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REVIEW ARTICLE

Phosphoinositide-3 Kinase/Protein Kinase-B/Mammalian Target of Rapamycin Pathway in Psoriasis Pathogenesis. A Potential Therapeutic Target?

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Psoriasis is a common chronic inflammatory disease of the skin. Its pathogenesis has not been completely elucidated. Phosphoinositide-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway has been identified as a key signaling pathway for important cellular functions. The data collected in this review suggest that overexpression of the PI3K/Akt/mTOR pathway may play an important role in the pathogenesis of psoriasis by mediating the immune-pathogenesis, the epidermal hyperplasia or/and the angiogenesis in the disease. Advances in understanding the pathogenesis of psoriasis has provided new insight into potential therapeutic targets, including the development of biological therapies, resulting in remarkable clinical responses in patients with severe psoriasis. More recently, small molecule oral preparations targeting intracellular signaling that may prove effective have been developed. Data suggest that PI3K/Akt/mTOR pathway may be a potential target for treatment of psoriasis. ***Key words: psoriasis; PI3K/Akt/mTOR pathway; therapeutic target.***

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Psoriasis is a common chronic inflammatory skin disease, affecting approximately 2% of the population in the world. It is associated with high morbidity and decreased quality of life (1). The most common clinical variant of psoriasis is psoriasis vulgaris, which affects approximately 85–90% of all psoriasis patients (1). Clinically, this disease presents as focal or diffuse red inflammatory papules or plaques with abundant, constantly shedding white scales. Pathologically, it features as hyperkeratosis, parakeratosis, acanthosis, papillary dermal capillary proliferation and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in lesional skin.

The pathophysiology of psoriasis is complex and dynamic, and has not been completely elucidated. Currently, it is considered that psoriasis results from a combination of genetic predisposition and environmental triggers (2). Multiple immunological, cellular and molecular pathways regulating epidermal proliferation and inflammation are involved in this disease process. In psoriasis skin, the binding of overexpressed cathelicidin LL-37 to extracellular self-DNA released from dying cells, leads to the synthesis of interferon (IFN)α by plasmacytoid dendritic cells (pDCs) and triggers an auto-inflammatory cascade (3). IFNα, in turn, activates and matures myeloid dendritic cells (mDCs), which migrate to lymph nodes and present antigen to naive T cells, leading to T-cell differentiation and clonal expansion. The polarized T-helper (Th) cells (Th1, Th17, Th22), which bear skin-homing receptors, then circulate to the skin (4). Pro-inflammatory cytokines produced by these cells, including tumor necrosis factor α (TNF-α), IFNγ, interleukin (IL)-17, IL-22, IL-23, IL-12 and IL-1β, have been linked to the pathogenesis of psoriasis by activating keratinocytes (KCs) and other cutaneous cells (5). The cytokines derived from immunocytes act on KCs to either induce inflammation-related genes or increase KC proliferation. In turn, factors produced by KCs can stimulate dendritic cells (DCs), neutrophils and other innate mediators, as well as T cells (6). KCs are also a relevant source of growth factors for angiogenesis. Other skin resident cells, such as fibroblasts, mast cells, and endothelial cells can also contribute to psoriasis pathogenesis by involving in T-cell recruitment and activation through their expressed molecules (7).

As understanding of the pathogenesis of psoriasis has advanced over the recent decades, there has been clearer appreciation of the genetic, cellular and immunological components of disease expression, which has provided new insight into potential therapeutic targets, including the development of biological therapies. Biologics offer a unique opportunity to block or inhibit specific key components of psoriasis pathogenesis, resulting in remarkable clinical responses in patients with severe psoriasis. More recently, research in KC biology and immune cell function, particularly intracellular signaling, has enabled further development of a range of small molecule oral preparations that may prove effective in

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disease control (8). Some of these preparations target molecules associated with PI3K/Akt/mTOR pathway. This pathway has been identified as a key intracellular signaling pathway for important cellular functions. This review focuses on published data investigating the possible role of the PI3K/Akt/mTOR pathway in the pathogenesis of psoriasis and the potential of using PI3K/Akt/mTOR as a therapeutic target for the treatment of psoriasis.

