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REVIEW ARTICLE

Role and function of plakophilin 3 in cancer progression and skin disease

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Abstract

Plakophilin 3 (PKP3), a component of desmosome, is aberrantly expressed in many kinds of human diseases, especially in cancers. Through direct interaction, PKP3 binds with a series of desmosomal proteins, such as desmoglein, desmocollin, plakoglobin, and desmoplakin, to initiate desmosome aggregation, then promotes its stability. As PKP3 is mostly expressed in the skin, loss of PKP3 promotes the development of several skin diseases, such as paraneoplastic pemphigus, pemphigus vulgaris, and hypertrophic scar. Moreover, accumulated clinical data indicate that PKP3 dysregulates in diverse cancers, including breast, ovarian, colon, and lung cancers. Numerous lines of evidence have shown that PKP3 plays important roles in multiple cellular processes during cancer progression, including metastasis, invasion, tumor formation, autophagy, and proliferation. This review examines the diverse functions of PKP3 in regulating tumor formation and development in various types of cancers and summarizes its detailed mechanisms in the occurrence of skin diseases.

KEYWORDS
cancer, desmosome, plakophilin 3, skin disease

1 | INTRODUCTION

Plakophilins are members of the armadillo protein family, comprising PKP1, PKP2, and PKP3, and function as the structural components of desmosomes, which play pivotal roles in mediating cell–cell adhesion and communication. All PKPs are crucial for the formation of desmosomes by directly interacting with or indirectly regulating the expression of other desmosomal proteins.[1] The location of PKP3 in different cellular substructures also affects various cellular processes, such as signal transduction, tumorigenesis, and tumor progression, which are attributed to their multiple cellular localizations.[2]

The *PKP3* gene is located at the chromosomal region 11p15.5 and expressed in various mammals such as cow, dog, mouse, and rat, and these species have over 80% similarity within the orthologs of the human *PKP3* gene (Figure 1). The PKP3 mRNA comprises 13 exons in the size of 2817 base pairs (Figure 1). Knockout of PKP3

Abbreviations: DNP, *N*,*N*′-dinitrosopiperazine; DSC, desmocollin; DSG, desmoglein; DSP, desmoplakin; ERK, extracellular signal-regulated kinase; HR, homology region; JNK, C-Jun N-terminal kinase; K8, keratin 8; miR, microRNA; mTOR, mammalian target of rapamycin; NSCLC, non-small-cell lung cancer; PG, plakoglobin; PKP, plakophilin; PNP, paraneoplastic pemphigus; PRL3, phosphatase of regenerating liver 3; PV, pemphigus vulgaris.

