The Role of Poly(ADP-Ribose) Polymerase-1 in Cutaneous Wound Healing

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Critical Issue: Chronic nonhealing wounds of the lower extremities resulting in major amputations are a major health problem worldwide.

Significance: Diabetes and ischemia are two major etiologies of nonhealing wounds of the lower extremities. Hyperglycemia from diabetes and oxidative stress from ischemia activate polyadenosine diphosphate (ADP)-ribose polymerase-1 (PARP-1), which is a nuclear enzyme that is best known for its role in DNA repair. However, the exact function of PARP-1 in ischemic/diabetic wound healing has not been well studied.

Recent Advances: Poly-ADP-ribose (PAR) polymer has been detected in the wound bed and many of the PARylation-related reactions (oxidative stress response, expression of inflammatory cytokines and chemokines, cell proliferation, and migration) are important in the wound healing process. However, the role of PARP-1 in wound healing and the potential of targeting PARP-1 therapeutically in wounds are only recently being elucidated, with much still unknown. This review summarizes the recent advances in this field, highlighting some of the mechanisms through which PARP-1 may affect normal wound closure.

Future Directions: The review also presents a perspective on some of the downstream targets of PARP-1 that may be explored for their role in wound healing and discusses about the therapeutic potential of PARP inhibitors for wound healing.

Keywords: poly(ADP-ribose) polymerase, PARP, PARylation, wound healing

SCOPE AND SIGNIFICANCE

CHRONIC WOUNDS OF THE lower extremities present a substantial economic burden to the health care system and significantly reduce the quality of life. In the United States, chronic wounds affect ~5.7 million people (~2% of population) and incur an annual cost of \$25 billion.^{1,2} This problem is further exacerbated by diabetes mellitus because it causes a 10–15% increase in foot ulceration. Approximately 40% of diabetic foot ulcers also suffer from inadequate perfusion because of arterial occlusive disease.^{3,4} Although revascularization

remains the best approach to improve perfusion, as many as 30% of patients with arterial occlusive disease are not candidates for revascularization.⁵ Therefore, medical therapy to enhance angiogenesis is urgently needed to promote wound healing and prevent major amputations.

TRANSLATIONAL RELEVANCE

Arterial occlusive disease associated with diabetes mellitus increases the risk of limb loss. Surgical revascularization is still the most effective way for limb salvage but not everyone is a candidate. Therefore, new thera-

peutic targets for medical therapy of angiogenesis are urgently needed.

CLINICAL RELEVANCE

Polyadenosine diphosphate (ADP)-ribose polymerase-1 (PARP-1) is a nuclear enzyme that is hyperactivated in ischemic/diabetic wounds and regulates wound healing by many different mechanisms. A better understanding of the function of PARP-1 in wound healing could introduce PARP-1-targeted therapeutic strategies to the clinics and repurpose several Food and Drug Administration (FDA)-approved PARP-1 inhibitors for wound healing.

BACKGROUND: STRUCTURE, MECHANISM OF ACTION, AND REGULATION AND FUNCTIONS OF PARP-1

Structure of PARP-1

PARPs are a family of enzymes that catalyze the transfer of poly-ADP-ribose (PARs) to target proteins through a process called poly-ADP-ribosylation or PARylation.^{6,7} PARP-1 is the most well characterized among 18 identified members of the human PARP family. Almost 85–90% of the enzymatic activity is exerted by PARP-1 alone.⁸ PARP-1 is a 116 kDa nuclear chromatin-associated protein that is well known for its role in DNA repair and regulation of gene transcription.^{7,9,10} There are three major functional domains in its structure: (1) the DNA binding domain at the N-terminus that includes two zinc finger subdomains, a zinc binding subdomain and a nuclear localization signal, (2) the automodification domain in the middle, and (3) the catalytic domain at the C-terminus that contains a nucleic acid binding WGR motif, a helical PARP regulatory domain, a helical PARP regulatory domain (PRD) and the highly conserved PARP signature motif.

regulatory subdomain, and the highly conserved ADP-ribosyl transferase subdomain^{6,10,11} (Fig. 1).

Role of PARP-1 and mechanism of action

PARP-1 is best known for its role in DNA repair, maintenance of genomic integrity, and regulation of telomerase activity.¹² It is also well known for its catalytic function where NAD⁺ is used as the substrate to generate PAR before attaching these large branched polymers to suitable protein acceptors (a process called PARylation⁷) and alters their functions.