PI3K/AKT/MTOR PATHWAY

The PI3K/Akt/mTOR signaling pathway is involved in a number of cellular mechanisms in a wide variety of cells. Four distinct PI3K subfamilies exist – commonly referred to as classes I, II, III, and IV. The class I PI3K enzyme family is composed of a regulatory subunit and a catalytic subunit. The class IA enzymes comprise 5 regulatory subunits: p85α, p55γ, p50α, p85β, and p55γ, encoded by 3 genes. Each of the 3 class IA p110 catalytic isoforms PI3Kα, PI3Kβ, and PI3Kδ, pairs with one of the regulatory subunits. The class IB catalytic isoform, PI3Kγ pairs with either of the 2 regulatory subunits p84/p87 or p101 (9).

Class IA PI3K is activated by receptor tyrosine kinases (RTK), G protein-coupled receptors (GPCRs), and some oncogenes (e.g., RAS), whereas class IB products are only regulated by GPCRs (10, 11). Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2] and converts it into phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P3]. PI(3,4,5)P3 binds to 3-phosphoinositide dependent protein kinase-1 (PDK1) and Akt, and recruits them to the plasma membrane. This process is negatively regulated by the tumor suppressors phosphatase and tensin homolog (PTEN) and inositol polyphosphate-4-phosphatase typII(INPP4B), which convert PI(3,4,5)P3 back to PI(4,5)P2, and PI(3,4)P2 back to phosphatidylinositol3-phosphate[PI(3)P], respectively. Once at the plasma membrane, Akt is activated. The activated Akt initiates a cascade of downstream signaling events, which promote cellular growth, metabolism, proliferation, survival, migration, apoptosis, and angiogenesis (11) (Fig. 1).

Akt phosphorylates a number of proteins, including mTOR. mTOR acts as a catalytic subunit in the protein complexes of mTORC1 and mTORC2. mTORC1 activates S6 kinase and 4E binding protein 1 (4EBP1), leading to translation initiation and protein synthesis. mTORC2 activates protein kinase C (PKC)-α and Akt (10, 12) (Fig. 1).

The PI3K/Akt/mTOR pathway is known to be important in regulating the innate and adaptive immune responses (13). Experimental observations show that PI3Ks represent important mediators in the signaling cascade leading to initiation of the inflammatory response (14). In addition, the PI3K/Akt pathway has a role in mediating the antiapoptotic and pro-inflammatory signals triggered by lipopolysaccharides (LPS), granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF-α (15). On the other hand, PI3K and mTOR seem to constrain full immune cell activation by upregulation of the key anti-inflammatory cytokine IL-10 and inhibition of pro-inflammatory cytokines (13). Further, the PI3K/Akt/mTOR pathway also plays a role in the proliferation of epidermal keratinocytes (16) and angiogenesis (17).

