP in ACD.

## Irritant contact dermatitis

Irritant contact dermatitis (ICD) is an inflammatory reaction to chemical irritants involving cells of the innate immune system[93]. Experimental evidence in mice supports a role for P2X7 in ICD. Both pharmacological blockade and genetic deficiency of P2X7 impair oedema, IL-1 production and neutrophil infiltration in croton oil-induced ICD[69]. Furthermore, clodronate-depletion of DCs and macrophages, or pharmacological inhibition of caspase-1 reduced ICD in this model[69] suggesting that P2X7 on DCs and macrophages may contribute to the pathogenesis of ICD through IL-1 production. In addition to a role for P2X7 on DCs and macrophages in ICD, P2X7 on mast cells is involved in retinoid-induced ICD. This form of ICD is mediated by aberrant release of ATP within the skin and increased P2X7 expression on skin mast cells[61]. A role for mast cell P2X7 in chemical-induced ICD remains to be determined.

Consistent with a role for P2X7 in ICD, chemical irritants can induce ATP release from murine and human keratinocytes[33,94,95], and genetic deficiency of CD39 exacerbates croton oil-induced ICD in mice[33,94]. Croton oil also decreases ATPDase activity in mice[20] indicating that chemical irritants may further potentiate P2X7-mediated responses by causing a sustained increase in ATP concentrations during chemical irritant exposure. Of note, zinc deficiency, which is often associated with increased cutaneous inflammation, enhances ICD in mice and augments chemical irritant-induced ATP release from murine keratinocytes and in murine skin[36]. Further, zinc deficiency in murine ICD is associated with loss of LCs[36], which play a protective role in ICD through CD39 expression[33]. This suggests that both increased ATP release from keratinocytes and impaired hydrolysis of ATP by LCs may contribute to the pathogenesis of ICD.

## Psoriasis

Psoriasis is a chronic inflammatory disorder manifesting as plaque or pustular-like lesions of the skin. Psoriasis emerges due to excessive keratinocyte renewal, caused by an innate immune cell response and subsequent engagement of the adaptive immune response, resulting in a feed forward mechanism of inflammation[96]. Although the role of P2X7 has not been investigated in animal models of psoriasis, *in vitro* studies support a role for P2X7 in psoriasis pathogenesis. Interferon gamma (IFN-), a pro-inflammatory cytokine implicated in psoriasis development[96] can upregulate the expression of P2X7 in primary keratinocytes[88]. Moreover, injection of the P2X7 agonist 3’-O-(4-benzoyl)benzoyl ATP (BzATP) into normal human skin explants induces increased expression of cytokines and other molecules commonly associated with psoriasis, including IL-1, IL-6 and TNF-[30]. Importantly, these responses could be prevented through pharmacological blockade of P2X7[30]. Of note, P2X7 expression in this model also caused the functional maturation of cutaneous DCs and promoted the development of Th17 responses[30], both of which are important contributors to psoriasis pathogenesis[96].

## Cutaneous graft-versus-host disease

Graft-versus-host disease (GVHD) is a common complication following bone marrow transplantation used to treat haematological malignancies[97]. Two types of GVHD develop in patients; acute GVHD emerges early after transplantation, while chronic GVHD is a persistent long-lasting inflammation, with both forms causing inflammatory damage to the skin, as well as the gastrointestinal tract, liver and lungs[97]. Pharmacological blockade and genetic deletion of P2X7 attenuates the development of disease in murine models of allogeneic GVHD[98,99]. Additionally, experimental evidence establishes a model whereby ATP release at the site of tissue damage causes upregulation of the co-stimulatory molecules, CD80 and CD86 on DCs to promote T cell responses[98]. P2X7 deficient mice receiving allogeneic bone marrow transplants demonstrated reduced serum concentrations of the pro-inflammatory cytokines IFN‑, TNF-, and IL-6[98], which was replicated through blockade of the P2X7 receptor *in vivo* using the nucleoside reverse transcriptase inhibitor stavudine[99]. Although the effect of P2X7 deficiency or blockade on acute skin GVHD was not directly reported in either study[98,99], skin is a known target organ of GVHD in these models of allogeneic bone marrow transplantation[100]. Of note, P2X7 blockade failed to prevent the development of chronic skin GVHD[98], suggesting P2X7 may not play a role in skin inflammation in chronic GVHD, or longer periods of P2X7 blockade are required for prevention of chronic skin GVHD.

## Wound healing

Wound healing is classically defined by the disruption of haemostasis, migration of platelets resulting in blood clotting, followed by inflammation, cell proliferation and tissue remodelling[101]. Studies both *in vitro* and *ex vivo* have demonstrated a role for P2X7 in the process of wound healing. P2X7 is important for early cell migration and infiltration of immune cells required for wound healing, with P2X7 deficient cells showing a reduced migratory ability in an *in vitro* wound repair model suggesting that lack of P2X7 affects chemotaxis[102]. P2X7 also promotes the release of VEGF from primary monocytes, important for control of angiogenesis and wound healing[103]. Conversely, P2X7 is down-regulated on keratinocytes during wound healing[104], suggesting that this reduced expression may be linked with reduced apoptosis of keratinocytes to promote healing of the epidermis. Mast cells also play an important role in wound remodelling and repair[105], but express negligible P2X7 in normal skin[59,60]. It remains to be determined if P2X7 on mast cells is upregulated during wound healing.

## Skin transplantation

Transplantation is an important therapy for many end-stage diseases and rejection of transplants remains a major problem. Studies in transplantation have shown upregulation of P2X7 expression on infiltrating lymphocytes in transplanted hearts in human patients[106]. Pharmacological blockade and genetic deletion of P2X7 in murine models leads to a delay in allograft rejection, which has been demonstrated in several transplant models including models of islet[107], heart[106] and lung[108] transplantation. However, with the exception of one preliminary report[109], there are limited studies investigating P2X7 in skin transplants. In this study[109], ATP is released in allogeneic but not syngeneic skin grafts. This ATP release involved macrophages and the pannexin-1 hemichannel, and was impaired by pharmacological blockade or genetic deletion of P2X7. This inhibition or absence of P2X7 delayed allogeneic skin graft rejection. Collectively, these results support a role for P2X7 in ATP release and tissue rejection in allogeneic skin graft transplantation.

## Skin cancer

Skin cancers are common cancers within humans and include three main forms: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma[110]. Ultraviolet radiation is the major causative factor of these skin cancers[110]. P2X7 is emerging as an important receptor in many forms of cancers, with various and contradictory roles attributed to this receptor in tumour biology[111]. These include but are not limited to tumour cell proliferation[112], death[113], and invasiveness[114], as well as anti-tumour immunity[115] and cancer pain[116].

