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REVIEW

The role of PI3K/AKT/FOXO signaling in psoriasis

Miao Zhang[1] · **Xiaoyan Zhang**[2]

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Abstract

Phosphatidylinositol 3-kinase (PI3K) and protein kinase B (AKT) signaling pathway play a central role in multiple cellular functions such as cell proliferation and survival. The forkhead box O (FOXO) transcription factors are negatively regulated by the PI3K/AKT signaling pathway and considered to have inhibitory effect on cell proliferation. Psoriasis is a multifactorial disease with a strong genetic background and characterized by hyperproliferative keratinocyte. PI3K signaling regulates proliferation of keratinocyte by activating AKT and other targets, and by inducing FOXO downregulation. The amplification of PI3K and AKT and the loss of the FOXO are gradually being recognized in psoriatic lesions. The upstream and downstream of PI3K/AKT signaling molecules such as tumor suppressor phosphatase and tensin homolog (PTEN) and mammalian target of Rapamycin (mTOR), respectively, are also frequently altered in psoriasis. In this review, we highlight the recent studies on the roles and mechanisms of PI3K and AKT in regulating hyperproliferation of keratinocyte, and the roles of the downstream targets FOXO in psoriasis. Finally, we summarized that PI3K/AKT/FOXO signaling and its upstream and downstream molecule which could be underlying therapeutic target for psoriasis. This article is part of a special issue entitled: PI3K–AKT–FOXO axis in psoriasis.

Keywords PI3K · AKT · FOXO · Psoriasis · PTEN · mTOR · Hyperproliferation of keratinocyte · Psoriatic lesions · Inhibitor

Abbreviations

PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
AKT/PKB	Protein kinase B
FOXO	Forkhead box O
PTEN	Phosphatase and tensin homolog
mTOR	Mammalian target of Rapamycin complex
PDK1	Phosphoinositide-dependent kinase-1
GFR	Growth factor receptor
PH	Pleckstrin homology
PIP3	Phosphatidylinositol 3–5 triphosphate
AFX	Acute-lymphocytic-leukemia-1 fused gene from chromosome X
FKHR	Forkhead in rhabdomyosarcoma
FKHR-L1	FKHR-like 1
IL-22	Interleukin 22
FasL	Fas ligand
TRAIL	TNF-related apoptosis-inducing ligand
TRADD	TNF receptor type 1 associated death domain
BCL2	B-cell lymphoma 2
BIM	Bcl-2-like protein 11
BAD	Bcl-2-associated death promoter
FLS	Synovial cells
NHEK	Normal human epidermal keratinocyte
IMQ	Imiquimod
ROS	Reactive oxygen species

✉ Xiaoyan Zhang
superfawn@aliyun.com

[1] Graduate School, Beijing University of Chinese Medicine, Beijing 100029, China

[2] Department of Dermatology, China-Japan Friendship Hospital, Beijing 100029, China

Introduction of PI3K/AKT signaling pathway

The Phosphoinositide 3-kinases (PI3Ks) in mammalian cells form a family which share the primary biochemical function to phosphorylate the 3-hydroxyl group of phosphoinositides [21]. PI3K is activated by diverse growth factor receptors(GFR) and oncogenes, and the rise of PI3K signaling is considered a characteristic of cancer [41, 50]. Based on their different structures, functions and substrate preferences, PI3Ks can be divided into three classes, class I, II, and III [36, 42]. Among these classes, class I PI3Ks

are the best understood to play vital roles in regulating cell proliferation, growth, and survival initiated by many growth and survival factors [57]. Akt/PKB (also known as protein kinase B) is a growth factor regulated serine/threonine kinase, a key downstream target of PI3K and a central medium for the PI3K pathway, which has multiple downstream effectors, shares structural homology within its catalytic domain and contributes to a variety of cellular processes. AKT family has three isoforms: AKT1, AKT2, and AKT3 (also known as PKBα, PKBβ, and PKBγ, respectively) [43, 110].

