

# Short Communication: Celecoxib, Angiogenesis, and Wound Healing



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**Citation** Norooznehad AH, Norooznehad F, Mostafaie A. Celecoxib, Angiogenesis, and Wound Healing. *Immunoregulation*. 2019; 1(4):239-242. <http://dx.doi.org/10.32598/Immunoregulation.1.4.239>

**doi** <http://dx.doi.org/10.32598/Immunoregulation.1.4.239>



## Article info:

**Received:** 13 Aug 2018

**Accepted:** 25 Nov 2018

**Available Online:** 01 Jan 2019

## Keywords:

Celecoxib, Angiogenesis,  
Wound healing,  
Cyclooxygenase-2 (COX-2) inhibitor

## ABSTRACT

**Background:** Wounds and their healing process are among the most crucial medical issues, especially in the field of dermatology and surgery that imposes notable costs to the health care system.

**Materials and Methods:** Wound healing requires specific fundamental steps, such as angiogenesis and inflammation. Angiogenesis is controlled by different cytokines such as Hypoxia-Inducible Factor  $\alpha$  (HIF- $\alpha$ ), Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), Platelet-Derived Growth Factor (PDGF), Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ), and Matrix Metalloproteinases (MMPs).

**Results:** Celecoxib, an inhibitor of Cyclooxygenase-2 (COX-2), is widely used in medicine and different fields. This medication can inhibit angiogenesis via suppressing all mentioned cytokines. Thus, suppression of angiogenesis by celecoxib, especially in chronic wounds, may result in the poor or delayed healing.

**Conclusion:** Authors suggest complementary clinical studies to evaluate the possible role of celecoxib on the wound healing focusing on angiogenesis.

## Introduction

Wounds and their healing are major issues in medicine, especially in surgery and dermatology and categorized into two major groups: acute and chronic. In the United State, (3-6) million individuals are suffering from chronic wounds [1]. Although chronic wounds can heal, a recurrence range of (23-70%) is reported, which depends on the etiology [2]. One of the most important complications associated with chronic wounds is infections that may lead

to various outcomes [3]. In the wound healing process, different steps are involved, among which angiogenesis is very crucial. Suppression of this phenomenon could disturb the wound healing process [2].

Angiogenesis is the formation of new blood vessels from pre-existing ones under physiologic and or pathologic conditions such as tumor growth, psoriasis, rheumatoid arthritis, diabetic retinopathy, multiple evanescence white dot syndrome, corneal neovascularization, and other types of angiogenic-dependent pathological conditions [4-6]. In other words, only a few physi-

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ological processes like wound healing and the female reproductive cycle are dependent on angiogenesis [7, 8]. In wound healing, angiogenesis is very important due to its role in supplying nutrition and oxygenation for proliferating cells and also removing waste materials from both necrotic and proliferating tissues [9, 10]. Angiogenesis is induced by different cytokines such as Hypoxia-Inducible Factor  $\alpha$  (HIF- $\alpha$ ), Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), Matrix Metalloproteinases (MMPs), Platelet-Derived Growth Factor (PDGF), Angiopoietin 1 (Ang-1) and Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ). Under the cellular hyper-proliferation state, a hypoxic condition is induced, and cells begin to secrete HIF- $\alpha$  which up-regulates VEGF gene expression as a key regulator of angiogenesis. VEGF is responsible for two main steps of vascularization: proliferation and migration of Endothelial Cells (ECs).

Also, MMPs, especially MMP-2, is responsible for the migration of proliferated ECs. TNF- $\alpha$  can stimulate the ECs strand formation in this system. Additionally, PDGF, which is widely secreted by ECs and activated macrophages, affect ECs strand formation. Another cytokine, bFGF, induces ECs chemotaxis, proliferation, and plasminogen activator expression. Ang-1, which seems to appear last in the angiogenesis process, affects ECs tube formation, inhibit their apoptosis and maturation of formed micro-vessels [4, 7, 11-14]. Also, it has been shown that cyclooxygenase-2 (COX-2) and its consequent products can induce angiogenesis via induction of VEGF, bFGF, and PDGF [15].

## Hypothesis

Celecoxib could impair wound healing through inhibiting angiogenesis. In the following part, the mechanism of this action would be discussed.

## Evaluation of Hypothesis

As mentioned earlier, angiogenesis and inflammation are crucial steps during wound healing. Angiogenesis occurs in a milieu filled with various cytokines such as VEGF, MMP-2, bFGF, PDGF, HIF- $\alpha$ , TGF- $\beta$ , and PDGF [4, 7, 12-14]. In vivo study of retinal angiogenesis has shown that celecoxib can inhibit the induced angiogenesis via suppression of HIF- $\alpha$  and VEGF on a transcription level [16]. Also, it can suppress the expression of MMP-2 as Wang et al. mentioned in their study [17].