However, in addition to its role in post-translational modification of targeted proteins, PARP-1 also regulates gene transcription through several mechanisms. It can either stimulate or inhibit gene transcription by binding to the regulatory elements in the promotor regions of target genes^{13–16} through the double zinc finger DNA-binding domain. PARP-1 can enhance gene transcription by forming the RNA polymerase-II preinitiation complex¹⁷ or acting as a scaffold protein and recruit coregulator complexes to the promoters of target genes.^{9,10} In contrast, PARylation of transcription factors prevents binding to their specific promoter target sites^{18–23} and inhibits gene transcription.

At the epigenetic level, PARP-1 regulates gene expression by modulating chromatin structure.^{24–27} PARylation of the core histones results in electrostatic repulsion and reduces histone–DNA affinity,²⁸ decondenses the chromatin, creates a more relaxed structure, and allowed the DNA to be more accessible to the transcriptional machineries.^{24,28,29} In addition, PARP-1 regulates gene transcription by inhibiting the expression and activity of DNA methyltransferase Dnmt1,^{30,31} and altering chromatin structure through changing the global levels of H3K27me3.²⁷

Figure 1. Description and functions of the domains of PARP-1. PARP-1, polyadenosine diphosphate (ADP)-ribose polymerase-1

Regulation of PARP-1 induction

In addition to understanding the downstream targets of PARP-1, it is also important to mention the different factors that lead to PARP-1 activation that includes transcriptional regulation and post-translational modification of PARP-1. PARP-1 is regulated at the transcriptional level by DNA and protein binding partners such as nucleosomes, histones H₁ and H₃, the TLE (transducin-like enhancer of split) corepressor complex, a condensin I/XRCC1 repair complex, a CTCF insulator complex, and regulation by transcription factors Sp1 and NF1.^{10,11,32,33}

Post-translational modifications that regulate PARP-1 include (1) ADP-ribosylation (through an auto-modification reaction), (2) ubiquitylation and SUMOylation (by E3 ligases), (3) phosphorylation (by ERK1/2 and JNK1), and (4) acetylation (by p300 and CBP).^{10,11,34}

The earliest known regulator of PARP-1 enzymatic activity has been damaged DNA³⁵ and DNA hairpins, cruciform, and stably unpaired regions.³⁶ Other recently identified regulators of PARP-1 activity are as follows (included in Fig. 2):

- (1) Phosphorylation state of nicotinamide mononucleotide adenylyltransferase-1 (NMNAT-1), which is the central enzyme in NAD⁺ biosynthesis. PARP-1 uses this NAD⁺ to generate PAR and PAR-ylate target proteins to modify their functions.^{37–39}

- (2) PARG or poly(ADP-ribose) glycohydrolase that degrades PAR, which is synthesized by PARP-1 and thus reverses the enzymatic effects of PARP-1.^{40,41}
- (3) Oxidative-nitrosative stress induces PARP-1.⁴²
- (4) High-glucose activates PARP-1.^{43,44}
- (5) Physiologic cellular concentrations of ATP inhibit PARP-1.³³
- (6) Mg²⁺, Ca²⁺, and polyamines allosterically activate PARP-1.³³

DISCUSSION: ROLE OF PARP IN DIFFERENT STAGES OF WOUND HEALING

Wound healing is a well-orchestrated process that proceeds through a cascade of events involving hemostasis, inflammation, proliferation, and remodeling. Ischemia and diabetes affect the healing process in all these stages, but their effect is most prominent in the proliferative phase where angiogenesis and granulation tissue formation occur.^{2,45–50} Even though it is well known that both diabetes mellitus and ischemia induce PARP-1 hyperactivity,^{51–55} and many of the PARylation-related reactions (oxidative stress response, expression of inflammatory cytokines and chemokines, cell proliferation, and migration)^{14,56} are very important in the wound healing process, the role of PARP-1 in ischemic diabetes wound healing has not been well elucidated. This review summarizes the recent advances in

Figure 2. Regulation and function of PARP-1. PARG, poly(ADP-ribose) glycohydrolase; ROS, reactive oxygen species.

this field, highlighting some of the mechanisms through which PARP-1 regulates the healing process of cutaneous wounds (Fig. 3).