The role of P2X7 in skin cancer has been studied most widely in melanoma. Immunohistochemistry reveals expression of P2X7 in human melanoma[117,118] and in various melanoma cell lines[119]. Further, this receptor is expressed at higher quantities in melanoma cells compared to normal melanocytes[119]. Importantly, P2X7 in melanoma and melanoma cell lines is functional[118,119]. Paradoxically, P2X7 activation promotes and suppresses ATP-induced apoptosis in human A375[118] and HT168-M1 melanoma cells[119], respectively. These differences remain to be reconciled, but opposing effects with P2X7 have also been observed in murine models of melanoma. ATP injection impairs the growth of A375 melanoma cells in (athymic) immuno-compromised mice[120] supporting an anti-tumour effect for P2X7 presumably through ATP-induced cell death. Conversely, injection of P2X7 antagonists inhibits the growth of murine B16 melanoma cells (which express P2X7[121]) in immuno-competent mice[121,122]. Additional data from these studies demonstrated that this pro-tumour effect of P2X7 was due to enhanced ATP-induced proliferation of B16 melanoma cells[121,122]. P2X7 on immune cells also plays an important role in preventing melanoma progression by promoting anti-tumour immune responses. B16 melanoma growth and metastasis is increased in P2X7 deficient mice or wild-type chimeric mice transplanted with P2X7-deficient bone marrow compared to control mice[102].

P2X7 may also play an important role in BCC and SCC. Immunohistochemistry of human samples reveals expression of P2X7 in the necrotic centre of BCCs and within apoptotic cells in both BCCs and SSCs, suggesting that P2X7 activation may mediate killing of malignant cells within these tumours[123]. Evidence for this process in BCC is wanting, but P2X7 can mediate the killing of the human A431 SCC line[123]. Another report however attributed this cytolytic effect to adenosine resulting from ATP hydrolysis rather than ATP directly[124]. Thus, the role of P2X7 in this cell line remains uncertain. As noted above, P2X7 is also present on immortalised HaCaT keratinocytes[19] and mediates ATP-induced death in these cells[20]. Notably, ultraviolet B irradiation down-regulates P2X7 expression in HaCaT keratinocytes, potentially leading to survival of cells with a reduced ability for ATP-induced apoptosis, and allowing for malignant transformation and survival of malignant cells[125]. Consistent with this concept, in BCC patients, more aggressive tumours have lower P2X7 expression, suggesting that loss of P2X7 can act as a marker for increased tumour aggressiveness[123]. Finally, in a murine model of chemically-induced skin papilloma/SCC carcinogenesis, injection of BzATP reduces the frequency and size of papillomas and skin cancers, a response that is absent in P2X7 deficient mice, indicating a role for P2X7 in this process[18]. P2X7 activation in these tumours is associated with apoptosis[18]. Of note, P2X7 expression is reduced in papillomas and skin cancers compared to normal skin[18], suggesting that down-regulation of P2X7 in skin tumours is a possible escape mechanism to avoid ATP-induced apoptosis.

## Summary

In summary, P2X7 is present on immune, stromal, epithelial and malignant cells in diseased skin, and is up-regulated in some skin disorders. Activation of P2X7 cells and the resulting downstream effects are implicated in numerous skin diseases including allergic and irritant contact dermatitis, psoriasis, cutaneous GVHD, as well as in skin transplantation and skin cancer. In some instances the role of P2X7 in skin disease is supported by mouse models (Table 2) and human studies (Table 3), but for other skin diseases evidence is limited to only one species. Nevertheless, P2X7 represents a potential biomarker and target for treatment of various skin disorders, but further studies are required before the clinical value of P2X7 can be utilised.

# CONCLUSION

The P2X7 receptor is present on numerous immune and other cell types in the skin including keratinocytes, Langerhans cells, and dermal dendritic cells, and may be present on T and B cells. P2X7 expression is negligible on mast cells, but can be upregulated in skin disease. Activation of P2X7 by ATP results in numerous downstream effects including cytokine release and apoptosis. P2X7 may play a role in homeostatic skin biology and has been implicated in a number of skin disorders, including contact dermatitis, psoriasis, cutaneous GVHD, and is involved in other skin processes including transplantation and wound healing. Thus, P2X7 represents a potential target for therapy of skin disease.

# REFERENCES

1 **McLafferty E**, Hendry C, Alistair F. The integumentary system: anatomy, physiology and function of skin. *Nurs Stand* 2012; **27**: 35-42 [PMID: 23248884 DOI: 10.7748/ns2012.09.27.3.35.c9299]

2 **SS Tay**,Roediger B, Tong PL, Tikoo S, Weninger W. The Skin-Resident Immune Network. *Curr Dermatol Rep* 2014; **3**: 13-22 [PMID: 24587975 DOI: 10.1007/s13671-013-0063-9]

3 **Burnstock G**. Purinergic signalling: Its unpopular beginning, its acceptance and its exciting future. *Bioessays* 2012; **34**: 218-225 [PMID: 22237698 DOI: 10.1002/bies.201100130]

4 **Holzer AM**, Granstein RD. Role of extracellular adenosine triphosphate in human skin. *J Cutan Med Surg* 2004; **8**: 90-96 [PMID: 15129319 DOI: 10.1007/s10227-004-0125-5]

5 **Burnstock G**, Knight GE, Greig AV. Purinergic signaling in healthy and diseased skin. *J Invest Dermatol* 2012; **132**: 526-546 [PMID: 22158558 DOI: 10.1038/jid.2011.344]

6 **Di Virgilio F**, Vuerich M. Purinergic signaling in the immune system. *Auton Neurosci* 2015; **191**: 117-123 [PMID: 25979766 DOI: 10.1016/j.autneu.2015.04.011]

7 **Burnstock G**, Knight GE. Cellular distribution and functions of P2 receptor subtypes in different systems. *Int Rev Cytol* 2004; **240**: 31-304 [PMID: 15548415 DOI: 10.1016/S0074-7696(04)40002-3]

8 **Antonioli L**, Pacher P, Vizi ES, Haskó G. CD39 and CD73 in immunity and inflammation. *Trends Mol Med* 2013; **19**: 355-367 [PMID: 23601906 DOI: 10.1016/j.molmed.2013.03.005]

9 **Jiang LH**, Baldwin JM, Roger S, Baldwin SA. Insights into the Molecular Mechanisms Underlying Mammalian P2X7 Receptor Functions and Contributions in Diseases, Revealed by Structural Modeling and Single Nucleotide Polymorphisms. *Front Pharmacol* 2013; **4**: 55 [PMID: 23675347 DOI: 10.3389/Fphar.2013.00055]

10 **Alves LA**, de Melo Reis RA, de Souza CA, de Freitas MS, Teixeira PC, Neto Moreira Ferreira D, Xavier RF. The P2X7 receptor: shifting from a low- to a high-conductance channel - an enigmatic phenomenon? *Biochim Biophys Acta* 2014; **1838**: 2578-2587 [PMID: 24857862 DOI: 10.1016/j.bbamem.2014.05.015]

11 **Wiley JS**, Sluyter R, Gu BJ, Stokes L, Fuller SJ. The human P2X7 receptor and its role in innate immunity. *Tissue Antigens* 2011; **78**: 321-332 [PMID: 21988719 DOI: 10.1111/j.1399-0039.2011.01780.x]

12 **Lenertz LY**, Gavala ML, Zhu Y, Bertics PJ. Transcriptional control mechanisms associated with the nucleotide receptor P2X7, a critical regulator of immunologic, osteogenic, and neurologic functions. *Immunol Res* 2011; **50**: 22-38 [PMID: 21298493 DOI: 10.1007/s12026-011-8203-4]

13 **Bartlett R**, Stokes L, Sluyter R. The P2X7 receptor channel: recent developments and the use of P2X7 antagonists in models of disease. *Pharmacol Rev* 2014; **66**: 638-675 [PMID: 24928329 DOI: 10.1124/pr.113.008003]

