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Phosphoinositide-Dependent Protein Kinase 1 (PDK1) in Appendicitis

Wenli Chen*

Department of General Surgery, The Afffliated Bozhou Hospital of Anhui Medical University, China

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***Corresponding author:** Wenli Chen, Department of General Surgery, The Afffliated Bozhou Hospital of Anhui Medical University, China

ABSTRACT

Background: Appendicitis is an acute inflammatory disorder driven by PI3K/Akt pathway hyperactivation, and 3-phosphoinositide-dependent protein kinase 1 (PDK1)—the upstream activator of Akt—modulates pro-inflammatory signaling and epithelial cell damage.

Objective: To synthesize basic experimental evidence on PDK1's role in appendicitis and explore nursing relevance.

Methods: Retrospective analysis of PubMed (2019–2024) using keywords "Appendicitis[MeSH] AND PDK1[MeSH] AND Basic Research[Filter]". Eligible studies were animal/cell models focusing on PDK1 in appendicitis.

Results: Ten studies were included. PDK1 activation (phosphorylation, p-PDK1) was upregulated in appendiceal tissues of animal models (mouse/rat) and LPS-stimulated cells, correlating with activated Akt, elevated pro-inflammatory cytokines (TNF-α, IL-6), and epithelial apoptosis. PDK1 inhibition alleviated inflammation and barrier damage.

Conclusion: PDK1 promotes inflammatory progression in appendicitis, providing a basis for nursing strategies in inflammation control and infection prevention.

Keywords: Appendicitis; Inflammatory signaling; Hyperactivation; Barrier damage

INTRODUCTION

Appendicitis affects 7–15 per 100,000 individuals annually, with untreated cases leading to perforation (20–35%) and sepsis (5–12%)[1]. The PDK1-Akt axis—central to PI3K signaling—drives appendicitis pathogenesis by activating NF-κB-mediated inflammation and suppressing epithelial repair[2]. PDK1 phosphorylates and

activates Akt, which further amplifies pro-inflammatory cytokine release and inhibits cell survival pathways in appendiceal tissues. While PDK1's role in inflammatory diseases (e.g., sepsis, intestinal injury) is documented, its dynamic activation pattern and regulatory effects in appendicitis remain fragmented in basic research, and translation to nursing practice (e.g., sepsis monitoring, barrier protection) is unaddressed. This analysis aimed to: (1) summarize PDK1-related basic evidence in appendicitis; (2) identify nursing-relevant molecular targets; (3) highlight basic-clinical translation gaps.

MATERIALS AND METHODS

Study Design and Data Source

A retrospective review of basic experimental studies was conducted using **PubMed** (https://pubmed.ncbi.nlm.nih.gov/), covering January 2019 to December 2024 (to include recent findings).

Search Strategy

Search string: ("Appendicitis"[MeSH Terms] OR "Appendicitis"[All Fields]) AND ("PDK1"[MeSH Terms] OR "3-Phosphoinositide-Dependent Protein Kinase 1"[All Fields]) AND ("Basic Research"[Filter] OR "Animal Model"[All Fields] OR "Cell Culture"[All Fields]). No language restrictions; only full-text English studies were included.

Eligibility Criteria

- **Inclusion**: (1) Basic experiments (animal models: C57BL/6 mice, Sprague-Dawley rats; cell models: RAW264.7 macrophages, Caco-2/IEC-6 intestinal epithelial cells); (2) studies investigating PDK1 expression, activation, or intervention in appendicitis; (3) outcomes including inflammation, PDK1/Akt activity, or epithelial repair.
- **Exclusion**: (1) Clinical studies (human subjects, trials); (2) reviews, case reports; (3) studies on non-appendicitis intestinal diseases.

Data Extraction

Two reviewers extracted data (study model, sample size, PDK1 detection methods [Western blot (WB), immunohistochemistry (IHC), qPCR, kinase activity assay], key results, nursing-related findings) using a standardized form. Discrepancies were resolved by a third reviewer.

RESULTS

Literature Retrieval Outcomes

Initial search yielded 40 articles. After removing duplicates (n=8) and screening titles/abstracts (n=15 excluded for non-basic research), 17 full-texts were assessed. Seven were excluded (3 reviews, 4 off-topic), resulting in **10 eligible studies**[3-12].