AKT consists of three conserved domains including a specific N-terminal pleckstrin homology (PH) domain, a central kinase catalytic domain and a C-terminal regulatory domain. After activated by GFR tyrosine kinase, PI3K is activated and produces phosphatidylinositol 3–5 three phosphoric acid (PIP3) on the plasma membrane. PIP3 functions as a docking site for PDK1 and AKT. The product of PI3K, PIP3, combines with AKT and causes the membrane recruitment of AKT, and also combines with upstream kinases including phosphoinositide-dependent kinase 1 (PDK1) through their PH domains [34, 36], then PDK1 phosphorylates AKT in the kinase domain (Thr 308 in AKT1). The complete activation of AKT requires the phosphorylation within the carboxyl-terminal hydrophobic motif (Ser 473 in AKT1) of AKT by PDK2 [52, 102, 112]. Once activated, AKT moves to the cytoplasm and nucleus, where a number of downstream targets are phosphorylated, activated, or suppressed to provide a survival signal that protects cells from apoptosis induced by various stresses, and also mediates a variety of metabolic effects [119]. The PI3K/AKT signal transduction pathway is mainly focused on regulating of a variety of important physiologic cellular functions, such as cell metabolism, protein synthesis, cell survival/inhibition of apoptosis, and cell cycle progression, cell proliferation, growth, and angiogenesis [1, 41, 81, 120]. The pathway is frequently deregulated in different malignancies [27, 63] and recent data indicate its clinical relevance in inflammatory diseases, including psoriasis [24, 25, 54]. PI3K/AKT axis has vital function in inflammatory skin diseases, especially its downstream signaling target mammalian target of Rapamycin (mTOR) plays a central role in some of the most common inflammatory dermatoses [5], such as mTOR expression is confirmed increased in acne patients' skin [86]. The pathway involves human diseases, and understanding the complexity of this pathway may provide new avenues for therapeutic intervention. Over the past decade, PI3K/AKT has become the core participant in the signal transduction pathways activated in response to growth factors and is thought to contribute to multiple cellular functions [10]. In this review, we will focus on the roles and mechanisms of PI3K, AKT and its downstream target FoxO in regulating proliferation of keratinocyte in psoriasis.

Canonical FOXO regulation and function

The forkhead box O (FOXO) transcription factor family has emerged as a central player in an evolutionary conserved pathway downstream of PI3K/AKT signaling [18]. The FOXO family of transcription factors and this signaling pathway was identified for the first time in the nematode worm Caenorhabditis elegans, where it plays a role in regulation of the life span of the organism [95]. Four isoforms of FOXO proteins (FOXO1/FKHR/FOXO1a, FOXO3/FKHRL1/FOXO3a, FOXO4/AFX and FOXO6) have been found to share high protein homology [58] and regulated by AKT and 14-3-3 protein [113]. The FOXO1, FOXO3 and FOXO4 transcription factors are directly phosphorylated by AKT, leading to nuclear export and transcriptional inhibition [8, 60]. Researches have shown that the phosphorylation of FOXO proteins can regulate cell survival by manipulating their target genes and some of the target genes may play an important role in the suppressing cell proliferation [16]. The target genes for the FOXO family are considered to be extracellular ligands, including the Fas ligand(FasL), TRAIL (TNF-related apoptosis-inducing ligand) and TRADD (TNF receptor type 1 associated death domain), as well as intracellular apoptotic components such as Bim (bcl-2 interacting mediator of cell death), a pro-apoptotic Bcl-2 family member, and Bcl-6 [8, 18].

FOXO transcription factors are negatively regulated by AKT-mediated phosphorylation and constitute and have been mainly considered to regulate the expression of a number of genes that are crucial for the proliferative status of a cell [37, 117]. As such, FOXO transcription factors appear to play an essential role in many of the effects of AKT on cell proliferation and survival [61, 80]. Transcriptional activity of FOXOs is regulated through shuttling between the nucleus and the cytoplasm. Phosphorylation of nuclear FOXOs by AKT induces the binding to 14-3-3 proteins, which facilitate nuclear export of FOXO1, FOXO3 & FOXO4 and simultaneously obstruct relocation into the nucleus [11, 12, 62]. Upon loss of GFR signaling, next dephosphorylation of PIP3 by PTEN results in reduced AKT activity, loss of FOXO phosphorylation and subsequent nuclear accumulation of FOXOs. In the nucleus, FOXOs mediate transcription of a wide array of target genes involved in proliferation, cell cycle and survival inhibition, apoptosis and so on (Fig. 1) [35, 59].