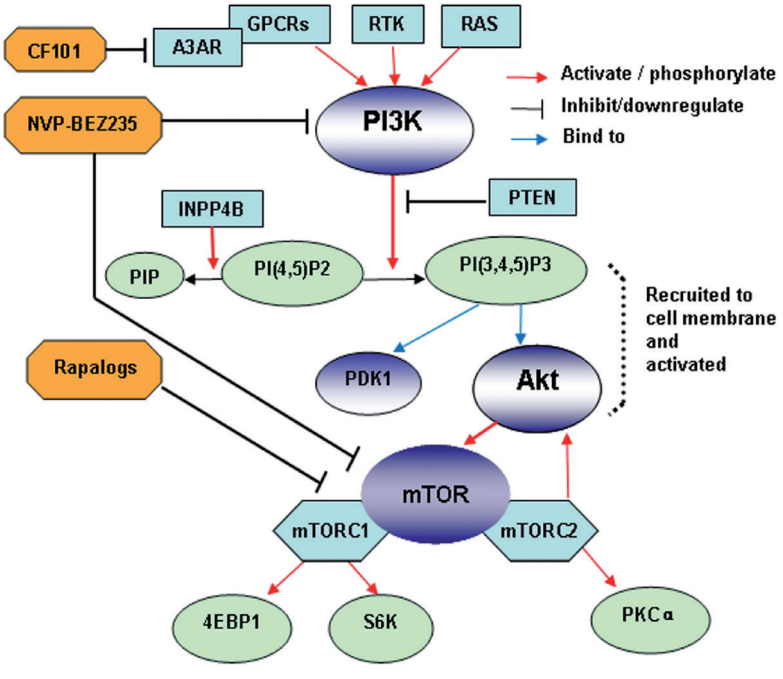

Fig. 1. Schematic of the phosphoinositide-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway. PI3K can be activated by receptor tyrosine kinases (RTK), G protein-coupled receptors (GPCRs) and RAS. Activated PI3K phosphorylates PI(4,5)P2 and converts it into PI(3,4,5)P3. PI(3,4,5)P3 binds to PDK1 and Akt, and recruits them to the plasma membrane. This process is negatively regulated by PTEN and INPP4B, which convert PI(3,4,5)P3 back to PI(4,5)P2, and PI(3,4)P2 back to PIP, respectively. Once at the plasma membrane, Akt is activated. The activated Akt then phosphorylates mTOR, which acts as a catalytic subunit in the protein complexes of mTORC1 and mTORC2. mTORC1 activates S6 kinase and 4EBP1 while mTORC2 activates PKCα and Akt. Targeted small molecules relevant to treatment of psoriasis are showed. Rapalogs including rapamycin are classical mTOR inhibitors. NVP-BEZ235 is a novel dual PI3K/mTOR inhibitor. CF101 binds to A3AR, resulting in receptor downregulation.

OVEREXPRESSION AND ACTIVATION OF PI3K/AKT/MTOR PATHWAY IN PSORIASIS

Pike et al. (18) measured PI3K activity in epidermal keratome biopsies from normal skin and the lesional and non-lesional skin of psoriasis patients. The PI3K activity in the epidermis of psoriatic plaques was increased 6.7-fold when compared with the epidermis from normal skin. The PI3K activity in biopsies of non-lesional psoriatic epidermis was not statistically different from that of normal epidermis. Madonna et al. (19) demonstrated that, in contrast to healthy and non-lesional skin, phosphorylated Akt is strongly expressed in lesional psoriatic skin *in vivo* and in activated psoriatic KCs *in vitro*. Ochaion et al. (20) reported that both PI3K and Akt are upregulated in peripheral blood mononuclear cells (PBMCs) of patients with psoriasis, compared to that of healthy subjects. Ainali et al. (21) performed a large-scale gene expression study to discover molecular subgroups within psoriatic skin samples. Classification of gene expression patterns revealed 2 molecular subgroups within the clinical phenotype of plaque psoriasis. ErbB pathway consists of a family of 4 related receptor tyrosine kinases, namely ErbB1 (EGFR), ErbB2(Neu), ErbB3 and ErbB4, which, when activated can trigger PI3K pathway. Enrichment for ErbB signaling pathways, including PI3K events in ErbB4 and ErbB2 signaling were noted in one of the 2 psoriasis subgroups. In addition, the pathway enrichment in this psoriatic subgroup also included PI3K/Akt activation and Akt phosphorylating targets in the nucleus, suggesting overexpression of PI3K/Akt pathway. Recently, Buerger et al. (22) found that mTOR and its downstream signaling molecule, the ribosomal S6 kinase, are activated in lesional psoriatic skin, suggesting a role of mTOR signaling in psoriatic epidermal changes.

PI3K/AKT/MTOR PATHWAY IN PSORIASIS IMMUNOPATHOGENESIS

The role of the immune system in psoriasis pathogenesis

Increasing evidence has defined the role of the immune system in psoriasis pathogenesis. These include the presence of an increased number of immune cells (especially DCs and T cells) in psoriatic lesions, and the appearance of clonal T cells in lesional skin over time. The functional roles of T cells and cytokines in human psoriasis models and the therapeutic activity of drugs targeting the immune system have been established. Moreover, it is found that psoriasis may be cured in patients who have undergone bone marrow transplantation and that psoriasis can be transferred from transplant donor to recipient. Recently, it has been observed that top hits in whole-genome scans of genes and messenger RNA are immune-related (1).

The role of the PI3K pathway in the immune function

The PI3K pathway has emerged as a key regulator of the immune function. It is well known that PI3K is important in regulating adaptive immune cell activation. For example, not only different PI3K heterodimers, but also mTOR, critically control cell survival, proliferation, B- and T-cell receptor (BCR and TCR, respectively) signaling and chemotaxis in B and T lymphocytes. Moreover, during the recent years, it has increasingly been recognized that the PI3K/Akt/mTOR pathway has broad and yet distinct roles in innate immune cells, including neutrophils, mast cells, monocytes, macrophages, myeloid DC (mDC) and plasmacytoid DC (pDC) (13). Some of the regulatory actions of the PI3K/Akt/mTOR pathway on the immune system may link to the immunopathogenesis of psoriasis.