Additionally, celecoxib could inhibit angiogenesis induced by bFGF at in vivo models of corneal neovascu-

larization in two separate studies [16, 18]. VEGF suppression has also been mentioned in many other studies which are mostly in vivo investigations [16-20]. Finally, it has been stated by El-Sayed et al. that celecoxib could decrease Ang-1 serum level in vivo. This COX-2 inhibitor can also inhibit inflammation besides angiogenesis through suppression of TNF- $\alpha$  as a shared cytokine in both mentioned steps [21].

## Discussion

As stated before, wound healing is an important issue in medicine due to its complications. In this study, we hypothesized that celecoxib could impair the wound healing process through anti-angiogenic activity. As Fairweather et al. reported, celecoxib would inhibit wound healing in vivo model. Also, in the histological analysis, they showed that celecoxib could decrease the number of blood vessels significantly in comparison to the physiologic condition [22]. Besides, the other COX-2 inhibitor meloxicam was confirmed to inhibit wound healing as well as celecoxib at an in vivo model [23]. It has been reported that celecoxib does not affect wound healing in the mice model of hemophilia [24].

On the other hand, evidence has proved that hemophilic patients experience significant elevated angiogenic and inflammatory cytokines in their plasma in comparison to healthy individuals. According to a study by Hoffman et al., cutaneous wound healing is different in hemophilia B following the activation of angiogenesis pathway [25]. Thus any phenomena which change angiogenic or inflammatory cytokines as a pathological condition using anti-angiogenic or anti-inflammatory agents may only reduce the cytokine levels to the physiological baseline. This issue was also reported in a wound bearing squamous carcinoma cell VII [24].

Obviously, tumors would not grow bigger than a few cubic millimeters if they don't reach new supply resources, which in turn depend totally on tumor angiogenesis. Thus seeding a tumor beside the location of the wound could inhibit the suppressing effect of celecoxib by releasing the angiogenic factors from the tumor cells [5]. Both these two studies, claiming that celecoxib does not affect wound healing, were performed in pathological situations with the excessive secretion of angiogenic factors. According to the authors' personal opinion, the inhibitory activity of celecoxib in wounds could be more important in wounds with tissue loss such as pilonidal cystectomy or anal fistulas compared to a surgical incision. Altogether, regarding the anti-angiogenic and anti-inflammatory potentials of celecoxib and the role of

both processes in wound healing, authors hypothesized that celecoxib could negatively affect wound healing although further investigations (in non-pathological conditions) are still required to reach a decisive conclusion.

## Ethical Considerations

### Compliance with ethical guidelines

There was no ethical considerations to be considered in this research.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Authors' contributions

All authors contributed in preparing this article.

### Conflicts of interest

Authors declare no conflict of interest related to this study.

### Acknowledgements

Authors are grateful for kind comments provided by Dr. Kamran Mansouri, Medical Biology Research Center (Kermanshah, Iran).