The early findings suggest in cells of the hematopoietic system, mere activation of a FOXO factor is sufficient to activate a variety of pro-apoptotic genes and to trigger apoptosis. In contrast, in most other cell types, activation of FOXO blocks cellular proliferation and drives cells into a quiescent state [18]. In agreement with these

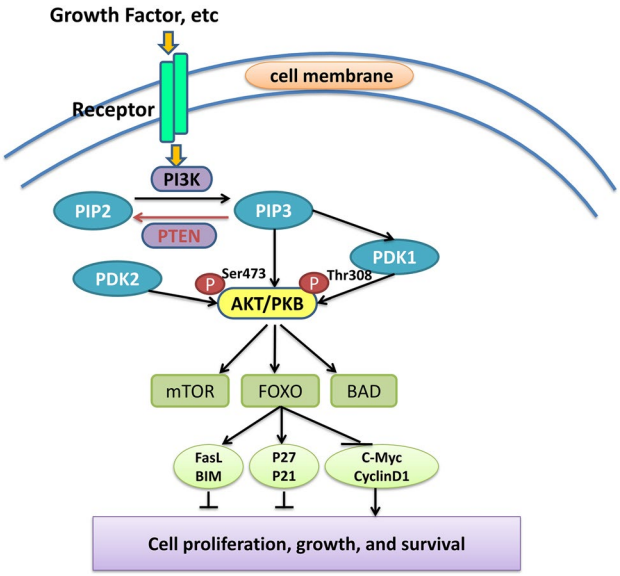

Fig. 1 The PI3K/AKT/FOXO signaling pathway. The PI3K/AKT pathway is the canonical pathway regulating transcriptional activity of FOXOs. Upon activation of GFR tyrosine kinases, PI3K becomes activated and generates PIP3 at the plasma membrane. PIP3 facilitates the phosphorylation of AKT by PDK1. Subsequently, phosphorylates nuclear FOXOs, facilitate nuclear export of FOXOs and simultaneously obstruct relocation into the nucleus. Upon accumulation in the nucleus FOXOs can bind various transcription-cofactors and regulate the transcription of genes involved in the cell proliferation, growth, survival, cell cycle, apoptosis and metabolism, etc. Pathway activity is negatively regulated by PTEN feedback loop

views on the role of FOXOs in psoriasis, clinic may use FOXO levels or activity as prognostic markers for psoriasis patient disease progression. In conclusion, the discovery and lucubration that certain FOXO family members (FOXO1,FOXO3,FOXO4,FOXO6) are targets of PI3K/AKT signaling provides new insights into the mechanism of AKT-induced abnormal hyperplasia [8, 60, 72], but possibly also into hyperproliferation of keratinocyte in psoriasis.

Proliferation of keratinocyte regulated by PI3K/AKT/FOXO signaling pathway

Cell proliferation is one of the important functions of the PI3K/AKT signaling cascade. And in this cascade, PI3K and AKT are the key upstream molecules that link the ligation of the phosphorylation and activation state of FOXO and mTOR with the GFR [81, 105]. In recent years, many reports clarify the importance of PI3K/AKT signaling in cell survival in several kinds of cancer [7, 46, 107, 118]. In a variety of malignancies, PI3K/AKT signaling has been found to be constitutionally active which correspondingly indicate the important roles of this signaling in cellular proliferation [81].