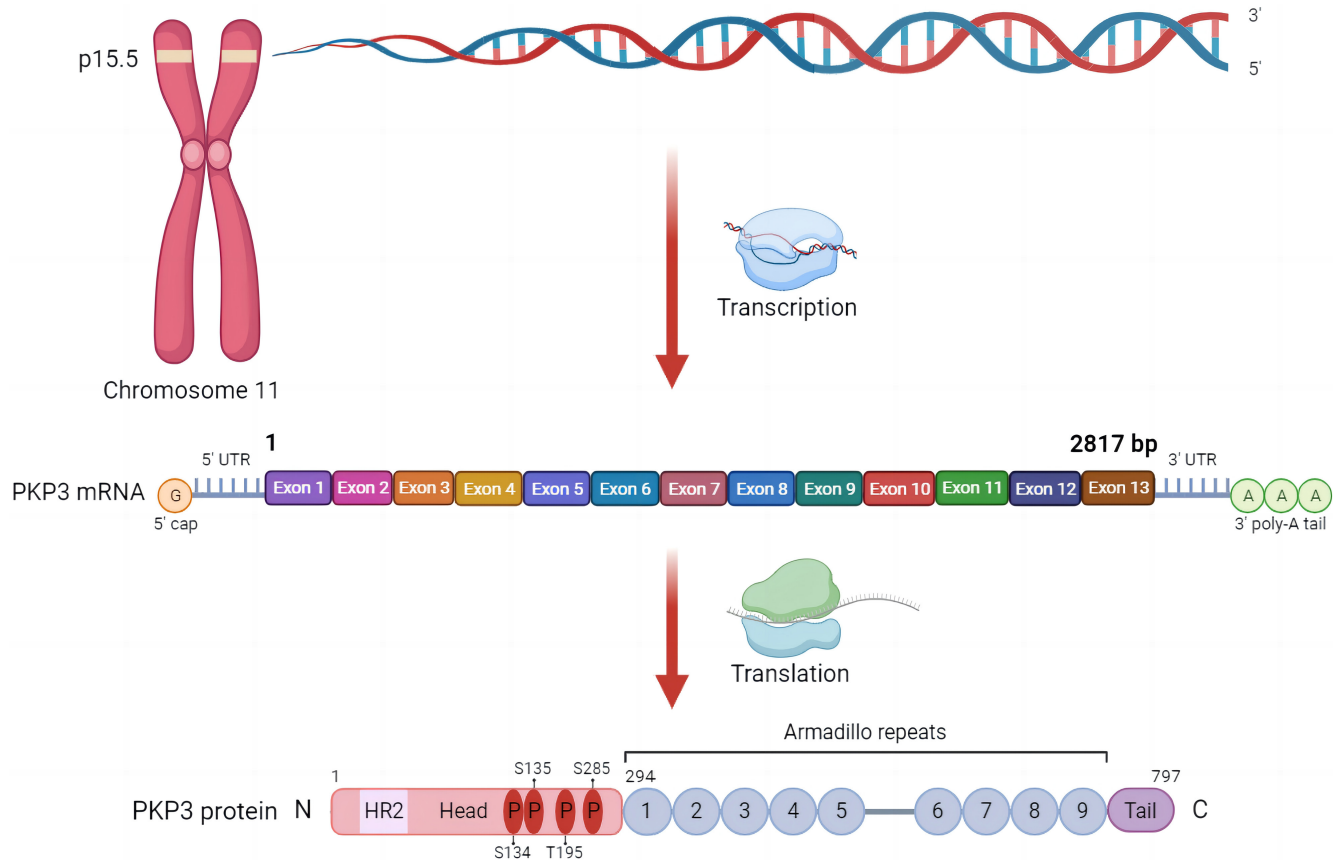

FIGURE 1 Gene and protein structures of plakophilin 3 (PKP3). The *PKP3* gene is located at the p15.5 locus of chromosome 11 and PKP3 mRNA comprises 13 exons of 2817 bp. The protein structure of PKP3 (797 amino acids in size) is characterized by a head domain at the N-terminal and nine armadillo repeats at C-terminal, with a flexible insert between armadillo repeats 5 and 6. Within the head domain, there is homology region 2 (HR2), which is conserved in PKPs. Four phosphorylation sites are located at the head domain, Ser-134, Ser-135, Ser-285, and Tyr-195.

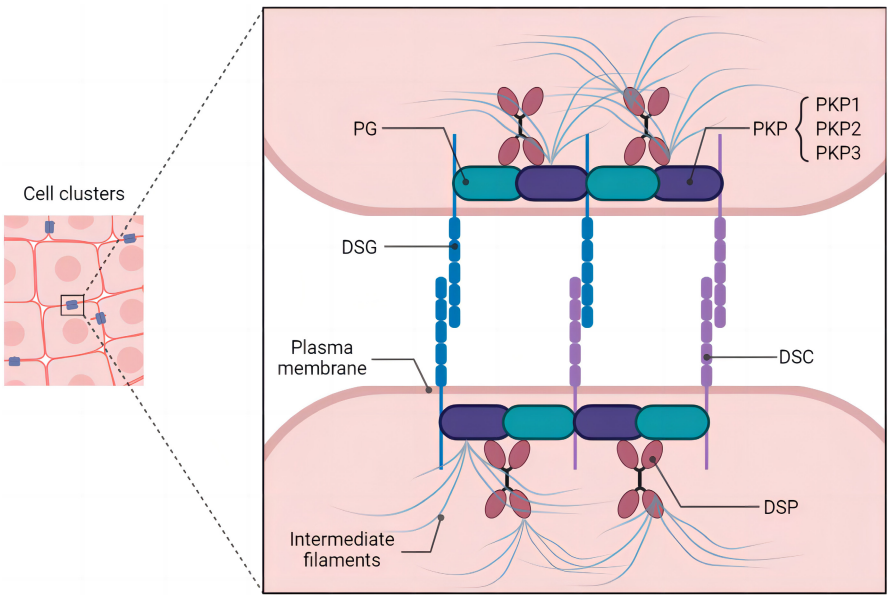

FIGURE 2 Role of plakophilin 3 (PKP3) in desmosome assembly. PKP3 is expressed in the cell plasma membrane, which accounts for the assembly of desmosome between cells, forming the cell clusters. PKP3 directly interacts with plakoglobin (PG), desmocollin (DSC), desmoglein (DSG), and intermediate filaments to form a stable complex, which mediates the formation of desmosome. The intracellular fraction of DSG and DSC bind with PKP3 while the extracellular parts anchor with each other to strengthen the stability of desmosome. As cytoplasmic plaque proteins of desmosome, PG and DSP combine with PKP3 to form the inner plaque of desmosome.