Inflammatory phase: targeting PARP to reduce wound inflammation

Although the initiation of wound healing starts with an inflammatory process, normal healing also requires the resolution of inflammation. Yet, in the chronic nonhealing wounds, the inflammation never resolves, leading to overproduction of reactive oxygen species (ROS), which can drive the hyperactivity of PARP-1.^{45,57} Subsequently, PARP-1 depletes cellular ATP supply due to excessive consumption of NAD⁺, resulting in cellular necrosis. PARP-1 contributes to the production of a variety of proinflammatory mediators.^{11,58,59} PARP-1 acts as a coactivator in NF- κ B-mediated transcription, leading to induction of proinflammatory mediators such as IL-6, pro-IL-1, ICAM-1, TNF- α , COX2, iNOS, CCL3, and CXCL2,^{58,60,61} and acts as a stimulator of the Akt pathway and can contribute to the activation of a variety of inflammation-related transcription factors, including AP1, AP2, TEF-1, SP1, Oct-1, YY1, and STAT1.⁶² Pharmacological inhibition of PARP-1 can attenuate the production of various proinflammatory mediators such as IL-6, pro-IL-1, ICAM-1, TNF- α , COX2, iNOS, CCL3, and CXCL2,⁶⁰ many of which are widely implicated in wound healing. Inhibition of PARP-1 by 3-aminobenzamide

(3-AB) has also been shown to attenuate oxidative/nitrosative stress response and accelerate healing.⁶³

Taken together, evidence suggests that reduction of oxidative stress and inflammation may be two potential mechanisms by which PARP-1 accelerates wound healing.⁶³

One potential risk of targeting wound inflammation by PARP-1 may be an increased favorability for wound infection. Any such treatment approach that reduces inflammation, therefore, should be applied after sufficient debridement and preparation of the wound bed with antimicrobials as per standard of care.

Proliferation phase: targeting PARP to improve angiogenesis and granulation tissue formation

This phase is marked by the formation of granulation tissue that is composed of proliferation and migration of keratinocytes, new connective tissue, and microscopic blood vessels that are formed by angiogenesis at the base of the wounds.⁶⁴

Keratinocytes proliferate and migrate faster (as assayed by a scratch wound healing assay) in the presence of PARP inhibitors 3-AB or PJ34.⁵⁶ Although the role of PARP-1/PARylation in cell proliferation is controversial,^{65–67} its role in cell migration has not yet been systematically investigated.

PARP-1 also has a major role to play in wound angiogenesis. There are some conflicting data on

Figure 3. Role of PARP-1 in the different phases of wound healing. Blue arrows indicate upregulation and red arrows indicate downregulation. The arrow on the X-axis indicates the progression of wound healing through the different phases (inflammation, followed by re-epithelialization, and angiogenesis followed by remodeling). VEGF, vascular endothelial growth factor.

the role of PARP in angiogenesis between *in vitro* experiments and uninjured tissue vs *in vivo* injured tissue, especially in diabetic ischemic wounds. Although in uninjured tissue, PARP inhibition may block angiogenesis-related endothelial properties leading to the inhibition of new blood vessel formation,⁶⁸ in a wound environment, PARP-1 has been shown as an antiangiogenic agent by suppression of multiple proangiogenic factors such as HIF-2 α , angiopoietin-like 4, erythropoietin, SIRT-1, Smad3/4, and VEGFR2.^{69,70} Indeed, a PARP-1 inhibitor 3-AB and an FDA-approved PARP-1 inhibitor olaparib both accelerate wound healing in mouse model by stimulating angiogenesis through upregulating the expression of urokinase type plasminogen activator and matrix metalloproteinase 2 (MMP-2) in transformed endothelial cells GM7373 and stimulating tubulogenic activity.^{62,63,71} Similarly, PARP-1 knockout mice exhibited accelerated wound healing by suppressing inflammatory mediators, promoting keratinocyte migration⁵⁶ and improving angiogenesis in animal models.⁷² Furthermore, FDA-approved PARP-1 inhibitor olaparib accelerates wound healing in mouse burn injury.^{62,63} Low doses of 3-AB, a PARP inhibitor, have also been reported to stimulate angiogenesis by regulating expression of urokinase type plasminogen activator and MMP-2 in transformed endothelial cells GM7373 and stimulating tubulogenic activity.⁷¹ PAR modification also has a reciprocal effect on the angiogenic effect of vascular endothelial growth factor (VEGF) in chorio allantoic membrane assay.⁷³ In an angiogenesis model under hyperglycemia using zebra fish, angiogenesis was impaired by hyperglycemia and it remained impaired even when the fish return to a euglycemic state.⁷² However, when PARP-1 inhibitor was added in a hyperglycemic setting, angiogenesis was rescued. Even though PARP-1 has been identified as an underlying cause of diabetic vasculopathy,⁴³ the exact molecular mechanisms by which it controls angiogenesis is still being elucidated.