The PI3K–AKT–FOXO signaling network provides a major intracellular hub for the regulation of cell proliferation [115]. PI3K/AKT signaling promotes cell survival by phosphorylating and inhibiting a FOXO transcription factor and influences cellular proliferation by inactivating cell cycle inhibitors (p27 and p21) and promoting cell cycle proteins (c-Myc and cyclin D1) [11, 32, 69]. Survival factors can suppress apoptosis in a transcription-independent manner by activating AKT, which then phosphorylates and inactivates components of the apoptotic machinery, including the pro-apoptotic Bcl-2 related protein BAD [122]. AKT phosphorylates FOXO, leading to FOXO's retention in the cytoplasm. Survival factor withdrawal leads to FOXO dephosphorylation, nuclear translocation, and target gene activation. Within the nucleus, FOXO triggers apoptosis and inhibits proliferation most likely by inducing the expression of genes that are critical for cell death and growth [11]. PI3K/AKT signaling has been reported in the epidermis associated with keratinocyte survival and differentiation and favored the execution of epidermal keratinocyte terminal differentiation program [19, 91, 96]. Recently, it has been found that candidate molecules implicated in keratinocyte regulation downstream of AKT are the mechanistic target of rapamycin complex one (mTORC1) signaling complex, positively regulated by AKT signaling [124], and the FOXO family of transcription factors, which are directly inhibited by AKT-dependent phosphorylation [11, 45, 93]. Thus, PI3K/AKT signaling that is believed to promote keratinocyte proliferation by phosphorylating and inhibiting a FOXO transcription factor.

Psoriasis is a multifactorial heritable disease characterized by severe inflammation resulting in poorly differentiated, hyperproliferative keratinocyte. Although studies over recent years have shown that the pathogenesis of psoriasis is closely related to the abnormality of T-lymphocytes in psoriatic lesions, the cause of excessive proliferation and abnormal apoptosis of keratinocyte remains unclear [90]. Interleukin 22 (IL-22), a relatively new Th17 cytokine has been found to induce significant proliferation of human keratinocyte and plays a critical role in the pathogenesis of autoimmune diseases like psoriasis [49, 83]. Recent results showed that IL-22 induced proliferation of NHEK (normal human epidermal keratinocyte) is dependent on PI3K/AKT signaling pathway [83, 84, 100]. The previous data indicated that FOXOs cross-talk with keratinocyte fate-regulatory genes [20, 114] and nuclear AKT2 can oppose normal epithelial stem cell and limbal keratinocyte stem cell self-renewal by repressing a FOXO-mTORC1 signaling pathway [2, 56, 79, 101]. Thereby, in keratinocyte hyperproliferative autoimmune diseases like psoriasis this PI3K/AKT/FOXO

signaling pathway may be considered as new therapeutic target.

Abnormal expressions of PI3K, AKT, and FOXO in psoriasis

It is well-established that psoriasis is an autoimmune and incurable chronic inflammatory dermatosis that impacts 2–3% of the world population [28, 48, 70]. The etiology of psoriasis is not completely clear, but the disease is characterized by erythema scalelike skin plaques caused by epidermal keratinocyte hyperplasia, aberrant differentiation, parakeratosis, and chronic dermis inflammation [89]. Nowadays, PI3K signaling can be targeted to determine its contribution to psoriatic arthritis where deregulated proliferation of keratinocytes, activated immune cells and synovial fibroblasts [9, 76, 77]. In recent researches also discovered that PI3K/AKT/FOXO to be pivotal in the regulation of mammalian keratinocyte proliferation [29].