leads to the morphological abnormality of specific hair follicles and facilitates inflammatory responses in the skin, accompanied by severe skin diseases in PKP3-deficent mice models.[3] The protein structure of PKP3 consists of a head domain and nine armadillo repeats, with a total of 797 amino acid residues (~87 kDa). A flexible insert between armadillo repeats 5 and 6 forms the special bending structure for binding of other proteins (Figure 1). Both the head domain and armadillo repeats of PKP3 are crucial for the interaction

with other desmosomal proteins. There is only a small conserved sequence stretch, designated HR2, in the head domain of PKP3 (Figure 1). Moreover, three phosphorylation sites of PKP3, including Ser-134, Ser-135, and Ser-285, located at the head domain, are responsible for the accumulation of PKP3 at cell contacts, while the Tyr-195 phosphorylation site in the head domain contributes to the release of PKP3 from desmosomes to the cytoplasm (Figure 1).[4–6] In addition, the exogenous PKP3-head and PKP3-armadillo fragments show different cellular localization; the PKP3-head fragment mainly aggregates in the cytoplasm, whereas the PKP3-armadillo fragment shows a high accumulation in the cell nucleus, indicating additional regulatory roles of PKP3 in cytoplasmic and nuclear processes.[7]

Plakophilin 3 is a desmosomal plaque protein highly expressed in epithelial cells and is essential for the maintenance of desmosomal integrity and cell–cell adhesion (Figure 2). Desmosomes are intercellular junctions that maintain the structural integrity of tissues through anchoring intermediate filaments to the plasma membrane.[8] Based on the origin and function of desmosome components, they consist of three main groups: plakins (e.g. DSP), cadherins (e.g. DSG and DSC), and armadillo proteins (e.g. PG and PKPs).[8] Plakophilin 3 initiates the assembly of desmosomes and promotes their stabilization through direct interactions with transmembrane desmosomal adhesion proteins including DSC and DSG, as well as by anchoring cytoplasmic plaque proteins, including DSP and PG (Figure 2).

Expression of PKP3 is dysregulated during cancer progression. To date, a large body of evidence suggests that PKP3 plays dual roles as an oncogene or tumor suppressor during tumorigenesis and progression. For instance, PKP3 deficiency promotes tumor invasion and metastasis, thereby accelerating tumor formation and progression in colon, breast, and bladder cancers, whereas overexpression of PKP3 promotes tumor cell proliferation in prostate and ovarian cancer.[9–13] Additionally, aberrant expression of PKP3 can lead to a variety of skin conditions such as dermatitis, pemphigus vulgaris, and hypertrophic scar.[3,14,15] Therefore, the elucidation of effective PKP3-targeted therapies seems to be a promising strategy for the treatment of diseases based on the various roles of PKP3 in tumor progression and a variety of skin diseases.

2 | PLAKOPHILIN 3 PLAYS IMPORTANT ROLE IN CANCER PROGRESSION

Plakophilin 3 is aberrantly expressed in a variety of cancers including colon, breast, prostate, ovarian, lung, and bladder cancers, in which it plays a crucial role in the clinical diagnosis and prognosis of cancers (Figure 3).[9] Moreover, PKP3 plays an important part in a variety of physiological processes such as metastasis, invasion, tumor formation, autophagy, and proliferation during cancer progression (Figure 4). Clinicopathologic evidence has shown that PKP3 is overexpressed in most clinical lung cancer samples and high PKP3 expression level correlates with short survival periods and poor disease stage, as well as node status, of patients with lung cancer.[16] Similarly, the protein expression of PKP3 is increased in breast cancer and positively correlates with node positivity and grade, which contributes to the aggressive features of breast cancer.[17] Patients with ovarian cancer with high expression levels of PKP3 show more significant lymph node metastasis and advanced disease stage, as well as shorter overall survival than patients with low expression levels of PKP3.[18] Inversely, PKP3 expression is significantly decreased in gastric cancer, and PKP3 deficiency is correlated with increased node number and advanced tumor stage, which indicate poor prognosis.[19] Additionally, upregulation of PKP3 mRNA in blood of patients with gastrointestinal cancer is related to advanced tumor stage and serious lymph node metastasis, and can serve as a biomarker for detecting circulating tumor cells in gastrointestinal cancer.[20,21]

Plakophilin 3 plays important roles in initiating desmosome assembly and maintaining cell–cell adhesion in epithelial cells, thus, the deficiency of the desmosome PKP3 leads to loss of cell polarity and adhesion, which in turn enhances its invasive and metastatic capacity. Invasion and metastasis are two major hallmarks of cancer.[22]