Initiation phase and maintenance phase in psoriasis immunopathogenesis

Currently, the immunopathogenesis of psoriasis can be divided into 2 phases: initiation and maintenance (5). In the initiation phase, antimicrobial peptide LL-37 is upregulated in lesional psoriatic skin, forming complexes with self-DNA (released from dying cells) and, through toll-like receptor 9 (TLR9) engagements, induces IFNα production by pDCs and the subsequent activation of $CD11^+$ inflammatory DCs (5). Using cultured human and mouse pDCs, Cao et al. (23) found that in the process of pDC activation by TLR9, inhibition of mTOR blocks the interaction of TLR9 with the adaptor protein myeloid differentiation factor 88 (MyD88), and subsequently activates interferon-regulatory factor 7 (IRF7), resulting in impaired type I IFN, i.e. IFNα/β, production. In addition, inhibition of PI3K also considerably suppresses TLR-mediated IFNα secretion in pDCs in a dose-dependent way, indicating that the PI3K-mTOR pathway is crucial for TLR-mediated IFNα production in pDCs. More recently, van de Laar et al. (24) further demonstrated that activation of PI3K, Akt, and mTOR are required for pDC survival, as well as for functioning.

In the maintenance phase, myeloid inflammatory $CD11c^+$ DCs are increased in psoriatic lesions. These DCs express high levels of TNF-α and inducible nitric oxide synthase (iNOS), and produce cytokines IL-23 and IL-20, which potentially activate T cells and KCs, respectively (5, 6). This subset of DCs may be derived from peripheral blood monocytes and is also named monocyte derived DCs (moDCs) (25). Studies have established that GM-CSF differentiates monocytes to DCs *in vitro* (26) and *in vivo* (27). High levels of GM-CSF can be detected in the lesional skin of psoriasis patients (28). Haidinger et al. (29) studied the role of PI3K/mTOR pathway in GM-CSF induced human moDC differentiation and found that the PI3K/Akt/mTOR

pathway is activated by GM-CSF during differentiation of moDCs and that the mTORC1 pathway is pivotal for moDC differentiation. These data suggest that in the pathogenesis of psoriasis, the PI3K/Akt/mTOR pathway might be activated by abnormally increased GM-CSF and subsequently might promote the differentiation of inflammatory $CD11c^+$DCs.

Th1-Th2-Th17 imbalance in the pathogenesis of psoriasis and the role of PI3K/Akt/mTOR pathway

Growing evidence has demonstrated that T cells play a major role in psoriasis. Disease manifestation is orchestrated by proinflammatory $CD4^+$ Th cells producing either IFNγ (Th1 cells) or IL-17 (Th17 cells). These Th1 and Th17 cells can cause inflammation through the involvements of IFNγ, TNF, IL-8, IL-12, IL-17A, IL-19, and IL-23 (30). IL-23, mainly produced by DCs in psoriatic skin, plays an important role in mediating Th17 terminal effector functions by favoring Th17 cell maintenance and the production of proinflammatory cytokines, such as IL-17A (4). Another subset of Th cells, Th2 cells, can suppress Th1 and Th17 activities by producing IL-4 and IL-13. As Th2 T cells, and consequently IL-4 and IL-13 expression, are reduced in psoriasis lesions, this suppression of Th1 and Th17 T-cell activity is likely absent (31). Therefore, there is a Th1-Th2-Th17 imbalance in patients with psoriasis.

A series of studies has revealed a central role for mTOR in regulating $CD4^+$ T-cell differentiation. Differentiation into the Th1 and Th17 subsets of Th cells is selectively regulated by signaling from mTORC1. mTORC1 signaling-deficient T cells fail to generate Th1 and Th17 responses *in vitro* and *in vivo*. Alternatively, when mTORC2 signaling is deleted from T cells, they fail to generate Th2 cells (32).