Deregulation of several elements of the PI3K signaling cascade is recognized in psoriasis, the occurrence of which promotes pathway activation. In previous study, Pike et al. [97] measured PI3K activity in epidermal keratome biopsies and found out that compared with the epidermis from normal skin, the PI3K activity in the epidermis of psoriatic plaques was increased 6.7-fold, but not statistically different in biopsies of non-lesional psoriatic epidermis. And Zhang et al. [121] also disclosed that overexpression of PI3K specifically in psoriatic lesions in comparison with that in lesions of chronic dermatitis, keratosis seborrheica, squamous cell carcinoma, basal cell carcinoma. Extensive researches revealed P-AKT protein level and expressions of PI3K and AKT in the keratinocyte in psoriasis lesions were elevated dominantly compared with normal and non-lesional skin [73, 92, 116, 123]. Further study on investigating the significance of the expression of three isoforms of AKT in the pathogenesis of psoriasis found out that the increased expression of AKT3 might be correlated to the elevation of phosphorylated AKT and AKT activity in psoriatic lesions [78]. Higher expression of PI3K may lead to excessive activity of AKT, which might promote keratinocyte proliferation through phosphorylation of the downstream target proteins FOXO and so on. At present, there were studies investigated the relationship between FOXO and the proliferation of psoriatic keratinocyte, and found out that FOXO isoform expression was mostly in nucleus, but it was localized mainly in cytoplasm of psoriatic keratinocyte, the transcription activities of FOXO isoforms were almost absent, and the protein level of FOXO4, the gene expression of FOXO1 and the activity of FOXO3A are both significantly decreased in psoriatic lesions compared with that uninvolved psoriatic lesions and normal skin [68]. The current knowledge also discovered that P-FOXO1 and P-AKT is significantly up-regulated in psoriatic lesions compared with the normal skin which may leads to the reduction of FOXO1 gene expression [53].

Therefore, the downregulation and inactivation of FOXO isoforms in psoriatic lesions might be related to the hyperproliferation of psoriatic keratinocyte and PI3K/AKT/FOXO signaling pathway may participate in the occurrence and progression of psoriasis. We can speculate that the up-regulated of P-AKT may change the localization of FOXO isoforms, transferring it from nucleus to cytoplasm, losing transcription factor activity, reducing the synthesis of downstream target genes, thereby losing the inhibition of proliferation and resulting in keratinocyte hyperproliferation. Whether selective blocking or inhibiting PI3K/AKT/FOXO signaling pathway might improve the clinical presentation of psoriasis need to be investigated in the future.

The upstream signaling molecule PTEN of PI3K/AKT in psoriasis

PTEN (Phosphatase and tensin homolog deleted on chromosome 10) is a well-established tumor suppressor gene that first discovered on human chromosome 10q23 in 1997 [111], and it was found as a putative phosphatase mutated in many human tumors [64, 74]. PTEN is a constitutive inhibitor of the PI3K/AKT pathway that induces apoptosis and controls cell growth by suppressing this pathway, and plays an important role in multiple cellular functions such as cell proliferation and survival [22, 57]. The product of PI3K, PIP3, is a second messenger for promoting cell proliferation and survival, PTEN hydrolyzes the 3- phosphate on PIP3 to produce PIP2, and inhibits PIP3-mediated signaling pathways [75]. It has been elucidated that in cells carried the PTEN mutation, the PI3K pathway is usually constituently active and resulting in inactivation of endogenous FOXOs [44]. Phosphorylation-dependent nuclear/cytoplasmic shuttling of FOXOs is major modulated by AKT and PTEN. AKT phosphorylates FOXO leads to of cytoplasm FOXOs sequestration and target gene transcription inhibition. FOXO dephosphorylation brings about translocation of nuclear and activation of target gene [17]. Accordingly, PTEN is also a FOXO target gene, FOXOs can strengthen PTEN transcription to enhance the biological function of keratinocyte hyperproliferation inhibition.

Loss of function or mutations in PTEN is not only related to the development of cancer but also exhibits histrionic consequences for proliferative disorders. The elevated activity and phosphorylation level of AKT in psoriatic lesions might be concerned with the imbalance of PTEN, and more researches concentrated upon the expressions of PTEN protein and gene in psoriatic lesions [77]. Lately, it has been illuminated that compared with that in normal skin, mRNA

expression and protein levels of PTEN in psoriatic skin were lessened [51, 66]. These results indicated decreased of PTEN and corresponding overactivation of AKT play a role in psoriatic lesions. Loss of PTEN expression in basal cells could demonstrate the excessive hyperplasia and anti-apoptosis in psoriatic epidermis; in normal skin, the PI3K/AKT pathway is vital for cell proliferation in the basal epidermis and for terminal differentiation in the upper layers [87]. Consequently, PTEN may be participate in the proliferation of psoriatic keratinocyte. It is necessary to in-depth study on the signaling mechanisms downstream of PTEN activity to elucidate the exact role of PTEN in the hyperplasia and abnormal apoptosis of psoriatic keratinocyte. Further work on the interaction between PTEN and psoriasis will undoubtedly contribute to the comprehension of the pathogenesis of psoriasis, and provide the basis to find therapeutic targets for psoriasis.

