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Review Article

Specialized pro-resolving lipid mediators: A future for conventional endodontics-A review

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ABSTRACT

Human dental pulp is a highly dynamic tissue that plays major roles in the defense against pathogens and during tissue injury. However, the efficiency of these mechanisms during dental pulp inflammation (pulpitis) varies due to anatomical and physiological restrictions. Uncontrolled progressive unresolved inflammation can lead to pulp tissue necrosis and subsequent apical periodontitis or it can develop into chronic inflammation and become a silent killer causing bone destruction. Considering the cause & effect model, the decision to perform pulp extirpation and endodontic treatment is justifiable only by the lack of therapeutic tools that limit the immune/inflammatory process. The resolution of acute inflammation is necessary to avoid the development of chronic inflammation and to promote repair or regeneration. This active process is orchestrated by Specialized Pro-resolving lipid Mediators (SPMs), which include several families of distinct local mediators (lipoxins, resolvins, protectins and Maresins). These immunoresolvents are distinct from immunosuppressive molecules as they not only dampen inflammation but also promote host defense. Experimental application of SPMs has shown promising result in wide range of inflammatory diseases. This article illustrates about the potential use of SPMs in dentistry

1. Introduction

The dental pulp is a connective tissue enclosed within a mineralized hard tissue. As I.B. Bender said “Pulp is a small tissue with Big Issue”, it can trigger an immune response by different stimuli such as dental caries, trauma and operative procedure. Progressive pulp inflammation may lead to pulp necrosis because of the low compliance environment and lack of collateral circulation.[1] Absence of therapeutic tools to limit the inflammatory process is the rationale behind performing endodontic procedures. But actually, the resolution of the inflammation is regulated and well coordinated by a number of mediators called SPMs including Lipoxins, Resolvins, Maresins and Protectins.[2]

2. Pulp Inflammation

Bacteria are the primary cause of pulp infection to elicit an inflammatory response. Odontoblasts are first involved in fighting bacterial invasion and activate innate defence mechanisms. These mechanisms secrete various Pro inflammatory cytokines and chemokines to recruit other immune cells to the site of infections. If innate immune system exceeds its capacity, adaptive immune system gets activated and facilitate pathogen clearance through specific T and B cells. If the inflammation becomes uncontrolled, it may lead to pulp necrosis. This in turn stimulates a secondary immune response in periapical region. Apical periodontitis results as a defence mechanism to confine bacteria to the infected tooth and prevents its spread to other sites. But it may also be aggressive and may lead to bone

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destruction.[3]

3. Resolution of the Inflammation

The extent of the inflammation can be counter regulated by promoting the active termination or resolution of the inflammation to re-establish homeostasis. This process mainly depends on actions of several anti inflammatory and Pro resolving mediators. The first evidence that the resolution of the inflammation is an active rather than a passive process came with the discovery of the pro resolution biochemical signalling circuits. The new genus of pro resolving mediators include Lipoxins (LXs) and Aspirin triggered lipoxins (ATL) (Levey et al., 2001; Serhan, 2005), Resolvins as well as the recently discovered Protectins and Maresins (Serhan et al.,2000;2008).[4] The five pillars of the resolution are Removal of the microorganism, dead cells and debris, Restoration of the vascular integrity and perfusion, Tissue regeneration, Remission of the fever and Relief of inflammatory pain.[5]

4. Specialized Pro Resolving Lipid Mediators

They are the derivatives of the poly unsaturated fatty acids which are produced during the endogenous activation of resolution phase of inflammation. They are derived from both w-6 poly-unsaturated fatty acids (Arachidonic acid) and w-3 polyunsaturated fatty acids [Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)]. Functions of the SPMs are 1) down regulation of the cell adhesion molecules molecule on both endothelial cells and leukocytes 2) reduction in activation of neutrophils and trans-endothelial migration 3) inhibition of formation and activation of pro inflammatory mediators.[6]

5. Lipoxins

Lipoxins are formed by transcellular biosynthesis via multiple distinct pathways. These pathways include conversion of AA by 5-LOX, 15-LOX and aspirin/COX2.[7] They modulate adaptive immune system by inducing M2 phenotype. They are called anti edemogenic mediators because they stimulate the return of the vascular homeostasis.[8]

6. Resolvins

Resolvins are the endogenous mediators synthesized from Omega 3 PUFA. Either by acetylation of the COX2 or by cytochrome p450, Eicosapentaenoic acid (EPA) produce E series Resolvins (RvE1, RvE2, RvE3) and Docosahexaenoic acid (DHA)produce D series Resolvins (RvD1-RvD2). Resolvin E1 stimulates the production of IL 10 to reduce the pro inflammatory cytokine. D series Resolvin gives protection against PMN mediated re-perfusion induced organ injury. RvD2 help in clearance of microbes.[9]