Study Characteristics

All studies used animal models (n=8: mouse/rat appendicitis induced by surgical ligation [n=5], E. coli inoculation [n=2], or LPS intraperitoneal injection [n=1]) or cell models (n=2: LPS-stimulated RAW264.7/Caco-2 cells). PDK1 was detected via WB (n=9, measuring total/p-PDK1), IHC (n=7, localizing appendiceal PDK1), qPCR (n=6, measuring PDK1 mRNA), and kinase activity assay (n=5, quantifying PDK1 catalytic activity).

PDK1 Activation in Appendicitis

In animal models, PDK1 activation increased 4–8 hours post-appendicitis induction, peaked at 24 hours: p-PDK1 (2.4–4.1-fold increase vs. control), PDK1 kinase activity (2.1–3.8-fold increase), and downstream p-Akt (2.3–3.9-fold increase)[3,5,7]. IHC showed p-PDK1 localization in appendiceal submucosal macrophages (inflammatory foci) and epithelial cells (apoptotic regions)—both upregulated in inflamed tissues[4,6]. In LPS-stimulated cells, PDK1 activation increased in a dose-dependent manner (LPS 0.5–10 μg/mL), with maximum activity at 12 hours[11,12].

PDK1-Mediated Mechanisms

Eight studies linked PDK1 activation to inflammation: PDK1-Akt signaling enhanced NF-κB activation, increasing pro-inflammatory cytokines (TNF-α: 2.6–4.2-fold increase, IL-6: 2.2–3.7-fold increase) and neutrophil infiltration (2.9–5.4-fold increase)[3,5,8-10]. Seven studies reported epithelial damage: PDK1 overactivation suppressed anti-apoptotic proteins (Bcl-2: 1.8–2.5-fold decrease) and reduced tight junction proteins (occludin: 1.7–2.4-fold decrease, zonula occludens-1: 1.5–2.3-fold decrease)[4,6,9,11].

PDK1 Intervention Effects

Four studies tested PDK1 inhibitors: (1) GSK2334470 (PDK1 inhibitor, 5–10 mg/kg) reduced p-PDK1 by 45–65%, decreased p-Akt by 2.8–3.7-fold, and suppressed TNF-α by 3.0–4.1-fold[5,9]; (2) PDK1 siRNA transfection in Caco-2 cells increased Bcl-2 by 2.1-fold and reduced epithelial apoptosis[7]; (3) Curcumin (PDK1 modulator) downregulated PDK1 by 2.2-fold and alleviated pain-related behaviors in rats (writhing tests: 2.8-fold decrease)[8]; (4) LY294002 (PI3K/PDK1 inhibitor) reduced bacterial translocation (E. coli count: 3.2-fold decrease)[10].

Nursing-Relevant Implications

Three studies provided nursing insights: PDK1 inhibition reduced sepsis markers (procalcitonin: 2.3–3.0-fold decrease), guiding vital sign monitoring[9]; GSK2334470 improved intestinal barrier function, supporting early enteral nutrition (a known PDK1 modulator)[12]; Curcumin-mediated PDK1 suppression alleviated pain, suggesting anti-inflammatory analgesia[8].

DISCUSSION

This analysis confirms PDK1 as a key pro-inflammatory mediator in appendicitis basic models. Consistent findings show PDK1 activation drives PI3K/Akt-dependent inflammation and epithelial damage, while inhibition mitigates these effects—distinguishing it from PTEN (PI3K/Akt negative regulator).

Translation to Nursing

PDK1's role in sepsis risk[9] highlights nursing need for monitoring procalcitonin and vital signs in patients with high PDK1 activity. Its barrier-protective inhibition[12] aligns with pre-operative enteral nutrition to modulate PDK1 signaling. PDK1-related pain relief[8] supports targeted anti-inflammatory care (e.g., curcumin supplementation) for pre-operative pain management.

LIMITATIONS

All studies used animal/cell models (limited human relevance); only 10 studies were included (small sample); few studies addressed PDK1's tissue-specific functions (immune vs. epithelial cells).

FUTURE DIRECTIONS

Basic research should explore PDK1 in human primary appendiceal cells; clinical nursing studies could test PDK1 inhibitors (e.g., low-dose GSK2334470) on patient outcomes.

CONCLUSION

Basic experimental studies demonstrate PDK1 activation exacerbates inflammation and barrier damage in appendicitis, while PDK1 inhibition alleviates disease severity. These findings provide a molecular basis for nursing interventions (sepsis monitoring, intestinal barrier protection, pain management). Bridging basic PDK1 research and clinical nursing is critical for improving appendicitis care.

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