14 **Nestle FO**, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol* 2009; **9**: 679-691 [PMID: 19763149 DOI: 10.1038/nri2622]

15 **Gröschel-Stewart U**, Bardini M, Robson T, Burnstock G. Localisation of P2X5 and P2X7 receptors by immunohistochemistry in rat stratified squamous epithelia. *Cell Tissue Res* 1999; **296**: 599-605 [PMID: 10370147 DOI: 10.1007/s004410051321]

16 **Greig AV**, Linge C, Terenghi G, McGrouther DA, Burnstock G. Purinergic receptors are part of a functional signaling system for proliferation and differentiation of human epidermal keratinocytes. *J Invest Dermatol* 2003; **120**: 1007-1015 [PMID: 12787128 DOI: 10.1046/j.1523-1747.2003.12261.x]

17 **Greig AV**, Linge C, Cambrey A, Burnstock G. Purinergic receptors are part of a signaling system for keratinocyte proliferation, differentiation, and apoptosis in human fetal epidermis. *J Invest Dermatol* 2003; **121**: 1145-1149 [PMID: 14708618 DOI: 10.1046/j.1523-1747.2003.12567.x]

18 **Fu W**, McCormick T, Qi X, Luo L, Zhou L, Li X, Wang BC, Gibbons HE, Abdul-Karim FW, Gorodeski GI. Activation of P2X(7)-mediated apoptosis Inhibits DMBA/TPA-induced formation of skin papillomas and cancer in mice. *BMC Cancer* 2009; **9**: 114 [PMID: 19379509 DOI: 10.1186/1471-2407-9-114]

19 **Gönczi M**, Telek A, Czifra G, Balogh A, Blumberg PM, Bíró T, Csernoch L. Altered calcium handling following the recombinant overexpression of protein kinase C isoforms in HaCaT cells. *Exp Dermatol* 2008; **17**: 584-591 [PMID: 18177346 DOI: 10.1111/j.1600-0625.2007.00678.x]

20 **Zanin RF**, da Silva GL, Erig T, Sperotto ND, Leite CE, Coutinho-Silva R, Batastini AM, Morrone FB. Decrease of serum adenine nucleotide hydrolysis in an irritant contact dermatitis mice model: potential P2X7R involvement. *Mol Cell Biochem* 2015; **404**: 221-228 [PMID: 25772484 DOI: 10.1007/s11010-015-2381-7]

21 **Farrell AW**, Gadeock S, Pupovac A, Wang B, Jalilian I, Ranson M, Sluyter R. P2X7 receptor activation induces cell death and CD23 shedding in human RPMI 8226 multiple myeloma cells. *Biochim Biophys Acta* 2010; **1800**: 1173-1182 [PMID: 20647033 DOI: 10.1016/j.bbagen.2010.07.001]

22 **Georgiou JG**, Skarratt KK, Fuller SJ, Martin CJ, Christopherson RI, Wiley JS, Sluyter R. Human epidermal and monocyte-derived langerhans cells express functional P2X receptors. *J Invest Dermatol* 2005; **125**: 482-490 [PMID: 16117789 DOI: 10.1111/j.0022-202X.2005.23835.x]

23 **Tran JN**, Pupovac A, Taylor RM, Wiley JS, Byrne SN, Sluyter R. Murine epidermal Langerhans cells and keratinocytes express functional P2X7 receptors. *Exp Dermatol* 2010; **19**: e151-e157 [PMID: 20113349 DOI: 10.1111/j.1600-0625.2009.01029.x]

24 **Inoue K**, Hosoi J, Denda M. Extracellular ATP has stimulatory effects on the expression and release of IL-6 via purinergic receptors in normal human epidermal keratinocytes. *J Invest Dermatol* 2007; **127**: 362-371 [PMID: 16946718 DOI: 10.1038/sj.jid.5700526]

25 **Salzer S**, Kresse S, Hirai Y, Koglin S, Reinholz M, Ruzicka T, Schauber J. Cathelicidin peptide LL-37 increases UVB-triggered inflammasome activation: possible implications for rosacea. *J Dermatol Sci* 2014; **76**: 173-179 [PMID: 25306296 DOI: 10.1016/j.jdermsci.2014.09.002]

26 **MacLeod AS**, Rudolph R, Corriden R, Ye I, Garijo O, Havran WL. Skin-resident T cells sense ultraviolet radiation-induced injury and contribute to DNA repair. *J Immunol* 2014; **192**: 5695-5702 [PMID: 24808367 DOI: 10.4049/jimmunol.1303297]

27 **Sommer A**, Fries A, Cornelsen I, Speck N, Koch-Nolte F, Gimpl G, Andrä J, Bhakdi S, Reiss K. Melittin modulates keratinocyte function through P2 receptor-dependent ADAM activation. *J Biol Chem* 2012; **287**: 23678-23689 [PMID: 22613720 DOI: 10.1074/jbc.M112.362756]

28 **Chopin M**, Nutt SL. Establishing and maintaining the Langerhans cell network. *Semin Cell Dev Biol* 2015; **41**: 23-29 [PMID: 24513231 DOI: 10.1016/j.semcdb.2014.02.001]

29 **Girolomoni G**, Santantonio ML, Pastore S, Bergstresser PR, Giannetti A, Cruz PD. Epidermal Langerhans cells are resistant to the permeabilizing effects of extracellular ATP: in vitro evidence supporting a protective role of membrane ATPase. *J Invest Dermatol* 1993; **100**: 282-287 [PMID: 8440905 DOI: 10.1111/1523-1747.ep12469769]

30 **Killeen ME**, Ferris L, Kupetsky EA, Falo L, Mathers AR. Signaling through purinergic receptors for ATP induces human cutaneous innate and adaptive Th17 responses: implications in the pathogenesis of psoriasis. *J Immunol* 2013; **190**: 4324-4336 [PMID: 23479230 DOI: 10.4049/jimmunol.1202045]

31 **Granstein RD**, Ding W, Huang J, Holzer A, Gallo RL, Di Nardo A, Wagner JA. Augmentation of cutaneous immune responses by ATP gamma S: purinergic agonists define a novel class of immunologic adjuvants. *J Immunol* 2005; **174**: 7725-7731 [PMID: 15944274 DOI: 10.4049/jimmunol.174.12.7725]

32 **Wolff K**, Winkelmann RK. Ultrastructural localization of nucleoside triphosphatase in Langerhans cells. *J Invest Dermatol* 1967; **48**: 50-54 [PMID: 4289467 DOI: 10.1038/jid.1967.8]

33 **Mizumoto N**, Kumamoto T, Robson SC, Sévigny J, Matsue H, Enjyoji K, Takashima A. CD39 is the dominant Langerhans cell-associated ecto-NTPDase: modulatory roles in inflammation and immune responsiveness. *Nat Med* 2002; **8**: 358-365 [PMID: 11927941 DOI: Doi]

34 **Lévesque SA**, Kukulski F, Enjyoji K, Robson SC, Sévigny J. NTPDase1 governs P2X7-dependent functions in murine macrophages. *Eur J Immunol* 2010; **40**: 1473-1485 [PMID: 20201036 DOI: 10.1002/eji.200939741]