PI3K is upstream of the mTOR. Based on the regulation of mTOR by PI3K, the PI3K knockout models should recapitulate the effects of mTOR deletion on $CD4^+$ T-cell differentiation. In the PI3K knockout models, T cells from the r1ΔT/r2n mice lacking all p85 regulatory subunits and having low or absent p110α, β, and δ catalytic subunit expression support normal Th1 polarization but Th2 cultures have decreased IL-4 (33). This may be due to impaired mTORC2 signaling and some preserved mTORC1 activity, and is consistent with the above-mentioned requirement of mTORC2 in Th2 differentiation and the relative preservation of mTORC1-dependent S6 phosphorylation over mTORC2-dependent Akt S473 phosphorylation that is reported in the r1ΔT/r2n mice (33). In addition, much evidence indicates that PI3K is involved in Th17 differentiation. Haylock-Jacobs et al. (34) reported that PI3Kδ drives the pathogenesis of experimental autoimmune encephalomyelitis by inhibiting effector T-cell apoptosis and promoting Th17 differentiation. IL-23 is important for the development of Th17 cells (35, 36). Kuwabara et al. (37) reported that PI3K/Akt and NF-κB signaling pathways play a critical role in CC-chemokine receptor type 7 (CCR7)-mediated IL-23 production in DCs, and that the DCs, which are stimulated by CCR7 ligands, induce the development of Th17 cells. Of note, immunohistologic analysis reveals that there are DCs expressing CCR7 in psoriatic lesions but not in healthy skin (38). Taken together, the PI3K/mTOR pathway likely plays a role in Th1 and Th17 upregulated differentiation and Th1-Th2-Th17 imbalance in psoriasis pathogenesis.

IL-17A-producing γδ T cells and PI3K

More recently, studies showed that IL-17-producing γδ T cells, a distinct population of skin-invading immune cells, are crucial for the development of psoriatic inflammation (39). van der Fits et al. (40) reported that Imiquimod (IMQ)-induced dermatitis in mice closely resembles human psoriasis lesions in terms of the phenotypic and histological characteristics, and that lesion development is critically dependent on the IL-23/IL-17 axis. Cai et al. (41) showed that dermal γδ T cells are the major source of IL-17A upon IL-23 stimulation in the imiquimod-induced dermatitis in mouse skin. Deficiency of γδ T cells or IL-17 receptor significantly decreases IL-23-induced epidermal thickness and neutrophil infiltration. Furthermore, IL-17A-secreting γδ T cells are present in high frequency in human psoriatic skin lesions. These observations support the idea that IL-17A-producing dermal γδ T cells are a key component in the pathogenesis of psoriasis. Roller et al. (42) used the imiquimod-induced psoriasis-like skin inflammation model to assess the potential roles of PI3Kδ and PI3Kγ in psoriasis, and found that PI3Kδ or PI3Kγ blockade ameliorates imiquimod-induced psoriasis-like disease correlating with decreased IL-17A–producing γδ T cells in mice. They also showed that PI3Kδ and PI3Kγ inhibitors reduce IFN-γ production by human TCRγδ T cells and IL-17A and IFNγ production by PBMCs from psoriatic or healthy donors. The authors deemed that PI3Kδ and/or PI3Kγ inhibitors should be considered for treating IL-17-driven diseases, such as psoriasis.

EPIDERMAL HYPERPLASIA IN PSORIASIS AND THE PI3K PATHWAY

Although the pivotal contribution of the immune cells to the pathogenesis of psoriasis has been demonstrated, some evidence suggests that intrinsic alterations of the epidermis may also be important to disease pathogenesis (43). Indeed, the most characteristic change in psoriasis is markedly increased persistent KC proliferation (44). The cell cycle time of psoriatic KCs is short. While maturation and shedding of KCs take 26 days in normal

epidermis, it occurs in 4 days in psoriatic epidermis. Growth factors, coming from various cell types, are believed to control the increased proliferation. Currently available antipsoriatic drugs act on KC proliferation. Calcipotriol, a vitamin D3 analog, and retinoids, the natural and synthetic vitamin A derivatives, modulate KC hyperproliferation and differentiation. Cyclosporine has strong antiproliferative effects on human epidermal KCs in addition to immunomodulatory effects (45). However, the underlying cause of the epidermal hyperplasia in psoriasis is still not completely understood.

Using cultured KCs with stable expression of an inducible, constitutively active PI3K mutant and organotypic skin cultures, Pankow et al. (46) demonstrated that enhanced PI3K activity promotes KC proliferation and PI3K is a negative regulator of KC differentiation. The authors supported the hypothesis that chronic activation of PI3K in KCs is causally involved in the pathogenesis of hyperproliferative skin diseases.