## References

- [1] Werdin F, Tennenhaus M, Schaller HE, Rennekampff HO. Evidence-based management strategies for treatment of chronic wounds. *Eplasty*. 2009; 9:e19. [PMID] [PMCID]
- [2] Bodnar RJ. Chemokine regulation of angiogenesis during wound healing. *Advances in Wound Care*. 2015; 4(11):641-50. [DOI:10.1089/wound.2014.0594] [PMID] [PMCID]
- [3] Clinton A, Carter T. Chronic wound biofilms: Pathogenesis and potential therapies. *Laboratory Medicine*. 2015; 46(4):277-84. [DOI:10.1309/LMBNSWKUI4JPN7SO] [PMID]
- [4] Norooznejhad AH, Norooznejhad F, Ahmadi K. Next target of tranilast: Inhibition of corneal neovascularization. *Medical Hypotheses*. 2014; 82(6):700-2. [DOI:10.1016/j.mehy.2014.03.007] [PMID]
- [5] Plank MJ, Sleeman BD. Tumour-induced angiogenesis: A review. *Journal of Theoretical Medicine*. 2003; 5(3-4):137-53. [DOI:10.1080/10273360410001700843]
- [6] Norooznejhad AH, Norooznejhad F. How could cannabinoids be effective in multiple evanescent white dot syndrome? a hypothesis. *Journal of Reports in Pharmaceutical Sciences*. 2016; 5(1):41-4.
- [7] Norooznejhad AH, Norooznejhad F, Bagheri N. Cannabinoids as treatment for hemophilic arthropathy: Hypothesized molecular pathways. *Journal of Reports in Pharmaceutical Sciences*. 2016; 5(2):89-93.
- [8] Mohammadi MH, Molavi B, Mohammadi S, Nikbakht M, Mohammadi AM, Mostafaei S, et al. Evaluation of wound healing in diabetic foot ulcer using platelet-rich plasma gel: A single-arm clinical trial. *Transfusion and Apheresis Science*. 2017; 56(2):160-4. [DOI:10.1016/j.transci.2016.10.020] [PMID]
- [9] Mostafaei S, Norooznejhad F, Mohammadi S, Norooznejhad AH. Effectiveness of platelet-rich plasma therapy in wound healing of pilonidal sinus surgery: A comprehensive systematic review and meta-analysis. *Wound Repair and Regeneration*. 2017; 25(6):1002-7. [DOI:10.1111/wrr.12597] [PMID]
- [10] Mohammadi S, Nasiri S, Mohammadi MH, Mohammadi AM, Nikbakht M, Panah MZ, et al. Evaluation of platelet-rich plasma gel potential in acceleration of wound healing duration in patients underwent pilonidal sinus surgery: A randomized controlled parallel clinical trial. *Transfusion and Apheresis Science*. 2017; 56:226-32. [DOI:10.1016/j.transci.2016.12.032] [PMID]
- [11] Keshavarz M, Norooznejhad AH, Mansouri K, Mostafaei A. Cannabinoid (JWH-133) therapy could be effective for treatment of corneal neovascularization. *Journal of Medical Hypotheses and Ideas*. 2010; 4:3:1-5.
- [12] Norooznejhad AH, Norooznejhad F. Cannabinoids: Possible agents for treatment of psoriasis via suppression of angiogenesis and inflammation. *Medical Hypotheses*. 2017; 99:15-8. [DOI:10.1016/j.mehy.2016.12.003] [PMID]
- [13] Norooznejhad AH. Missing angiogenic factors in hemophilic arthropathy. *Expert Review of Hematology*. 2018; 11(1):1-2. [DOI:10.1080/17474086.2018.1400904] [PMID]
- [14] Bahrehmand F, Vaisi-Raygani A, Kiani A, Rahimi Z, Tavilani H, Navabi SJ, et al. Matrix metalloproteinase-2 functional promoter polymorphism G1575A is associated with elevated circulatory MMP-2 levels and increased risk of cardiovascular disease in systemic lupus erythematosus patients. *Lupus*. 2012; 21(6):616-24. [DOI:10.1177/0961203312436857] [PMID]
- [15] Chu AJ, Chou T-H, Chen BD. Prevention of colorectal cancer using COX-2 inhibitors: Basic science and clinical applications. *Frontiers in Bioscience*. 2004; 9:2697-713. [DOI:10.2741/1429]
- [16] Liu N, Chen L, Cai N. Celecoxib attenuates retinal angiogenesis in a mouse model of oxygen-induced retinopathy. *International Journal of Clinical and Experimental Pathology*. 2015; 8(5): 4990-8. [PMID] [PMCID]
- [17] Wang L, Chen W, Xie X, He Y, Bai X. Celecoxib inhibits tumor growth and angiogenesis in an orthotopic implantation tumor model of human colon cancer. *Experimental Oncology*. 2008; 30(1):42-51. [PMID]

- [18] Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Research*. 2000; 60(5):1306-11. [PMID]
- [19] Wei D, Wang L, He Y, Xiong HQ, Abbruzzese JL, Xie K. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. *Cancer Research*. 2004; 64(6):2030-8. [DOI:10.1158/0008-5472.CAN-03-1945] [PMID]
- [20] Rosas C, Sinning M, Ferreira A, Fuenzalida M, Lemus D. Celecoxib decreases growth and angiogenesis and promotes apoptosis in a tumor cell line resistant to chemotherapy. *Biological Research*. 2014; 47:27. [DOI:10.1186/0717-6287-47-27] [PMID] [PMCID]
- [21] El-Sayed R, Moustafa Y, El-Azab M. Evening primrose oil and celecoxib inhibited pathological angiogenesis, inflammation, and oxidative stress in adjuvant-induced arthritis: Novel role of angiopoietin-1. *Inflammopharmacology*. 2014; 22(5):305-17. [DOI:10.1007/s10787-014-0200-5] [PMID]
- [22] Fairweather M, Heit YI, Buie J, Rosenberg LM, Briggs A, Orgill DP, et al. Celecoxib inhibits early cutaneous wound healing. *Journal of Surgical Research*. 2015; 194(2):717-24. [DOI:10.1016/j.jss.2014.12.026] [PMID]
- [23] Gourevitch D, Kossenkov AV, Zhang Y, Clark L, Chang C, Showe LC, et al. Inflammation and its correlates in regenerative wound healing: An alternate perspective. *Advances in Wound Care*. 2014; 3(9):592-603. [DOI:10.1089/wound.2014.0528] [PMID] [PMCID]
- [24] Roh J-L, Sung M-W, Park S-W, Heo D-S, Lee DW, Kim KH. Celecoxib can prevent tumor growth and distant metastasis in postoperative setting. *Cancer Research*. 2004; 64:3230-5. [DOI:10.1158/0008-5472.CAN-03-3050]
- [25] Hoffman M, Harger A, Lenkowski A, Hedner U, Roberts HR, Monroe DM. Cutaneous wound healing is impaired in hemophilia B. *Blood*. 2006; 108(9):3053-60. [DOI:10.1182/blood-2006-05-020495] [PMID]