The downstream signaling molecule mTOR mediated by PI3K/AKT in psoriasis

mTOR is the target of a molecule named rapamycin or sirolimus, which is a macrolide produced by Streptomyces Hygroscopius bacteria and that first gained attention because of its broad anti-proliferative properties [63]. The mTOR complex is a central hub of the PI3K/AKT/mTOR signal transduction pathway and the serine/threonine protein kinase TOR forms two structurally and functionally distinct complexes, termed TOR Complex 1 (TORC1) and TORC2 [3]. mTORC1 positively regulates anabolic processes such as protein synthesis, and mTORC2 signaling regulates many cellular processes such as ribosome biogenesis [104]. PI3K/AKT and mTOR signaling which regulate cell proliferation, survival, apoptosis, and frequently deregulated in diverse cancers, being fundamental components of immune cell-signaling networks, play a crucial role in skin homeostasis and morphogenesis, especially in the regulation of keratinocyte differentiation and epidermal stratification [31, 33, 94], and it has recently emerged as a clinical relevant target for inflammatory diseases including psoriasis [26, 54]. PI3K activation triggers the phosphorylation of phosphatidylinositol on the 3-hydroxyl group to PI (3, 4, 5) P3, then activates AKT kinase and which in turn activates mTOR, thus promoting keratinocyte hyperproliferation and inhibiting differentiation, as observed in psoriasis [98]. It has been reported that the mechanisms for the role of the mTOR pathway in psoriasis may be the dysregulation cytokines and growth factors in this inflammatory disease activates the mTOR signaling system, and the activated mTOR kinase system may be a key regulator of the inflammatory and proliferative cascades of psoriatic disease process [30, 103]. It have already reported that relevant growth factors and relevant cytokines (IL-17 and IL-22) activate mTOR signaling proteins in effectors cells (keratinocytes and synovial cells (FLS)) for psoriasis [30, 67, 71, 84, 99]. These researches suggest a role for mTOR signaling in the epidermal changes leading to the psoriatic phenotype.

The previous studies shown that the PI3K downstream effector, mTOR kinase itself and its downstream targets are hyperactivated in psoriatic lesions [5, 13, 108]. In a research by direct immunofluorescence studies have observed that mTOR is activated throughout the whole epidermis in lesional psoriatic skin [13], and the recent investigations suggest that is specifically mTORC1 to be involved in psoriasis pathogenesis [4, 6, 82]. Recently, it has been reported that there is increase in mTOR expression and its phosphorylation in lesional psoriatic skin compared to that of non-lesional psoriatic skin [98]. In addition, the PI3K/AKT/mTOR pathway is thought to play a role in Th1–Th2–Th17 imbalance in the pathogenesis of psoriasis [54]. Recent data have also shown that the mTOR signaling proteins are upregulated in psoriatic skin and proliferation of keratinocytes and synovial cells (FLS) of psoriatic arthritis are dependent on the PI3K–AKT–mTOR kinase system [98]. Taken together, the mTOR pathway is hyperactivated in lesional psoriatic skin, which probably contributes to the disease by interfering with maturation of keratinocyte [14]. And because the PI3K/AKT/mTOR pathway is hyperactivated both in human and murine psoriasis, it is an attractive antipsoriatic drug target [24, 38].

Inhibition of PI3K/AKT signaling pathway for psoriasis treatment

In view of the vital function of PI3K signaling pathway in regulating keratinocyte proliferation, development of therapeutic drugs using PI3K and AKT inhibitors is of great significance for the treatment of psoriasis [39]. As we know psoriasis is an immune-mediated disease with process of chronic recurrence, and the especially serious forms that are refractory to traditional therapies are often difficult to manage [47]. At present, palliative care is the main treatment option for psoriasis, including corticosteroids, UV-light therapy and immunomodulatory therapy. The PI3K/AKT pathway is aberrantly stimulated in hyperproliferation keratinocyte and has emerged as a therapeutic target. Recently, the results of researches in psoriatic arthritis using PI3K signaling inhibitors enlightenments that small molecule inhibitor strategies directed at PI3K signaling may be a useful treatment for immune-mediated diseases including psoriasis [76, 77]. Hence, it is urgent to exploit novel PI3K/AKT-based targets and mechanism-based strategies to improve treatment effectiveness.