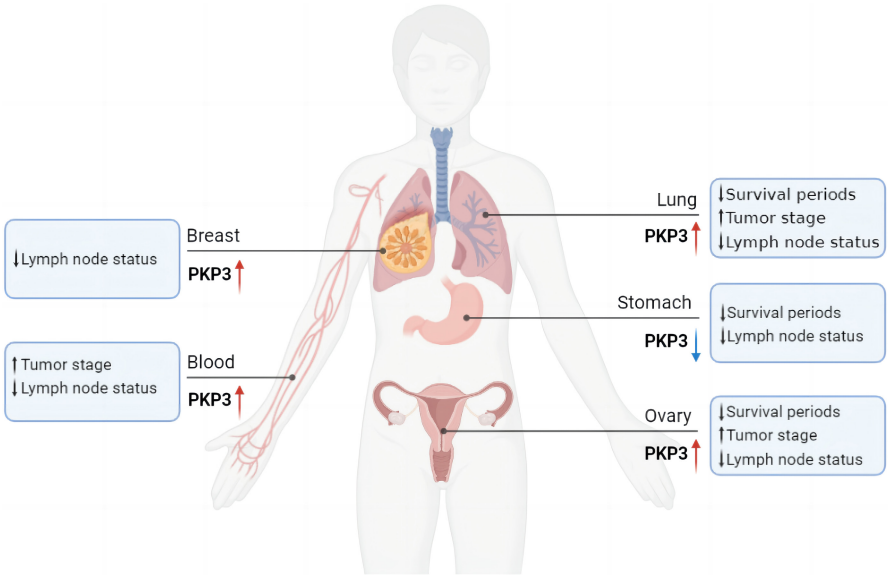

FIGURE 3 Clinicopathologic features of cancer patients with aberrant plakophilin 3 (PKP3) expression. The overexpression of PKP3 in diverse cancer patients, including breast, blood, gastrointestinal, lung, and ovarian cancer, shows short survival periods, poor lymph node status, and advanced tumor stage, whereas gastric cancer patients with low PKP3 expression show the same clinicopathologic features.