We have shown that PARP-1 hyperactivity in ischemic/diabetic wounds impairs *in vitro* endothelial cell migration.⁷⁴ PARP-1 inhibition by a PARP-1 inhibitor PJ34 enhances both endothelial cell migration and tube formation.⁷⁴ In a mouse ischemic/diabetic wound model, PARP-1 inhibition increases mobilization of endothelial progenitor cells into the systemic circulation,⁷⁴ resulting in better perfusion in the wound bed, measured by laser Doppler scanning and higher levels of endothelial cell markers such as VEGFR2 and eNOS.⁷⁴

Taken together, PARP-1 plays an important role in angiogenesis, and a better understanding of the

mechanisms behind this will potentially provide a novel therapeutic target to enhance angiogenesis and promote wound healing.

Remodeling phase: targeting PARP to reduce scarring

The remodeling phase starts at the end of the granulation tissue development. In this phase, fibroblasts differentiate into myofibroblasts and induce healing by some contraction.^{75,76} Collagen I is the predominant form of the extracellular matrix that rebuilds the tensile strength of the tissue.

Cleavage of PARP-1 facilitates cellular disassembly and induces cells toward apoptosis. Apoptotic mechanisms are necessary for resolution of inflammation and development of the granulation tissue and are, therefore, an important mechanism of wound healing. This phenomenon is performed by neutrophils and macrophages after they infiltrate the wound.^{77,78} As the wound heals, fibroblast downregulation and apoptosis occur along with decreased vascularity through apoptosis of endothelial cells and myofibroblasts.^{75,76} Apoptosis also regulates number of fibroblasts and collagenase activity and thus plays a role in remodeling by regulating collagen synthesis and degradation within the wound.⁷⁹ MMPs are important in the remodeling phase of wound healing, and increased MMP-9 has been suggested to predict poor wound healing in diabetic foot ulcers.^{80,81} Interestingly, MMP-9 expression is suppressed in PARP-1-deficient mice, suggesting that PARP-1 silencing may enhance the remodeling process and accelerate wound healing. Furthermore, PARP-1 silencing inhibits TGF- β /Smad3 pathway,⁸² which is widely implicated in scarring. PARP-1 upregulation also promotes transcription of profibrotic gene CCN2/CTGF in tubular epithelial cells,⁸³ and absence of PARP-1 protects peritoneal mesothelial cells from fibrotic responses induced by high glucose.⁸⁴ These data suggest a potential role of PARP-1 in scarless wound healing. It is interesting to know that PARP-1 may also have a role in fetal scarless wound repair. Cutaneous wounds in E15 fetal mice heal in a scarless manner, whereas similar wounds in E18 mice heal with scar formation. PARP-1 cleavage has been associated with scarless healing (at E15, PARP-1 is increased by greater than twofold), whereas scar-forming healing (E18) only showed a small amount of cleaved PARP.⁸⁵

Genomic analysis of PARP-1 binding genes that may be implicated in wound healing

One of the mechanisms by which PARP-1 regulates gene expression is by directly binding to the gene near the transcription start site (TSS).^{9,86,87}

Genetic analysis of PARP-1 binding sites and the genes regulated by PARP-1 can further elucidate the role of PARP-1 in wound healing. Although there is currently no reported consensus sequence for PARP-1 binding site, a sequence 5'-GGAAAGG-3' has been found to be in proximity to PARP-1 binding sites.⁸⁷ Recent studies using chromatin immunoprecipitation (ChIP)-seq analyses provide some clues to wound healing-related genes regulated by PARP-1.⁸⁷ Better understanding of these downstream pathways of PARP-1 could reveal novel therapeutic targets to enhance wound healing.

PARP-1 binding to many genes has been reported to silence gene expression.^{87,88} A ChIP-seq approach was used to study PARP-1 protein interaction with chromatin in HEK293 cells.⁸⁷ A search for wound healing-related genes among the PARP-1 binding genes revealed from the ChIP-seq data (MGI database, ID: GO: 0042060) at least six genes to have PARP-1 binding near the TSS.