As we know the PI3K/AKT inhibitors were primitively investigated as antifungal agents and were used for its immunosuppressant properties and also showed anti-tumourigenic potential [15]. Initial evidence from clinical data suggests that PI3K/AKT inhibitors may improve therapeutic benefit for psoriasis [40], and calcitriol, a well-known anti-psoriatic drug, regulates the proliferation/survival of keratinocytes by inhibiting the phosphorylation of mTOR and this could be a possible mechanism for its therapeutic efficacy [30]. Rapamycin and its analogs are the best-known allosteric inhibitors of the PI3K/AKT/mTOR pathway and are being used for treating several types of cancers [88, 109]. The previous evidences placed the rapamycin has long been known for its immune suppressive properties, but it has shown limited therapeutic success when given systemically to patients with psoriasis [108]. Recently, studies have pointed out that IL-22-induced proliferation of normal human epidermal keratinocytes and FLS was inhibited by the dual kinase, PI3K/mTOR inhibitor, NVP-BEZ235 and specific mTOR inhibitor, rapamycin [84]. Recent data also have indicated that topical rapamycin can ameliorate the imiquimod (IMQ)-induced psoriatic phenotype in mice through blocking mTOR signaling [15]. Additionally, research have point out that delphinidin, a dietary antioxidant found abundantly in pigmented fruits and vegetables for the management of psoriasis, can inhibit PI3K/AKT and mTOR involved in psoriasis pathogenesis and alleviates IMQ-induced murine psoriasis-like disease [23, 25]. Some studies found that matrine, a low-toxic alkaloid extracted from dry roots of Sophora flavescens Aiton, may inhibit cell proliferation through FOXO and PI3K/AKT signaling pathways [65] and silibinin exerts its effects through down-regulation of PI3K/AKT pathways [55]. Moreover, previous study reported that Britannin, a sesquiterpene lactone and a class of secondary metabolites, which is able to induce mitochondrial apoptotic pathway through ROS production and modulation of the AKT-FOXO1 signaling axis [85]. The research indicated that activation of FOXO transcription factors through inhibition of PI3K/AKT pathway may have physiological significance in management of psoriasis [106]. Taken together, inhibition of PI3K/AKT signaling pathway could be developed to be a novel way to treat psoriasis.

Conclusions and future directions

Previous studies have shown that PI3K/AKT/FOXO signaling pathway plays a central role in regulating various kinds of cellular functions such as cell proliferation. The intensive interests are on the study of PI3K/AKT and FOXO in tumorigenesis. Emerging new evidence has indicated that PI3K/AKT/FOXO signaling involved in chronic inflammatory skin condition of psoriasis [19]. Psoriasis is characterized by keratinocyte hyperproliferation and associated with significant decline in quality of life and an increased risk of arthritis and cardiovascular disease. We surveys recent developments in understanding the molecular mechanisms of PI3K/AKT/FOXO signaling and its roles in keratinocyte proliferation in psoriasis. Our understanding of this complex network and tight regulation is probably at its beginning and will require much more work to fully unfold this pathway. Now targeting PI3K/AKT pathway, such as FOXO, mTOR, has been shown to prevent keratinocyte hyperproliferation [96, 98, 101]. Indeed, some inhibitors, targeting PI3K/AKT pathway, prevented psoriasis development in IMQ-induced mouse models [15, 23]. Given the importance of the PI3K/AKT/FOXO pathway in the psoriatic phenotype, further optimization of the clinical use of these inhibitors in the coming years is warranted and should lead to better patient outcomes. We anticipate that the therapeutic methods targeting PI3K/AKT/FOXO pathway would represent the promising psoriasis therapy in the near future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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