7. Maresins and Protectins

The biosynthesis of Maresins and Protectins involves the formation of the epoxide intermediate of Docosahexaenoic acid DHA) by oxygenation through LOX. They reduce Pro inflammatory cytokines, activates M2 macrophages. They are also involved in pain reducing mechanism and tissue regeneration.[10]

8. SPMs in Endodontics

Xu H et al stated that the application of RvE1 in pathogen induced disease model of rat incisors and molars showed reduced inflammation and also induced pulpal alteration by producing less degeneration of the pulp tissue. It also down regulated the expression of chemR23, a transmembrane receptor to which RvE1 can bind, explaining the inhibition of leukocyte infiltration.[11] Azuma MM et al proved that supplementation with Omega 3 regimen showed reduction in inflammatory symptoms of aphthous stomatitis.[12] Van DTE et al proved that the application of RvE1 in a rat model of immature tooth with apical periodontitis produced greater radiological root lengths and greater thickness of the dentinal walls which leads to increased fracture resistance of the root.[13] Siddiqui et al proved that the application of RvD2 in a tooth revascularization model allowed calcification around the root apex and reversed apical periodontitis. They also resulted in tissue regeneration and apical root closure.[14]

9. Therapeutic Role

Even though SPMs are highly potent and efficacious ligands they are delicate in their physicochemical nature, require complex chemical synthesis and are prone to metabolic inactivation. In an invitro study conducted by Van dyke et al, incorporation of SPM in the form of microparticles and nano particles have been effective in resolving periodontitis.[15] Despite its advantages these particles have drawbacks such as non-specific bio distribution, poor water solubility and limited bio availability.[16] Implanting a preformed scaffold into the root canal space is difficult because of the narrow and small volume of the pulp.[17] Therefore, drug delivery systems such as microspheres, fibres and hydrogels must be considered for a sustained drug release. But hydrogels are limited carrying only hydrophilic drugs.[18] In order to improve their drug loading capacity, different formulations had been tested in invitro studies using polyisocyanopeptide gel and poloxamer 407(P407). Wang B et al indicated that the PIC-PLGA vehicle exhibited suitable injectability and long-term structural stability.[19]

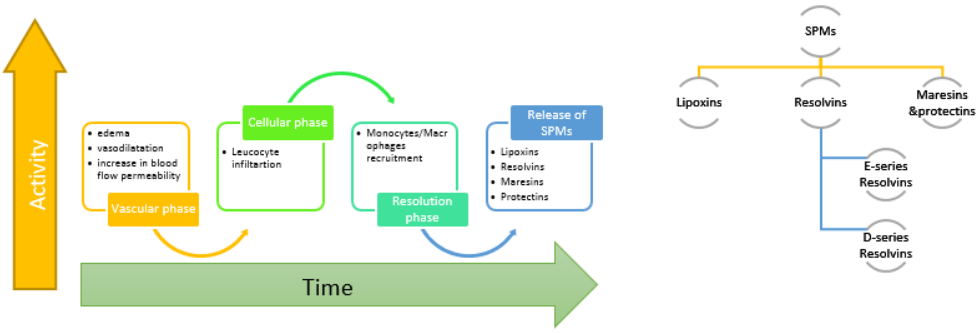

Fig. 1: This figure illustrates the resolution phase of inflammation and the production of the specialized pro resolving lipid mediators