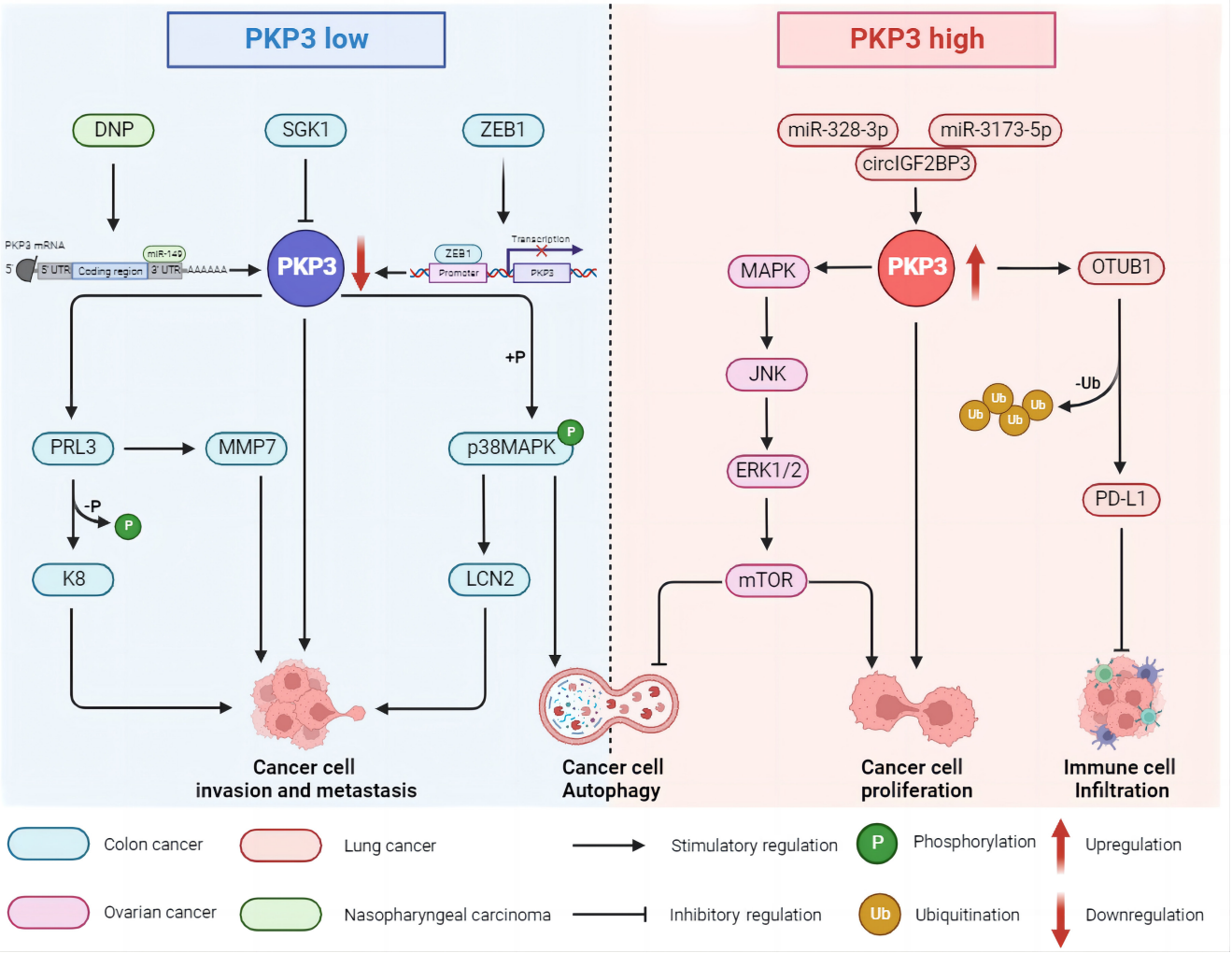

FIGURE 4 Aberrant expression of plakophilin 3 (PKP3) is involved in regulating diverse signaling pathways associated in cancer progression. PKP3 is expressed at low levels in colon cancer and nasopharyngeal carcinoma both at mRNA and protein levels, which induces cancer cell invasion, metastasis, and autophagy. Inversely, high expression of PKP3 stimulates cancer cell proliferation and inhibits cancer cell autophagy by activating the MAPK-JNK-ERK1/2-mTOR axis in ovarian cancer. Overexpression of PKP3, resulting from the competitive binding of microRNA (miR)-328-3p and miR-3173-5p with circIGF2BP3, promotes programmed cell death 1 ligand 1 (PD-L1) expression, which inhibits immune cell infiltration in lung cancer. DNP, *N*,*N*′-dinitrosopiperazine; K8, keratin 8; LCN2, lipocalin 2; MMP7, matrilysin; OTUB1, otubain-1; PRL3, phosphatase of regenerating liver 3; SGK1, serum/glucocorticoid-regulated kinase 1; ZEB1, zinc finger E-box binding homeobox 1.

The invasion–metastasis cascade, characterized by local invasion and distant metastasis, is a crucial stage during tumor progression, in which primary malignant tumor cells infiltrate into the surrounding stroma, followed by interaction with platelets, lymphocytes, and other blood components in blood circulation and, finally, the development of a secondary tumor in other distant sites and organs.[23] Emerging evidence has indicated that PKP3 deficiency has a significant impact on the invasion and metastasis of cancer progression. Previous studies have shown that PKP3 downregulation leads to loosening of intercellular adhesion along with increased cell migration, ultimately stimulating tumor formation and increasing the ability of colon cancer to metastasize to the lung.[11] Furthermore, zinc finger E-box binding homeobox 1 (ZEB1), a classical transcription factor that promotes tumor invasion and metastasis, inhibits PKP3 transcription during colon cancer cell invasion by directly binding to the PKP3 promoter, thereby inhibiting PKP3 expression at both the mRNA and protein levels, which further suggests that deletion of PKP3 might promote the oncogenic process of invasive human cancer cells.[9] Similar findings show that downregulation of PKP3 promotes the invasion of 5637 and J82 bladder cancer cells.[10] With in-depth studies, more detailed molecular mechanisms linking PKP3 to tumor cell invasion and metastasis have been identified in different cancers. Loss of PKP3 promotes the expression of PRL3, followed by the increased dephosphorylation of K8 and upregulation of pan-K8, which leads to the increased metastasis of HCT116 colon cancer cells and tumor progression of colon cancer.[24] Furthermore, PKP3 downregulation induces matrilysin (MMP7) expression by promoting PRL3 expression and thus promotes the invasion of

HCT116 colon cancer cells and tumor formation of colon cancer.[25] Additionally, PKP3 directly interacts with p38MAPK to block its translocation to the nucleus, while PKP3 loss promotes its phosphorylated activation and nuclear localization, which finally leads to metastasis and growth of HCT116 colon cancer cells through increasing expression of lipocalin 2 (LCN2).[26,27] Loss of PKP3 induces autophagy and reactive oxygen species clearance by activating p38MAPK, then increases radioresistance and promotes survival of HCT116 colon cancer cells.[28] In addition, several proteins have been identified to regulate PKP3 expression during tumor metastasis in a variety of cancers. *N*,*N*′-dinitrosopiperazine (DNP), as a carcinogenic factor, increases miR-149 expression and inhibits the transcriptional activity of the *PKP3* gene by promoting the binding of miR-149 to the 3′-UTRs of *PKP3* to induce invasion and metastasis of 6-10B nasopharyngeal carcinoma cells.[29] Conversely, serum/glucocorticoid-regulated kinase 1 (SGK1), a member of the AGK kinase family, stimulates PKP3 expression and induces differentiation of HT29 and LS174T cells, accompanied by the inhibition of metastasis of HT29 and LS174T colon cancer cells.[30]