Toll-like receptor 4 (TSS to PARP-1 binding-downstream 285 bp). Toll-like receptor 4 (TLR4) is a proinflammatory molecule and acts as a proangiogenic factor by stimulating VEGF. TLR4 increases in murine cutaneous wounds at the early stages, and closure of excisional wounds is significantly delayed in TLR4-deficient mice. IL-1 β , IL-6, as well as epidermal growth factor production are significantly lower in the wounds of TLR4-deficient mice.^{89,90} TLR4 protein is also significantly downregulated in diabetic foot ulcer patients as compared with controls and is one of the main contributors implicated in impaired diabetic wound healing.⁹¹

TEK (TEK receptor tyrosine kinase)/TIE2 (TSS to PARP-1 binding-downstream 89 bp). TEK/TIE2 is a regulator of angiogenesis and vessel maturation. Pericyte TIE2 controls sprouting angiogenesis, which is an important aspect of wound healing.⁹²

FOSL1/Fos-related antigen 1 (TSS to PARP-1 binding-downstream 4,838 bp). FOSL1 controls the assembly of endothelial cells into organized capillary tubes by repressing integrin $\alpha_v\beta_3$ transcription,⁹³ inducing MMP-2 expression,⁹⁴ and driving endothelial cell migration.⁹⁵ The pivotal role of FOSL1 in angiogenesis is evident from the lethality of FOSL1^{-/-} embryos due to vascular defects.⁹³ Data from our laboratory (unpublished) demonstrate that silencing PARP-1 increases FOSL1 expression by multiple folds, but when FOSL1 is also silenced along with PARP-1 in PARP-1-silenced endothelial cells, tube formation was impaired, suggesting that PARP-1 silencing enhances endothelial

tube formation through the expression of FOSL1. This novel PARP-1-FOSL1 axis in wound angiogenesis should be further explored. Interestingly, PARP-1 was found to bind to FOSL1 in the mitotic phase,⁸⁵ suggesting that PARP-1 remains bound to FOSL1 within mitotic chromatin. This suggests "mitotic bookmarking," where regulatory information is transmitted through the transcriptionally silent mitotic phase,⁹⁶ leading to delayed reactivation of FOSL1 even after exit from mitosis.⁹⁷

SERPINB2/plasminogen activator inhibitor 2 (TSS to PARP-1 binding-upstream 215 bp). SerpinB2/plasminogen activator inhibitor 2 (PAI-2) is induced by inflammation, infection, or injury. It inhibits urokinase and proteolysis and thus protects the integrity and barrier function of the stratum corneum during inflammation assault.^{98,99} SerpinB2^{-/-} mice show impaired skin barrier function, a defective stratum corneum and increased trans-epidermal water loss. Protease activity is also important for cell migration, matrix degradation, and cellular adhesion, and thus protease activators can potentially influence wound healing through multiple pathways. The concentration of SERPINB2/PAI-2 has been reported to be significantly lower in nonhealing wounds.¹⁰⁰

CXCR1 (TSS to PARP-1 binding-downstream 478 bp). CXCR1 is a chemokine receptor that is expressed in epidermis and can induce keratinocyte migration and/or proliferation. Blocking of receptor-ligand interactions can delay re-epithelialization and wound closure after skin injury.¹⁰¹

CD24/heat stable antigen (TSS to PARP-1 binding-upstream 987 bp). CD24 is a heavily glycosylated cell surface protein that plays an important role in the inflammation, proliferation, and migration. Wound healing has been shown to be impaired in CD24 knockout mice.¹⁰²

PARP inhibitors and their potential in facilitating wound healing

PARP inhibitors have been well studied for their therapeutic efficacy in a variety of diseases,^{103,104} although most of the clinical trials have been aimed at cancers.¹⁰⁵ Topically applied pharmacological inhibitors have been shown to accelerate wound closure in mouse models of excision wounds.^{56,74} The approval and clinical availability of PARP-1 inhibitors have opened the door for repurposing of these drugs, as well as those that are expected to be approved in the future, for other nononcological indications.

Table 1. PARP-1 inhibitors in clinical development that may be repurposed for wound healing

PARP Inhibitor	Target PARP
Talazoparib (BMN-673)—most potent	PARP-1/2
Velliparib (ABT-888)	PARP-1/2
Rucaparib (AG-014699, CO-338)	PARP-1/2
Olaparib (AZD-2281)	PARP-1/2/3
CEP-9722	PARP-1/2
Niraparib (MK-4827)	PARP-1/2

PARP, polyadenosine diphosphate (ADP)-ribose polymerase.

Some of the well-studied PARP inhibitors are highlighted (Table 1).