Epidermal growth factor receptor (EGFR) is an upstream activator of PI3K (47). EGFR and its ligands EGF (48–50), heparin-binding EGF-like growth factor (HB-EGF), transforming growth factor α (TGF-α), and epiregulin (51) are overexpressed in psoriasis. All of these factors function to promote KC proliferation (52–54). When bound to ligand, EGFR activates PI3Ks, leading to the phosphorylation of phosphatidylinositol on the 3-hydroxyl group. The resulting product, PI(3,4,5)P3, activates Akt kinase (55). PI3K pathway may therefore contribute to the EGFR-induced KC proliferation in psoriasis.

Several lines of evidence implicate local perturbations at all levels of the insulin-like growth factor (IGF) system in the hyperproliferative psoriatic epidermis. In psoriasis, IGF-I receptor (IGF-IR) expression in the epidermis is more widespread and correlates with the expanded proliferative compartment. Blister fluid from psoriatic lesions contains higher levels of IGF-II. Furthermore, IGF-IRs of psoriatic lesions exhibit upregulated tyrosine kinase activity (56). Continuous stimulation with IGF-I causes prolonged tyrosine phosphorylation of IGF-IR and prolonged association of PI3K with IGF-IR, and PI3K activity bound to IGF-IR is essential for IGF-I-dependent cell proliferation (57). Yoo et al. (58) studied the relationship between IGF-II and 12-lipoxygenase (12-LOX) that are upregulated in psoriasis, and found that IGF-II induced 12-LOX mRNA and protein levels in human KCs through two major signal transduction pathways, namely, the extracellular signaling-regulated kinase (ERK)-mitogen-activated protein kinase (MAPK) and PI3K pathways.

D-type cyclins are one of the key components of the cell-cycle machinery. Three D cyclins, cyclin D1, D2, and D3, operate in mammalian cells and play a major role in positive regulation of G1 progression (59). Several studies found overexpression of cyclin D1 in psoriasis, causing epidermal hyperproliferation (60). PI3K triggers a network that positively regulates G1/S cell cycle progression and increases cyclin D1 expression (61).The translation of cyclin D1 is largely regulated by mTOR activity (62), and one of the primary ways that mTOR exerts its regulatory effects on cell proliferation is by controlling the production of cyclin D1 (63).

IL-22 is one of the cytokines produced by Th17 and Th1 cells. Earlier studies revealed that in psoriasis patients, IL-22 mRNA expression in lesional skin is upregulated and circulating IL-22 levels are significantly higher than that in normal subjects. T cells isolated from psoriatic skin produce higher levels of IL-22 in comparison to peripheral T cells isolated from the same patients (64). Later, a study by utilizing transgenic mice and a three-dimensional epidermis model demonstrated that IL-22 directly acts on KCs and causes epidermal alterations typical for psoriasis (65). These data indicate that IL-22 plays an important role in the pathogenesis of psoriasis, which is characterized by hyperproliferation of KCs. Very recently, Mitra et al. (16) found that in cultured human epidermal keratinocytes (HEK), IL-22 upregulated AKT1 and MTOR gene, induced phosphorylation of Akt and mTOR, and promoted cell proliferation, which was inhibited by mTOR inhibitors. Therefore, they concluded that IL-22-induced proliferation of KCs is dependent on the PI3K/Akt/mTOR signaling pathway, and may link to the pathogenesis of psoriasis.

The studies of Lai et al. (66) showed that antimicrobial protein regenerating islet-derived protein 3-alpha (REG3A) is highly expressed in KCs during psoriasis and wound repair and in imiquimod-induced psoriatic skin lesions. The expression of REG3A by KCs is induced by IL-17A via activation of KC-encoded IL-17 receptor A (IL-17RA) and feeds back on KCs to inhibit terminal differentiation and increase cell proliferation by binding to exostosin-like 3 (EXTL3) followed by activation of PI3K and the kinase Akt. This observation suggests that IL-17A may induce the epidermal hyperproliferation observed in psoriasis by activating the PI3K pathway.