Together with invasion and metastasis, emerging evidence has also indicated that PKP3 plays a pivotal role in cell autophagy, growth, and proliferation. Plakophilin 3 promotes cellular proliferation and inhibits autophagy of SKOV3 and A2780 ovarian cancer cells by activating the MAPK-JNK-ERK1/2-mTOR axis, which accelerates the progression of ovarian tumor.[12] Analogously, upregulation of PKP3 expression promotes the proliferation of prostate cancer and NSCLC.[13,16] Plakophilin 3 is also reported to mediate the infiltration of immune cells in the tumor matrix, which is deemed as the pivotal factor in regulating progression and metastasis of cancers.[31] Competitive binding of miR-328-3p and miR-3173-5p to circIGF2BP3 results in the upregulation of PKP3 expression, which promotes deubiquitinating enzyme otubain-1 (OTUB1) expression by increasing its mRNA stability, and then prevents the proteasomal degradation of programmed cell death 1 ligand 1 (PD-L1) by inducing its deubiquitination, and ultimately inhibits the activation and infiltration of $CD8^+$ T cells in the tumor region and thus facilitates tumor immune evasion in NSCLC.[32]

3 | ROLE AND FUNCTION OF PKP3 IN SKIN DISEASES

Considering that PKP3 is abundantly expressed in the skin, PKP3 may be involved in the regulation of certain skin diseases. Accumulated evidence has shown that aberrant PKP3 expression occurs in the development of a variety of skin diseases, such as PNP, PV, and hypertrophic scar (Figure 5). It also reported that PKP3 serves as a contributor for the morphogenesis of hair follicles, while PKP3 deficiency blocks hair formation and leads to an increased sensitivity to dermatitis, rendering patients prone to cutaneous inflammation.[3] Loss of hematopoietic PKP3 promotes the development of irritant contact dermatitis and dextran sulfate sodium-induced colitis, simultaneously with increased sensitivity to endotoxemia.[33] Likewise, the downregulation of PKP3 in hypertrophic scar might be involved in intraepidermal blister formation.[15] Additionally, PKP3 promotes the desmosomal adhesion of keratinocytes and induces cell–cell detachment and acantholysis in PV.[14] The Src-mediated phosphorylation of PKP3 resulting from binding of PV autoimmune globulin enables PKP3 to detach from DSG3 and translocate to the cytoplasm, suggesting the crucial role of PKP3 in PV acantholysis.[34] Plakophilin 3 is reported to be associated with PNP, a malignancy-associated autoimmune disease, in which the Abs against PKP3 are consistently present in PNP sera through activated PKP3 autoreactivity, implying a novel autoantigen reacting against PNP sera.[35]