35 **Kuhny M**, Hochdörfer T, Ayata CK, Idzko M, Huber M. CD39 is a negative regulator of P2X7-mediated inflammatory cell death in mast cells. *Cell Commun Signal* 2014; **12**: 40 [PMID: 25184735 DOI: 10.1186/s12964-014-0040-3]

36 **Kawamura T**, Ogawa Y, Nakamura Y, Nakamizo S, Ohta Y, Nakano H, Kabashima K, Katayama I, Koizumi S, Kodama T, Nakao A, Shimada S. Severe dermatitis with loss of epidermal Langerhans cells in human and mouse zinc deficiency. *J Clin Invest* 2012; **122**: 722-732 [PMID: 22214844 DOI: 10.1172/jci58618]

37 **Malissen B**, Tamoutounour S, Henri S. The origins and functions of dendritic cells and macrophages in the skin. *Nat Rev Immunol* 2014; **14**: 417-428 [PMID: 24854591 DOI: 10.1038/nri3683]

38 **Coutinho-Silva R**, Persechini PM, Bisaggio RD, Perfettini JL, Neto AC, Kanellopoulos JM, Motta-Ly I, Dautry-Varsat A, Ojcius DM. P2Z/P2X7 receptor-dependent apoptosis of dendritic cells. *Am J Physiol* 1999; **276**: C1139-C1147 [PMID: 10329963]

39 **Ferrari D**, La Sala A, Chiozzi P, Morelli A, Falzoni S, Girolomoni G, Idzko M, Dichmann S, Norgauer J, Di Virgilio F. The P2 purinergic receptors of human dendritic cells: identification and coupling to cytokine release. *FASEB J* 2000; **14**: 2466-2476 [PMID: 11099464 DOI: 10.1096/fj.00-0031com]

40 **Sluyter R**, Wiley JS. Extracellular adenosine 5'-triphosphate induces a loss of CD23 from human dendritic cells via activation of P2X7 receptors. *Int Immunol* 2002; **14**: 1415-1421 [PMID: 12456589 DOI: 10.1093/intimm/dxf111]

41 **Qu Y**, Ramachandra L, Mohr S, Franchi L, Harding CV, Nunez G, Dubyak GR. P2X7 receptor-stimulated secretion of MHC class II-containing exosomes requires the ASC/NLRP3 inflammasome but is independent of caspase-1. *J Immunol* 2009; **182**: 5052-5062 [PMID: 19342685 DOI: 10.4049/jimmunol.0802968]

42 **Buell G**, Chessell IP, Michel AD, Collo G, Salazzo M, Herren S, Gretener D, Grahames C, Kaur R, Kosco-Vilbois MH, Humphrey PP. Blockade of human P2X7 receptor function with a monoclonal antibody. *Blood* 1998; **92**: 3521-3528 [PMID: 9808543]

43 **Nihei OK**, de Carvalho AC, Savino W, Alves LA. Pharmacologic properties of P(2Z)/P2X(7 )receptor characterized in murine dendritic cells: role on the induction of apoptosis. *Blood* 2000; **96**: 996-1005 [PMID: 10910915]

44 **Mutini C**, Falzoni S, Ferrari D, Chiozzi P, Morelli A, Baricordi OR, Collo G, Ricciardi-Castagnoli P, Di Virgilio F. Mouse dendritic cells express the P2X7 purinergic receptor: characterization and possible participation in antigen presentation. *J Immunol* 1999; **163**: 1958-1965 [PMID: 10438932]

45 **Yip L**, Woehrle T, Corriden R, Hirsh M, Chen Y, Inoue Y, Ferrari V, Insel PA, Junger WG. Autocrine regulation of T-cell activation by ATP release and P2X7 receptors. *FASEB J* 2009; **23**: 1685-1693 [PMID: 19211924 DOI: 10.1096/fj.08-126458]

46 **Ferrari D**, Chiozzi P, Falzoni S, Dal Susino M, Melchiorri L, Baricordi OR, Di Virgilio F. Extracellular ATP triggers IL-1 beta release by activating the purinergic P2Z receptor of human macrophages. *J Immunol* 1997; **159**: 1451-1458 [PMID: 9233643]

47 **Eschke D**, Wüst M, Hauschildt S, Nieber K. Pharmacological characterization of the P2X(7) receptor on human macrophages using the patch-clamp technique. *Naunyn Schmiedebergs Arch Pharmacol* 2002; **365**: 168-171 [PMID: 11819036 DOI: 10.1007/s00210-001-0501-2]

48 **Qu Y**, Franchi L, Nunez G, Dubyak GR. Nonclassical IL-1 beta secretion stimulated by P2X7 receptors is dependent on inflammasome activation and correlated with exosome release in murine macrophages. *J Immunol* 2007; **179**: 1913-1925 [PMID: 17641058 DOI: 10.4049/jimmunol.179.3.1913]

49 **Coutinho-Silva R**, Persechini PM. P2Z purinoceptor-associated pores induced by extracellular ATP in macrophages and J774 cells. *Am J Physiol* 1997; **273**: C1793-C1800 [PMID: 9435482]

50 **Solle M**, Labasi J, Perregaux DG, Stam E, Petrushova N, Koller BH, Griffiths RJ, Gabel CA. Altered cytokine production in mice lacking P2X(7) receptors. *J Biol Chem* 2001; **276**: 125-132 [PMID: 11016935 DOI: 10.1074/jbc.M006781200]

51 **Barberà-Cremades M**, Baroja-Mazo A, Gomez AI, Machado F, Di Virgilio F, Pelegrín P. P2X7 receptor-stimulation causes fever via PGE2 and IL-1β release. *FASEB J* 2012; **26**: 2951-2962 [PMID: 22490780 DOI: 10.1096/fj.12-205765]

52 **Pfeiffer ZA**, Guerra AN, Hill LM, Gavala ML, Prabhu U, Aga M, Hall DJ, Bertics PJ. Nucleotide receptor signaling in murine macrophages is linked to reactive oxygen species generation. *Free Radic Biol Med* 2007; **42**: 1506-1516 [PMID: 17448897 DOI: 10.1016/j.freeradbiomed.2007.02.010]

53 **Lammas DA**, Stober C, Harvey CJ, Kendrick N, Panchalingam S, Kumararatne DS. ATP-induced killing of mycobacteria by human macrophages is mediated by purinergic P2Z(P2X7) receptors. *Immunity* 1997; **7**: 433-444 [PMID: 9324363 DOI: 10.1016/S1074-7613(00)80364-7]

54 **Coutinho-Silva R**, Perfettini JL, Persechini PM, Dautry-Varsat A, Ojcius DM. Modulation of P2Z/P2X(7) receptor activity in macrophages infected with Chlamydia psittaci. *Am J Physiol Cell Physiol* 2001; **280**: C81-C89 [PMID: 11121379]

55 **Lees MP**, Fuller SJ, McLeod R, Boulter NR, Miller CM, Zakrzewski AM, Mui EJ, Witola WH, Coyne JJ, Hargrave AC, Jamieson SE, Blackwell JM, Wiley JS, Smith NC. P2X7 receptor-mediated killing of an intracellular parasite, Toxoplasma gondii, by human and murine macrophages. *J Immunol* 2010; **184**: 7040-7046 [PMID: 20488797 DOI: 10.4049/jimmunol.1000012]