Rucaparib (AG-014,69, CO-338). Rucaparib has been investigated in epithelial ovarian cancers. The recommended Phase 2 dose is 600 mg twice a day for oral rucaparib.¹⁰⁶ Treatment-induced adverse events (AEs) include nausea, vomiting, asthenia/fatigue, anemia, and transient transaminitis, and are mainly lower grade AEs, occur early in treatment, and are transient and easily managed with supportive treatment, dose interruption, or discontinuation.¹⁰⁶

Olaparib. Olaparib is a competitive inhibitor of PARP-1. Olaparib can affect PARP activity (PARP-1/2/3) by multiple mechanisms. It competes with the binding of NAD⁺ to PARP and can also trap PARP on DNA.¹⁰⁷ Olaparib maximally inhibits PARP enzyme at a dose of 40 mg,¹⁰⁸ whereas rucaparib maximally inhibits PARP enzyme at a dose of 92 mg.¹⁰⁹

Talazoparib (BMN-673). Talazoparib has a significantly greater potency *in vitro* and lowest clinical dose efficacy, relative to other PARP inhibitors in clinical development.¹¹⁰ It is the most specific PARP inhibitor in clinical development¹¹¹ and has lower off-target cell toxicity.¹¹²

Niraparib (MK4827). Niraparib is an oral PARP inhibitor that is currently approved for the maintenance treatment of women with recurrent ovarian cancer. Niraparib inhibits PARP enzymatic activity as well as increases formation of PARP–DNA complexes through “trapping” the PARP enzyme on damaged DNA. Phase 1 testing established the maximally tolerated dose of 300 mg daily administered orally. Toxicities include hematologic (thrombocytopenia, anemia, neutropenia, and leukopenia), gastrointestinal, fatigue, and cardiovascular (hypertension, tachycardia, and palpitations).¹¹³

Puerarin. Puerarin [8- β -D-glucopyranosyl-7-hydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-

one] is a major bioactive ingredient extracted from the root of the *Pueraria lobata*.^{114–116} Puerarin has been reported to inhibit PARP-1 expression and prevent CCl₄-induced liver fibrosis in mice.¹¹⁷ Puerarin fits tightly into the active pocket of PARP-1 and has structure similar to the structures of well-known PARP-1 inhibitors such as olaparib.^{118,119} Inhibition of PARP-1 by puerarin can provide protection by dramatic suppression of NF- κ B, ROS, and effective maintaining of mitochondrial homeostasis.

3-Aminobenzamide. Benzamides, particularly the 3-AB, inhibit/deactivate PARP-1 by interfering with the binding of NAD to the enzyme's active site, and by binding to DNA and preventing the recognition of DNA breaks by the enzyme.¹²⁰ Application of 3-AB has been reported to restore cellular energy, decrease inflammation, and reduce oxidative/nitrosative stress. 3-AB inhibits PARP-1 around 1 mM concentration.

Nicotinamide. Nicotinamide is a water-soluble amide active form of vitamin B3 or niacin. This was identified as the first inhibitor of PARP. Nicotinamide inhibits PARP activity at concentrations starting at 0.5 mM.³⁵

SUMMARY

PARP-1 is hyperactivated in ischemic diabetic wounds and this review clarifies some of the mechanisms by which elevated PARP-1 may regulate the process of wound healing, implicating that PARP-1 may be an important therapeutic target for improving ischemic diabetic wound healing.

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TAKE-HOME MESSAGES

- PARP-1 is a nuclear enzyme that is upregulated in ischemic diabetic wounds and impairs wound healing by multiple mechanisms.
- PARP inhibitors attenuate wound inflammation, accelerate keratinocyte migration, and improve angiogenesis in ischemic diabetic wounds.
- FDA-approved PARP inhibitors for the treatment of cancers can be repurposed to treat ischemic diabetic wound healing.

gery at the George Washington University School of Medicine & Health Sciences. Her study is focused on the angiogenesis/vasculogenesis in ischemic diabetic wound healing.

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Abbreviations and Acronyms

3-AB = 3-aminobenzamide
 AEs = adverse events
 ChIP = chromatin immunoprecipitation
 FDA = Food and Drug Administration
 MMP = matrix metalloproteinase
 PAI-2 = plasminogen activator inhibitor 2
 PAR = poly-ADP-ribose
 PARP = polyadenosine diphosphate (ADP)-ribose polymerase
 ROS = reactive oxygen species
 TLR4 = toll-like receptor 4
 TSS = transcription start site
 VEGF = vascular endothelial growth factor