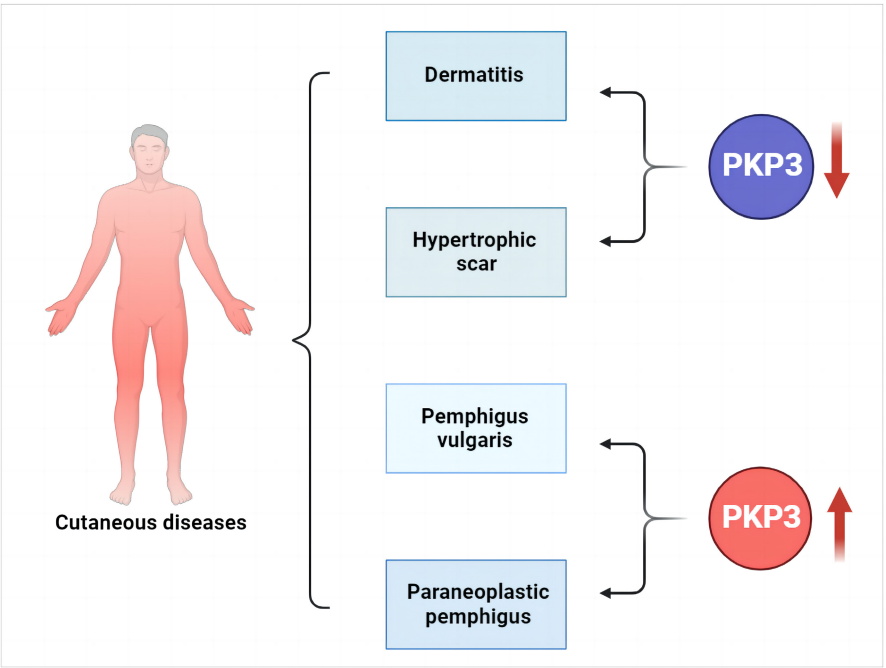

FIGURE 5 Aberrant plakophilin 3 (PKP3) expression-derived cutaneous diseases. Four cutaneous diseases have been reported to be promoted by PKP3 dysregulation in human, including dermatitis, hypertrophic scar, pemphigus vulgaris, and paraneoplastic pemphigus. The low expression of PKP3 promotes the development of cutaneous diseases, such as dermatitis and hypertrophic scar, and the overexpression of PKP3 promotes the development of pemphigus vulgaris and paraneoplastic pemphigus.

4 | CONCLUSION AND PERSPECTIVES

In general, PKP3 plays a crucial role in the tumor progression, such as metastasis, invasion, proliferation, and autophagy. Plakophilin 3 shows potent potential in the clinical diagnosis and prognostic evaluation of diverse cancers, and can be identified as a biomarker for tumor progression of cancer patients. Moreover, given the high level of PKP3 in the skin, PKP3 also participates in the development of several skin diseases. Taken together, PKP3 will be a promising therapeutic target for antitumor treatment and other human diseases. Therefore, the underlying mechanisms of PKP3 in tumor progression deserve deeper investigation, rendering the targeting of PKP3 as a more accurate and effective approach in cancer therapy.

AUTHOR CONTRIBUTIONS

Yefei Zhang: Writing – original draft. **Jiahui Chen:** Writing – original draft. **Jia Tian:** Writing – original draft. **Yehui Zhou:** Writing – review and editing. **Yan Liu:** Conceptualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol by an institutional review board: N/A.

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

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REFERENCES

1. Delva E, Tucker DK, Kowalczyk AP. The desmosome. *Cold Spring Harb Perspect Biol*. 2009;1:a002543.
2. Wolf A, Hatzfeld M. A role of plakophilins in the regulation of translation. *Cell Cycle (Georgetown, Tex)*. 2010;9:2973-2978.
3. Sklyarova T, Bonné S, D'Hooge P, et al. Plakophilin-3-deficient mice develop hair coat abnormalities and are prone to cutaneous inflammation. *J Invest Dermatol*. 2008;128:1375-1385.
4. Rietscher K, Keil R, Jordan A, Hatzfeld M. 14-3-3 proteins regulate desmosomal adhesion via plakophilins. *J Cell Sci*. 2018;131:jcs212191.
5. Müller L, Rietscher K, Keil R, Neuholz M, Hatzfeld M. Plakophilin 3 phosphorylation by ribosomal S6 kinases supports desmosome assembly. *J Cell Sci*. 2020;133:jcs238295.
6. Neuber S, Jäger S, Meyer M, et al. c-Src mediated tyrosine phosphorylation of plakophilin 3 as a new mechanism to control desmosome composition in cells exposed to oxidative stress. *Cell Tissue Res*. 2015;359:799-816.
7. Bonné S, Gilbert B, Hatzfeld M, Chen X, Green KJ, van Roy F. Defining desmosomal plakophilin-3 interactions. *J Cell Biol*. 2003;161:403-416.
8. Nekrasova O, Green KJ. Desmosome assembly and dynamics. *Trends Cell Biol*. 2013;23:537-546.
9. Aigner K, Descovich L, Mikula M, et al. The transcription factor ZEB1 (deltaEF1) represses plakophilin 3 during human cancer progression. *FEBS Lett*. 2007;581:1617-1624.
10. Takahashi H, Nakatsuji H, Takahashi M, et al. Up-regulation of plakophilin-2 and Down-regulation of plakophilin-3 are correlated with invasiveness in bladder cancer. *Urology*. 2012;79(240):e241-e248.
11. Kundu ST, Gosavi P, Khapare N, et al. Plakophilin3 downregulation leads to a decrease in cell adhesion and promotes metastasis. *Int J Cancer*. 2008;123:2303-2314.
12. Lim V, Zhu H, Diao S, Hu L, Hu J. PKP3 interactions with MAPK-JNK-ERK1/2-mTOR pathway regulates autophagy and invasion in ovarian cancer. *Biochem Biophys Res Commun*. 2019;508:646-653.
13. Breuninger S, Reidenbach S, Sauer CG, et al. Desmosomal plakophilins in the prostate and prostatic adenocarcinomas: implications for diagnosis and tumor progression. *Am J Pathol*. 2010;176:2509-2519.
14. Cirillo N, Prime SS. Desmosomal interactome in keratinocytes: a systems biology approach leading to an understanding of the pathogenesis of skin disease. *Cell Mol Life Sci*. 2009;66:3517-3533.
15. Tan J, He W, Luo G, Wu J. Involvement of impaired desmosome-related proteins in hypertrophic scar intraepidermal blister formation. *Burns*. 2015;41:1517-1523.
16. Furukawa C, Daigo Y, Ishikawa N, et al. Plakophilin 3 oncogene as prognostic marker and therapeutic target for lung cancer. *Cancer Res*. 2005;65:7102-7110.
17. Demirag GG, Sullu Y, Yucel I. Expression of plakophilins (PKP1, PKP2, and PKP3) in breast cancers. *Med Oncol*. 2012;29:1518-1522.
18. Qian H, Yuan D, Bao J, et al. Increased expression of plakophilin 3 is associated with poor prognosis in ovarian cancer. *Medicine*. 2019;98:e14608.
19. Demirag GG, Sullu Y, Gurgenyatagi D, Okumus NO, Yucel I. Expression of plakophilins (PKP1, PKP2, and PKP3) in gastric cancers. *Diagn Pathol*. 2011;6:1.
20. Valladares-Ayerbes M, Díaz-Prado S, Reboredo M, et al. Evaluation of plakophilin-3 mRNA as a biomarker for detection of circulating tumor cells in gastrointestinal cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1432-1440.
21. Valladares-Ayerbes M, Díaz-Prado S, Reboredo M, et al. Bioinformatics approach to mRNA markers discovery for detection of circulating tumor cells in patients with gastrointestinal cancer. *Cancer Detect Prev*. 2008;32:236-250.
22. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
23. Saha T, Solomon J, Samson AO, Gil-Henn H. Invasion and metastasis as a central hallmark of breast cancer. *J Clin Med*. 2021;10:10.
24. Khapare N, Kundu ST, Sehgal L, et al. Plakophilin3 loss leads to an increase in PRL3 levels promoting K8 dephosphorylation, which is required for transformation and metastasis. *PLoS One*. 2012;7:e38561.
25. Basu S, Thorat R, Dalal SN. MMP7 is required to mediate cell invasion and tumor formation upon Plakophilin3 loss. *PLoS One*. 2015;10:e0123979.
26. Basu S, Chaudhary N, Shah S, et al. Plakophilin3 loss leads to an increase in lipocalin2 expression, which is required for tumour formation. *Exp Cell Res*. 2018;369:251-265.