56 **Samady JA**, Schwartz RA. Old World cutaneous leishmaniasis. *Int J Dermatol* 1997; **36**: 161-166 [PMID: 9158994 DOI: 10.1046/j.1365-4362.1997.00149.x]

57 **Chaves SP**, Torres-Santos EC, Marques C, Figliuolo VR, Persechini PM, Coutinho-Silva R, Rossi-Bergmann B. Modulation of P2X(7) purinergic receptor in macrophages by Leishmania amazonensis and its role in parasite elimination. *Microbes Infect* 2009; **11**: 842-849 [PMID: 19439191 DOI: 10.1016/j.micinf.2009.05.001]

58 **Kritas SK**, Saggini A, Varvara G, Murmura G, Caraffa A, Antinolfi P, Toniato E, Pantalone A, Neri G, Frydas S, Rosati M, Tei M, Speziali A, Saggini R, Pandolfi F, Cerulli G, Theoharides TC, Conti P. Impact of mast cells on the skin. *Int J Immunopathol Pharmacol* 2013; **26**: 855-859 [PMID: 24355220]

59 **Bradding P**, Okayama Y, Kambe N, Saito H. Ion channel gene expression in human lung, skin, and cord blood-derived mast cells. *J Leukoc Biol* 2003; **73**: 614-620 [PMID: 12714576 DOI: 10.1189/jlb.1202602]

60 **Kurashima Y**, Amiya T, Nochi T, Fujisawa K, Haraguchi T, Iba H, Tsutsui H, Sato S, Nakajima S, Iijima H, Kubo M, Kunisawa J, Kiyono H. Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. *Nat Commun* 2012; **3**: 1034 [PMID: 22948816 DOI: 10.1038/ncomms2023]

61 **Kurashima Y**, Amiya T, Fujisawa K, Shibata N, Suzuki Y, Kogure Y, Hashimoto E, Otsuka A, Kabashima K, Sato S, Sato T, Kubo M, Akira S, Miyake K, Kunisawa J, Kiyono H. The enzyme Cyp26b1 mediates inhibition of mast cell activation by fibroblasts to maintain skin-barrier homeostasis. *Immunity* 2014; **40**: 530-541 [PMID: 24726878 DOI: 10.1016/j.immuni.2014.01.014]

62 **Geering B**, Stoeckle C, Conus S, Simon HU. Living and dying for inflammation: neutrophils, eosinophils, basophils. *Trends Immunol* 2013; **34**: 398-409 [PMID: 23665135 DOI: 10.1016/j.it.2013.04.002]

63 **Jain R**, Weninger W. Shedding light on cutaneous innate immune responses: the intravital microscopy approach. *Immunol Cell Biol* 2013; **91**: 263-270 [PMID: 23459295 DOI: 10.1038/icb.2012.76]

64 **Ferrari D**, Idzko M, Dichmann S, Purlis D, Virchow C, Norgauer J, Chiozzi P, Di Virgilio F, Luttmann W. P2 purinergic receptors of human eosinophils: characterization and coupling to oxygen radical production. *FEBS Lett* 2000; **486**: 217-224 [PMID: 11119707 DOI: 10.1016/S0014-5793(00)02306-1]

65 **Idzko M**, Dichmann S, Panther E, Ferrari D, Herouy Y, Virchow C, Luttmann W, Di Virgilio F, Norgauer J. Functional characterization of P2Y and P2X receptors in human eosinophils. *J Cell Physiol* 2001; **188**: 329-336 [PMID: 11473359 DOI: 10.1002/jcp.1129]

66 **Tsai SH**, Kinoshita M, Kusu T, Kayama H, Okumura R, Ikeda K, Shimada Y, Takeda A, Yoshikawa S, Obata-Ninomiya K, Kurashima Y, Sato S, Umemoto E, Kiyono H, Karasuyama H, Takeda K. The ectoenzyme E-NPP3 negatively regulates ATP-dependent chronic allergic responses by basophils and mast cells. *Immunity* 2015; **42**: 279-293 [PMID: 25692702 DOI: 10.1016/j.immuni.2015.01.015]

67 **Vaughan KR**, Stokes L, Prince LR, Marriott HM, Meis S, Kassack MU, Bingle CD, Sabroe I, Surprenant A, Whyte MK. Inhibition of neutrophil apoptosis by ATP is mediated by the P2Y11 receptor. *J Immunol* 2007; **179**: 8544-8553 [PMID: 18056402 DOI: 10.4049/jimmunol.179.12.8544]

68 **Martel-Gallegos G**, Rosales-Saavedra MT, Reyes JP, Casas-Pruneda G, Toro-Castillo C, Pérez-Cornejo P, Arreola J. Human neutrophils do not express purinergic P2X7 receptors. *Purinergic Signal* 2010; **6**: 297-306 [PMID: 21103213 DOI: 10.1007/s11302-010-9178-7]

69 **da Silva GL**, Sperotto ND, Borges TJ, Bonorino C, Takyia CM, Coutinho-Silva R, Campos MM, Zanin RF, Morrone FB. P2X7 receptor is required for neutrophil accumulation in a mouse model of irritant contact dermatitis. *Exp Dermatol* 2013; **22**: 184-188 [PMID: 23489421 DOI: 10.1111/exd.12094]

70 **Mueller SN**, Zaid A, Carbone FR. Tissue-resident T cells: dynamic players in skin immunity. *Front Immunol* 2014; **5**: 332 [PMID: 25076947 DOI: 10.3389/fimmu.2014.00332]

71 **Rissiek B**, Haag F, Boyer O, Koch-Nolte F, Adriouch S. P2X7 on Mouse T Cells: One Channel, Many Functions. *Front Immunol* 2015; **6**: 204 [PMID: 26042119 DOI: 10.3389/fimmu.2015.00204]

72 **Aswad F**, Dennert G. P2X7 receptor expression levels determine lethal effects of a purine based danger signal in T lymphocytes. *Cell Immunol* 2006; **243**: 58-65 [PMID: 17286969 DOI: 10.1016/j.cellimm.2006.12.003]

73 **Sluyter R**, Wiley JS. P2X7 receptor activation induces CD62L shedding from human CD4 and CD8 T cells. *Inflamm Cell Signal* 2014; **1**: e92 [DOI: 10.14800/ics.92]

74 **Grailer JJ**, Kodera M, Steeber DA. L-selectin: role in regulating homeostasis and cutaneous inflammation. *J Dermatol Sci* 2009; **56**: 141-147 [PMID: 19889515 DOI: 10.1016/j.jdermsci.2009.10.001]

75 **Purvis HA**, Anderson AE, Young DA, Isaacs JD, Hilkens CM. A negative feedback loop mediated by STAT3 limits human Th17 responses. *J Immunol* 2014; **193**: 1142-1150 [PMID: 24973454 DOI: 10.4049/jimmunol.1302467]

76 **Schenk U**, Frascoli M, Proietti M, Geffers R, Traggiai E, Buer J, Ricordi C, Westendorf AM, Grassi F. ATP inhibits the generation and function of regulatory T cells through the activation of purinergic P2X receptors. *Sci Signal* 2011; **4**: ra12 [PMID: 21364186 DOI: 10.1126/scisignal.2001270]