Both mRNA and protein expression levels of another antimicrobial protein, human β-defensin 2 (hBD-2), are much higher in psoriasis compared to normal skin and atopic dermatitis (67). High levels of serum hBD-2 are observed in psoriasis patients compared to healthy individuals. Moreover, the hBD-2 serum levels of psoriasis patients correlate with clinical severity (68). The role of hBD-2 in psoriasis pathogenesis may be related to its ability to stimulate epidermal KC migration, proliferation and production of proinflammatory cytokines and chemokines (69). Interestingly, various studies have shown an involvement of PI3K in the regulation of hBD-2. Jang et al. (70) reported that IL-1β induces hBD-2 mRNA expression through activation of PI3K/Akt, and Méndez-Samperio et al. (71) studied the mechanism by which *M. bovis* BCG triggers gene transcription of hBD-2 and found that BCG upregulates hBD-2 gene

expression in human epithelial cells at least partly via activation of the PI3K/Akt signaling pathway. We just take this finding as an example (an indirect evidence) to support our hypothesis that the PI3K/Akt signaling might link to the epidermal KC hyperproliferation in psoriasis via its impact on hBD-2 gene expression.

As mentioned above, psoriatic KCs exhibit a marked hyperproliferation in response to mitogenic signals. In addition, they are characterized by an aberrant resistance to apoptosis, which contributes to the epidermal thickening in psoriasis. Madonna et al. (19) demonstrated that suppressor of cytokine signaling (SOCS) 1 and SOCS3 molecules, both abundantly expressed in psoriatic epidermis, suppress the IFNγ/TNF-α-induced apoptosis in psoriatic KCs by specifically sustaining the activation of the anti-apoptotic PI3K/Akt pathway.

ANGIOGENESIS

There is ample evidence of angiogenesis driving the psoriasiform phenotype (72). Plasma and tissue vascular endothelial growth factor (VEGF) levels are elevated in psoriasis. The VEGF levels correlate directly with disease activity and severity, but correlate inversely with clinical improvement. The VEGF receptors, VEGFR1 and VEGFR2, are overexpressed in psoriatic lesional epidermis, and angiogenesis induced by VEGF is an important feature in psoriasis (72, 73). To date, a number of pro-angiogenic factors have been defined. VEGF is the only specific mitogen for endothelial cells. It stimulates endothelial cell growth and inhibits apoptosis, promoting angiogenesis (74).

In psoriasis, cell proliferation could increase oxygen consumption, and epidermal thickening could lead to impaired oxygen supply. Rosenberger et al. (73) indicated that hypoxic adaptation is conferred through hypoxia-inducible transcription factors (HIFs). VEGF and its receptor Flt-1 are HIF target genes. Growth factors and inflammatory cytokines activate the PI3K pathway, and via activated Akt (phosphor-Akt) augment HIF activity. Their studies demonstrated that the major oxygen-dependent HIF isoforms are strongly upregulated in psoriatic skin. Furthermore, phospho-Akt expression is markedly enhanced in the dermal capillaries and in surrounding interstitial/inflammatory cells. These data suggest that hypoxia initiates a potentially self-perpetuating cycle involving HIF, VEGF, and Akt activation, which may exist in psoriasis in dermal capillaries and contribute to disease progression.

TARGETING PI3K/AKT/MTOR PATHWAY FOR TREATMENT OF PSORIASIS

Already in 2001, the prototype of classical mTOR inhibitor rapamycin was tried in treating psoriasis. A phase II, randomized, double-blind, multicenter study was performed on treating severe chronic plaque psoriasis with oral rapamycin, cyclosporine, and a combination of the two. An enhanced effect of concomitant administration of the 2 drugs was confirmed. However, rapamycin monotherapy was ineffective (75). Later, a randomized, double-blind trial of treating chronic plaque psoriasis with topical sirolimus (rapamycin) was reported. A significant reduction in the clinical score was achieved, but measurements of plaque thickness and erythema did not show significant improvement (76). These results represented only a moderate impact of rapamycin on the treatment of psoriasis.