27. Raghavan R, Koyande N, Beher R, et al. Plakophilin3 loss leads to increased adenoma formation and rectal prolapse in APC(min) mice. *Biochem Biophys Res Commun*. 2022;586:14-19.
28. Chaudhary N, Joshi N, Doloi R, Shivashankar A, Thorat R, Dalal SN. Plakophilin3 loss leads to an increase in autophagy and radio-resistance. *Biochem Biophys Res Commun*. 2022;620:1-7.
29. Li Y, Ju K, Wang W, et al. Dinitrosopiperazine-decreased PKP3 through upregulating miR-149 participates in nasopharyngeal carcinoma metastasis. *Mol Carcinog*. 2018;57:1763-1779.
30. Lee LYW, Woolley C, Starkey T, et al. Serum- and glucocorticoid-induced kinase Sgk1 directly promotes the differentiation of colorectal cancer cells and restrains metastasis. *Clin Cancer Res*. 2019;25:629-640.
31. Ruan S, Shi J, Wang M, Zhu Z. Analysis of multiple human tumor cases reveals the carcinogenic effects of PKP3. *J Healthc Eng*. 2021;2021:9391104.
32. Liu Z, Wang T, She Y, et al. N(6)-methyladenosine-modified circIGF2BP3 inhibits CD8(+) T-cell responses to facilitate tumor immune evasion by promoting the deubiquitination of PD-L1 in non-small cell lung cancer. *Mol Cancer*. 2021;20:105.
33. Sklyarova T, van Hengel J, Van Wonterghem E, Libert C, van Roy F, Vandenbroucke RE. Hematopoietic plakophilin-3 regulates acute tissue-specific and systemic inflammation in mice. *Eur J Immunol*. 2015;45:2898-2910.
34. Cirillo N, AlShwaimi E, McCullough M, Prime SS. Pemphigus vulgaris autoimmune globulin induces Src-dependent tyrosine-phosphorylation of plakophilin 3 and its detachment from desmoglein 3. *Autoimmunity*. 2014;47:134-140.
35. Lambert J, Bracke S, van Roy F, Pas HH, Bonné S, de Schepper S. Serum plakophilin-3 autoreactivity in paraneoplastic pemphigus. *Br J Dermatol*. 2010;163:630-632.

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