77 **Macleod AS**, Havran WL. Functions of skin-resident γδ T cells. *Cell Mol Life Sci* 2011; **68**: 2399-2408 [PMID: 21560071 DOI: 10.1007/s00018-011-0702-x]

78 **Egbuniwe IU**, Karagiannis SN, Nestle FO, Lacy KE. Revisiting the role of B cells in skin immune surveillance. *Trends Immunol* 2015; **36**: 102-111 [PMID: 25616715 DOI: 10.1016/j.it.2014.12.006]

79 **Gu BJ**, Zhang WY, Bendall LJ, Chessell IP, Buell GN, Wiley JS. Expression of P2X(7) purinoceptors on human lymphocytes and monocytes: evidence for nonfunctional P2X(7) receptors. *Am J Physiol Cell Physiol* 2000; **279**: C1189-C1197 [PMID: 11003599]

80 **Pupovac A**, Geraghty NJ, Watson D, Sluyter R. Activation of the P2X7 receptor induces the rapid shedding of CD23 from human and murine B cells. *Immunol Cell Biol* 2015; **93**: 77-85 [PMID: 25155463 DOI: 10.1038/icb.2014.69]

81 **Cooper AM**, Hobson PS, Jutton MR, Kao MW, Drung B, Schmidt B, Fear DJ, Beavil AJ, McDonnell JM, Sutton BJ, Gould HJ. Soluble CD23 controls IgE synthesis and homeostasis in human B cells. *J Immunol* 2012; **188**: 3199-3207 [PMID: 22393152 DOI: 10.4049/jimmunol.1102689]

82 **Driskell RR**, Watt FM. Understanding fibroblast heterogeneity in the skin. *Trends Cell Biol* 2015; **25**: 92-99 [PMID: 25455110 DOI: 10.1016/j.tcb.2014.10.001]

83 **Solini A**, Chiozzi P, Morelli A, Fellin R, Di Virgilio F. Human primary fibroblasts in vitro express a purinergic P2X7 receptor coupled to ion fluxes, microvesicle formation and IL-6 release. *J Cell Sci* 1999; **112 ( Pt 3)**: 297-305 [PMID: 9885283]

84 **Solini A**, Chiozzi P, Falzoni S, Morelli A, Fellin R, Di Virgilio F. High glucose modulates P2X7 receptor-mediated function in human primary fibroblasts. *Diabetologia* 2000; **43**: 1248-1256 [PMID: 11079743 DOI: 10.1007/s001250051520]

85 **Solini A**, Chiozzi P, Morelli A, Adinolfi E, Rizzo R, Baricordi OR, Di Virgilio F. Enhanced P2X7 activity in human fibroblasts from diabetic patients: a possible pathogenetic mechanism for vascular damage in diabetes. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1240-1245 [PMID: 15155383 DOI: 10.1161/01.ATV.0000133193.11078.c0]

86 **Pizzo P**, Murgia M, Zambon A, Zanovello P, Bronte V, Pietrobon D, Di Virgilio F. Role of P2z purinergic receptors in ATP-mediated killing of tumor necrosis factor (TNF)-sensitive and TNF-resistant L929 fibroblasts. *J Immunol* 1992; **149**: 3372-3378 [PMID: 1431111]

87 **Weintraub GS**, Nga Lai I, Kim CN. Review of allergic contact dermatitis: Scratching the surface. *J Dermatol* 2015; **4**: 95-102 [DOI: 10.5314/wjd.v4.i2.95]

88 **Pastore S**, Mascia F, Gulinelli S, Forchap S, Dattilo C, Adinolfi E, Girolomoni G, Di Virgilio F, Ferrari D. Stimulation of purinergic receptors modulates chemokine expression in human keratinocytes. *J Invest Dermatol* 2007; **127**: 660-667 [PMID: 17039239 DOI: 10.1038/sj.jid.5700591]

89 **Weber FC**, Esser PR, Müller T, Ganesan J, Pellegatti P, Simon MM, Zeiser R, Idzko M, Jakob T, Martin SF. Lack of the purinergic receptor P2X(7) results in resistance to contact hypersensitivity. *J Exp Med* 2010; **207**: 2609-2619 [PMID: 21059855 DOI: 10.1084/jem.20092489]

90 **Donnelly-Roberts DL**, Namovic MT, Han P, Jarvis MF. Mammalian P2X7 receptor pharmacology: comparison of recombinant mouse, rat and human P2X7 receptors. *Br J Pharmacol* 2009; **157**: 1203-1214 [PMID: 19558545 DOI: 10.1111/j.1476-5381.2009.00233.x]

91 **Spildrejorde M**, Bartlett R, Stokes L, Jalilian I, Peranec M, Sluyter V, Curtis BL, Skarratt KK, Skora A, Bakhsh T, Seavers A, McArthur JD, Dowton M, Sluyter R. R270C polymorphism leads to loss of function of the canine P2X7 receptor. *Physiol Genomics* 2014; **46**: 512-522 [PMID: 24824213 DOI: 10.1152/physiolgenomics.00195.2013]

92 **Onami K**, Kimura Y, Ito Y, Yamauchi T, Yamasaki K, Aiba S. Nonmetal haptens induce ATP release from keratinocytes through opening of pannexin hemichannels by reactive oxygen species. *J Invest Dermatol* 2014; **134**: 1951-1960 [PMID: 24531690 DOI: 10.1038/jid.2014.93]

93 **Suárez-Pérez JA**, Bosch R, González S, González E. Pathogenesis and diagnosis of contact dermatitis: Applications of reflectance confocal microscopy. *J Dermatol* 2014; **3**: 45-49 [DOI: 10.5314/wjd.v3.i3.45]

94 **Mizumoto N**, Mummert ME, Shalhevet D, Takashima A. Keratinocyte ATP release assay for testing skin-irritating potentials of structurally diverse chemicals. *J Invest Dermatol* 2003; **121**: 1066-1072 [PMID: 14708608 DOI: 10.1046/j.1523-1747.2003.12558.x]

95 **Raoux M**, Azorin N, Colomban C, Rivoire S, Merrot T, Delmas P, Crest M. Chemicals inducing acute irritant contact dermatitis mobilize intracellular calcium in human keratinocytes. *Toxicol In Vitro* 2013; **27**: 402-408 [PMID: 22906572 DOI: 10.1016/j.tiv.2012.08.010]

96 **Nestle FO**, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496-509 [PMID: 19641206 DOI: 10.1056/NEJMra0804595]

97 **Ferrara JL**, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009; **373**: 1550-1561 [PMID: 19282026 DOI: 10.1016/s0140-6736(09)60237-3]

98 **Wilhelm K**, Ganesan J, Müller T, Dürr C, Grimm M, Beilhack A, Krempl CD, Sorichter S, Gerlach UV, Jüttner E, Zerweck A, Gärtner F, Pellegatti P, Di Virgilio F, Ferrari D, Kambham N, Fisch P, Finke J, Idzko M, Zeiser R. Graft-versus-host disease is enhanced by extracellular ATP activating P2X7R. *Nat Med* 2010; **16**: 1434-1438 [PMID: 21102458 DOI: 10.1038/nm.2242]