At the same time, rapamycin and its derivatives (rapalogs) were also used to treat malignancies, in which the mTOR pathway is frequently dysregulated. However, their therapeutic effects did not appear as expected. The overall objective response rates in major solid tumors achieved with rapalogs as single-agent therapy were moderate (77). This is likely due to 2 reasons: (*i*) the hyperactivation of Akt with loss of the mTORC1/S6K1/IRS-1/PI3K negative feedback loop; (*ii*) the poor activity of rapalogs on mTORC2, with subsequent Akt phosphorylation and activation (78). Recently, 2nd generation mTOR inhibitors that target the ATP binding site in the mTOR kinase domain and repress both mTORC1 and mTORC2 activity have been developed. This class of mTOR inhibitors includes (*i*) mTOR and PI3K dual specific inhibitors, which target PI3K in addition to mTORC1 and mTORC2, and (*ii*) selective mTORC1/2 inhibitors, which target mTORC1 and mTORC2. The use of 2nd generation mTOR inhibitors may overcome some of the limitations of rapalogs. As expected, 2nd generation mTOR inhibitors, which can block PI3K mediated or mTORC2 mediated Akt activation, have demonstrated improved efficacy, particularly in cancer cells with PI3K mutations. Data from early phase of clinical trials have recently shown significant clinical activity and good tolerability for most of these inhibitors (79).

Among the 2nd generation mTOR inhibitors, NVP-BEZ235 is a novel dual PI3K/mTOR inhibitor and is currently in phase I/II clinical trial (79). Recently NVP-BEZ235 was found to be able to effectively inhibit the proliferation of human KCs induced by IL-22 (16). Taking into account that IL-22 has been shown to play an important role in psoriasis (16), this novel finding provides the scope to develop new therapeutics targeting PI3K/Akt/mTOR signaling pathway for treatment of psoriasis (65).

Roller et al. (42) found that PI3Kδ or PI3Kγ block ameliorates imiquimod-induced psoriasis-like disease and PI3Kδ and PI3Kγ inhibitors can reduce IL-17 and IFNγ production by PBMCs from psoriatic donors. The authors deemed that PI3Kδ and/or PI3Kγ inhibitors should be considered for treating IL-17–driven diseases, such as psoriasis.

The G protein-associated A3 adenosine receptor (A3AR) is recently defined as a novel anti-inflammatory target. Overexpression of A3AR was found in PBMCs derived from psoriasis patients compared with those from healthy subjects. Bioinformatics analysis demonstrated the presence of DNA binding sites for nuclear factor-κB (NF-κB) and cyclic AMP-responsive element binding protein (CREB) in A3AR gene promoter. Upregulation of NF-κB and CREB was found in the PBMCs from patients with psoriasis. The PI3K/Akt signaling pathway, known to regulate both the NF-κB and CREB, was also upregulated in PBMCs of psoriasis patients (20).

CF101 is an oral anti-inflammatory agent that binds with high affinity and selectivity to the A3AR. In a phase 2, multicenter, randomized, double-blind, dose-ranging, placebo controlled study, 75 patients with moderate to severe plaque-type psoriasis were enrolled, randomized and treated with CF101 (1, 2, or 4 mg) or placebo administered orally twice daily for 12 weeks. In the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in the PASI score vs. placebo throughout the study period was observed, with a statistically significant difference on weeks 8 and 12 ($p=0.047$; $p=0.031$, respectively). CF101 was well tolerated and demonstrated clear evidence of efficacy in patients with moderate to severe plaque psoriasis (80). Adenosine receptors (AR) including A3AR, belong to the superfamily of GPCRs (81), which is one of the upstream activators of PI3K (11). Therefore, A3AR may activate the PI3K pathway and trigger the phosphorylation of Akt. Upon CF101 binding to the A3AR, receptor downregulation takes place, giving rise to the modulation of downstream signal transduction pathways (82). More specifically, in experimental animal models of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, and auto-immune uveitis, CF101 treatment decreases the expression levels of key signaling proteins downstream to A3AR activation including the levels of PI3K, Akt and NF-κB, resulting in inhibition of TNF-α and induction of apoptosis of inflammatory cells (82–85). This might also occur in the CF101 treatment on psoriasis.

SUMMARY

Although substantial advances have been made in recent years, the pathogenesis of psoriasis remains to be further elucidated. As we have summarized in this review, data suggest an important function of the PI3K/Akt/mTOR pathway in psoriasis pathogenesis. Through increased understanding of the pathogenesis of psoriasis, major progresses are constantly made in the field of biologics and small molecule drug development for the treatment of this disease. Drugs targeting the PI3K/Akt/mTOR are among the emerging small molecule drugs. Although it is too early to say how effective and safe these agents will be, it is evident that our range of options in treating this perplexing disease will greatly increase in the future.

The authors declare no conflict of interest.

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