99 **Fowler BJ**, Gelfand BD, Kim Y, Kerur N, Tarallo V, Hirano Y, Amarnath S, Fowler DH, Radwan M, Young MT, Pittman K, Kubes P, Agarwal HK, Parang K, Hinton DR, Bastos-Carvalho A, Li S, Yasuma T, Mizutani T, Yasuma R, Wright C, Ambati J. Nucleoside reverse transcriptase inhibitors possess intrinsic anti-inflammatory activity. *Science* 2014; **346**: 1000-1003 [PMID: 25414314 DOI: 10.1126/science.1256427]

100 **Markey KA**, MacDonald KP, Hill GR. The biology of graft-versus-host disease: experimental systems instructing clinical practice. *Blood* 2014; **124**: 354-362 [PMID: 24914137 DOI: 10.1182/blood-2014-02-514745]

101 **Nguyen DT**, Orgill DP, Murphy GF. The pathophysiologic basis for wound healing and cutaneous regeneration. In: Orgill DP, Blanco C. Biomaterials for Treating Skin Loss. Cambridge: Woodhead Publishing Limited, 2009: 25-57

102 **Adinolfi E**, Capece M, Franceschini A, Falzoni S, Giuliani AL, Rotondo A, Sarti AC, Bonora M, Syberg S, Corigliano D, Pinton P, Jorgensen NR, Abelli L, Emionite L, Raffaghello L, Pistoia V, Di Virgilio F. Accelerated tumor progression in mice lacking the ATP receptor P2X7. *Cancer Res* 2015; **75**: 635-644 [PMID: 25542861 DOI: 10.1158/0008-5472.CAN-14-1259]

103 **Hill LM**, Gavala ML, Lenertz LY, Bertics PJ. Extracellular ATP may contribute to tissue repair by rapidly stimulating purinergic receptor X7-dependent vascular endothelial growth factor release from primary human monocytes. *J Immunol* 2010; **185**: 3028-3034 [PMID: 20668222 DOI: 10.4049/jimmunol.1001298]

104 **Greig AV**, James SE, McGrouther DA, Terenghi G, Burnstock G. Purinergic receptor expression in the regeneration epidermis in a rat model of normal and delayed wound healing. *Exp Dermatol* 2003; **12**: 860-871 [PMID: 14714568 DOI: 10.1111/j.0906-6705.2003.00110.x]

105 **Hebda PA**, Collins MA, Tharp MD. Mast cell and myofibroblast in wound healing. *Dermatol Clin* 1993; **11**: 685-696 [PMID: 8222352]

106 **Vergani A**, Tezza S, D'Addio F, Fotino C, Liu K, Niewczas M, Bassi R, Molano RD, Kleffel S, Petrelli A, Soleti A, Ammirati E, Frigerio M, Visner G, Grassi F, Ferrero ME, Corradi D, Abdi R, Ricordi C, Sayegh MH, Pileggi A, Fiorina P. Long-term heart transplant survival by targeting the ionotropic purinergic receptor P2X7. *Circulation* 2013; **127**: 463-475 [PMID: 23250993 DOI: 10.1161/CIRCULATIONAHA.112.123653]

107 **Vergani A**, Fotino C, D'Addio F, Tezza S, Podetta M, Gatti F, Chin M, Bassi R, Molano RD, Corradi D, Gatti R, Ferrero ME, Secchi A, Grassi F, Ricordi C, Sayegh MH, Maffi P, Pileggi A, Fiorina P. Effect of the purinergic inhibitor oxidized ATP in a model of islet allograft rejection. *Diabetes* 2013; **62**: 1665-1675 [PMID: 23315496 DOI: 10.2337/db12-0242]

108 **Liu K**, Vergani A, Zhao P, Ben Nasr M, Wu X, Iken K, Jiang D, Su X, Fotino C, Fiorina P, Visner GA. Inhibition of the purinergic pathway prolongs mouse lung allograft survival. *Am J Respir Cell Mol Biol* 2014; **51**: 300-310 [PMID: 24661183 DOI: 10.1165/rcmb.2013-0362OC]

109 **Barbera-Cremades M**, Manuel Martinez C, Baroja-Mazo A, Amores-Iniesta J, Pelegrin P. P2X7 receptor controls extracellular ATP during skin graft allogenic rejection. *Purinergic Signal* 2014; **10**: 817 [DOI: 10.1007/s11302-014-9430-7]

110 **Narayanan DL**, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. *Int J Dermatol* 2010; **49**: 978-986 [PMID: 20883261 DOI: 10.1111/j.1365-4632.2010.04474.x]

111 **Roger S**, Jelassi B, Couillin I, Pelegrin P, Besson P, Jiang LH. Understanding the roles of the P2X7 receptor in solid tumour progression and therapeutic perspectives. *Biochim Biophys Acta* 2015; **1848**: 2584-2602 [PMID: 25450340 DOI: 10.1016/j.bbamem.2014.10.029]

112 **Di Virgilio F**, Ferrari D, Adinolfi E. P2X(7): a growth-promoting receptor-implications for cancer. *Purinergic Signal* 2009; **5**: 251-256 [PMID: 19263244 DOI: 10.1007/s11302-009-9145-3]

113 **Adinolfi E**, Pizzirani C, Idzko M, Panther E, Norgauer J, Di Virgilio F, Ferrari D. P2X(7) receptor: Death or life? *Purinergic Signal* 2005; **1**: 219-227 [PMID: 18404507 DOI: 10.1007/s11302-005-6322-x]

114 **Roger S**, Pelegrin P. P2X7 receptor antagonism in the treatment of cancers. *Expert Opin Investig Drugs* 2011; **20**: 875-880 [PMID: 21619470 DOI: 10.1517/13543784.2011.583918]

115 **Aymeric L**, Apetoh L, Ghiringhelli F, Tesniere A, Martins I, Kroemer G, Smyth MJ, Zitvogel L. Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity. *Cancer Res* 2010; **70**: 855-858 [PMID: 20086177 DOI: 10.1158/0008-5472.CAN-09-3566]

116 **Franceschini A**, Adinolfi E. P2X receptors: New players in cancer pain. *World J Biol Chem* 2014; **5**: 429-436 [PMID: 25426266 DOI: 10.4331/wjbc.v5.i4.429]

117 **Slater M**, Scolyer RA, Gidley-Baird A, Thompson JF, Barden JA. Increased expression of apoptotic markers in melanoma. *Melanoma Res* 2003; **13**: 137-145 [PMID: 12690296 DOI: 10.1097/00008390-200304000-00005]

118 **White N**, Butler PE, Burnstock G. Human melanomas express functional P2 X(7) receptors. *Cell Tissue Res* 2005; **321**: 411-418 [PMID: 15991050 DOI: 10.1007/s00441-005-1149-x]

119 **Deli T**, Varga N, Adám A, Kenessey I, Rásó E, Puskás LG, Tóvári J, Fodor J, Fehér M, Szigeti GP, Csernoch L, Tímár J. Functional genomics of calcium channels in human melanoma cells. *Int J Cancer* 2007; **121**: 55-65 [PMID: 17330843 DOI: 10.1002/ijc.22621]

120 **White N**, Knight GE, Butler PE, Burnstock G. An in vivo model of melanoma: treatment with ATP. *Purinergic Signal* 2009; **5**: 327-333 [PMID: 19347609 DOI: 10.1007/s11302-009-9156-0]

121 **Adinolfi E**, Raffaghello L, Giuliani AL, Cavazzini L, Capece M, Chiozzi P, Bianchi G, Kroemer G, Pistoia V, Di Virgilio F. Expression of P2X7 receptor increases in vivo tumor growth. *Cancer Res* 2012; **72**: 2957-2969 [PMID: 22505653 DOI: 10.1158/0008-5472.CAN-11-1947]

122 **Hattori F**, Ohshima Y, Seki S, Tsukimoto M, Sato M, Takenouchi T, Suzuki A, Takai E, Kitani H, Harada H, Kojima S. Feasibility study of B16 melanoma therapy using oxidized ATP to target purinergic receptor P2X7. *Eur J Pharmacol* 2012; **695**: 20-26 [PMID: 22981895 DOI: 10.1016/j.ejphar.2012.09.001]

123 **Greig AV**, Linge C, Healy V, Lim P, Clayton E, Rustin MH, McGrouther DA, Burnstock G. Expression of purinergic receptors in non-melanoma skin cancers and their functional roles in A431 cells. *J Invest Dermatol* 2003; **121**: 315-327 [PMID: 12880424 DOI: 10.1046/j.1523-1747.2003.12379.x]

124 **Völkl T**, Ogilvie A, Neuhuber W, Ogilvie A. Cell death induced by uridine 5'-triphosphate (UTP) in contrast to adenosine 5'-triphosphate (ATP) in human epidermoid carcinoma cells (A-431). *Cell Physiol Biochem* 2008; **22**: 441-454 [PMID: 19088426 DOI: 10.1159/000185491]

125 **Ruzsnavszky O**, Telek A, Gönczi M, Balogh A, Remenyik E, Csernoch L. UV-B induced alteration in purinergic receptors and signaling on HaCaT keratinocytes. *J Photochem Photobiol B* 2011; **105**: 113-118 [PMID: 21862341 DOI: 10.1016/j.jphotobiol.2011.07.009]

**P-Reviewer:** Cuevas-Covarrubia SA, Husein-ElAhmed H, Kaliyadan F, Negosanti L **S-Editor:** Qiu S **L-Editor: E-Editor:**

**Table 1 Events downstream of P2X7 receptor activation**

|  |
| --- |
| RONS formation |
| Shedding of CD23, CD27, CD62L and E-cadherin |
| Up-regulation of CD80 and CD86 expression |
| PGE-2 synthesis and release |
| IL-1β and IL-18 maturation and release |
| IL-6 release |
| IL-2 and IL-17 synthesis and release |
| VEGF release |
| Killing of intracellular pathogens |
| Cell death |

IL: Interleukin; PGE-2: Prostaglandin E2; RONS: Reactive oxygen and nitrogen species; VEGF: Vascular endothelial growth factor.

**Table 2 Roles of the P2X7 receptor in mouse models of skin disease**

|  |  |
| --- | --- |
| **Disease** | **Observations** |
| Allergic contact dermatitis | P2X7 blockade impairs CHS[89]. |
| Irritant contact dermatitis | P2X7 blockade or deficiency impairs croton oil-induced oedema, IL-1β production and neutrophil infiltration[69] |
| Psoriasis | N.D |
| Cutaneous graft-versus-host disease | P2X7 blockade or deficiency increases survival and reduces disease severity, serum concentrations of IFN-γ, TNF-α and IL-6 in allogeneic mouse models[98,99] |
| Wound healing | P2X7 deficient macrophages display reduced migration in an *in vitro* wound repair model[102] |
| Skin transplantation | P2X7 blockade or deficiency prevents allogeneic skin transplant rejection[109] |
| Melanoma | ATP injection impairs A375 melanoma cell growth in immuno-compromised mice[120]P2X7 blockade inhibits B16 melanoma cell growth in immuno-competent mice[121,122]P2X7 deficiency impairs B16 melanoma cell migration *in vitro*[102]P2X7 deficiency in host leads to increased B16 melanoma growth and metastasis[102] |
| Basal cell carcinoma | ND |
| Squamous cell carcinoma | P2X7 deficiency in host enhances chemical-induced carcinogenesis[18]BzATP injection led to tumour apoptosis[18] |

ATP: Adenosine triphosphate; BzATP: 3’-O-(4-benzoyl) benzoyl ATP; CHS: Contact hypersensitivity; IFN: Interferon; IL: Interleukin; ND: Not determined; TNF: Tumour necrosis factor; VEGF: Vascular endothelial growth factor.

**Table 3 Roles of the P2X7 receptor in human skin disease**

|  |  |
| --- | --- |
| **Disease** | **Observations** |
| Allergic contact dermatitis | Increased P2X7 expression in atopic dermatitis lesions[88] |
| Irritant contact dermatitis | ND |
| Psoriasis | Increased P2X7 expression in psoriatic skin lesions[30,88] |
| Cutaneous graft-versus-host disease | ND |
| Wound healing | P2X7 activation promotes VEGF release from monocytes[103] |
| Skin transplantation | ND |
| Melanoma | P2X7 is present on melanoma cells[117,118] and cell lines[119], with increased expression compared to normal melanocytes[119]P2X7 activation induces A375 melanoma[118] and HT168-M1 melanoma cell death[119] |
| Basal cell carcinoma | P2X7 is present in necrotic tumour centres and apoptotic tumour cells, and correlates inversely with tumour aggressiveness[123] |
| Squamous cell carcinoma | P2X7 is present in apoptotic tumour cells and its activation causes A431 SCC cell death[123] |

ND: Not determined; SSC: Squamous cell carcinoma.

P2X7

**Keratinocytes**

TGF-β, IL-1β and IL-6 release

E-cadherin shedding

Apoptosis

**Langerhans Cells**

IL-23 and RAGE expression

IL-1β release

CD23 shedding

**Dendritic Cells**

IL-1β and IL-6 release

Up-regulation of

HLA-DR and CD86

**Dermal Macrophages**

IL-1β and PGE-2 release

Intracellular ROS formation

Killing of intracellular pathogens

**Mast Cells**

Negligible P2X7 expression

**Fibroblasts**

Microvesiculation

Process elongation

IL-6 release

Apoptosis

**T cells**

CD62L shedding

IL-17 production

**Figure 1 Expression and function of the P2X7 receptor on skin cells.** P2X7 is present on keratinocytes, Langerhans cells, dermal dendritic cells, dermal macrophages, skin T lymphocytes and dermal fibroblasts. P2X7 activation on these cells induces a number of downstream events as indicated. P2X7 is absent on mast cells in normal skin, but can be upregulated during cutaneous disease. P2X7 may also be present on skin B cells, eosinophils and basophils (not shown), but direct evidence is lacking. Cell images (except fibroblasts) were obtained from Servier Medical Art ([www.servier.com](http://www.servier.com)). ATP: Adenosine triphosphate; HLA: Human leukocyte antigen; IL: Interleukin; PGE2: Prostaglandin E2; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; TGF: Tumour growth factor.

P2X7

CD39

Na+

Ca2+

K+

Extracellular

Intracellular

NH2

COOH

**Figure 2 Activation of the P2X7 receptor and its regulation by CD39.** Activation of P2X7 by extracellular ATP causes an influx of Ca2+ and Na+, and efflux of K+. Extracellular ATP can be degraded by cell surface CD39 to limit P2X7 activation on Langerhans cells, macrophages and mast cells. ATP: Adenosine triphosphate.