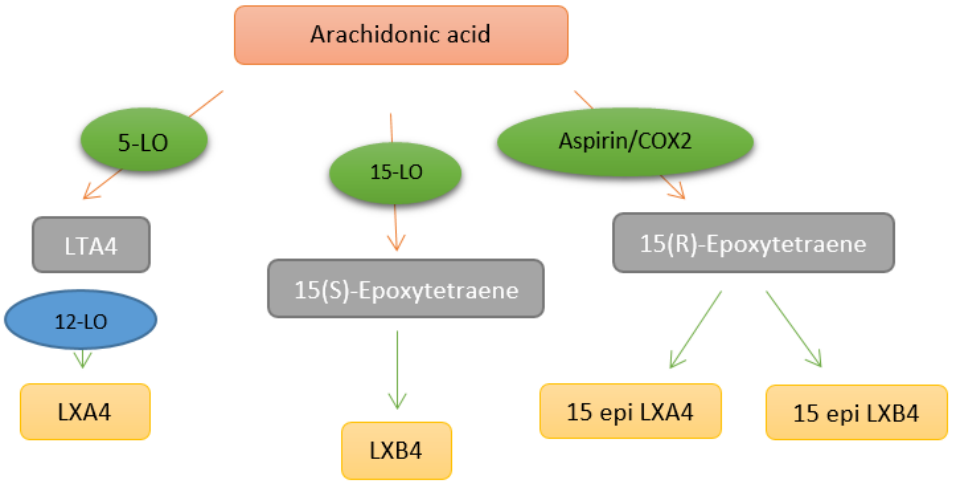

Fig. 2: This figure illustrates about the synthesis of lipoxins via multiple distinct pathways

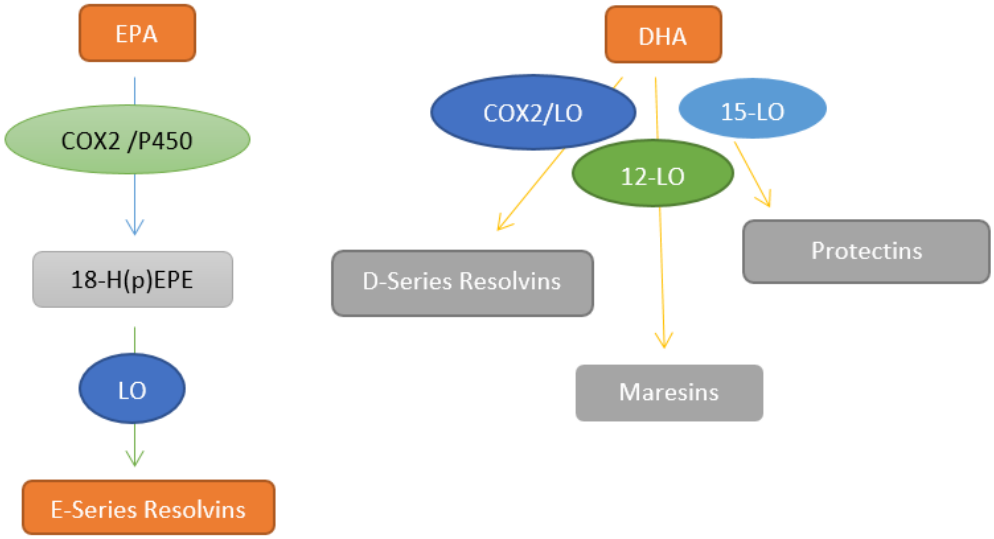

Fig. 3: This figure illustrates about the synthesis of Resolvins, Maresins and Protectins

10. Conclusion

SPMs can dampen excess inflammation without compromising the host defence mechanism. They act locally to halt leukocyte recruitment by not impairing with the endogenous healing pathways. Only limited studies had explored the endodontic role of SPMs, but showed promising results in the form of control of pulp inflammation, resolution of inflammation and by reversing excessive bone destruction. If the above mentioned scientific and technical barriers have been resolved SPM will show promising result in the revolution of conventional endodontic procedures. Further clinical studies should be carried to formulate the specific drug delivery system for their application in the treatment of pulpitis and apical periodontitis.

11. Abbreviations

AA-arachidonic acid, IL-Interleukin, LT-leukotriene LOX-Lipoxygenase, COX-Cyclooxygenase, LX-Lipoxin, ATL-aspirin triggered lipoxin, EPA-Eicosapentaenoic acid, DHA-Docosahexaenoic acid, RvE-Resolvin E series, RvD-Resolvin D series, PIC-Polyisocyapeptide, PLGA-Polylactic co-glycolic acid, H(p) EPE-hydroxy eicosapentaenoic acid.

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13. Conflict of Interest

None.

References

1. Aubeux D. Specialized pro-resolving lipid mediators in endodontics: a narrative review. *BMC Oral Health*. 1276;21:276. doi:10.1186/s12903-021-01619-8.
2. Cotti E, Ideo F, Pedrazzini A, Bardini G, Musu D, Kantarci A, et al. Proresolving Mediators in Endodontics: A Systematic Review. *J Endod*. 2021;47(5):711–20. doi:10.1016/j.joen.2021.01.008.
3. Bannenberg G, Serhan CN. Specialized pro-resolving lipid mediators in the inflammatory response: An update. *Biochim Biophys Acta*. 2010;1801(12):1260–73. doi:10.1016/j.bbalip.2010.08.002.
4. Maderna P, Godson C. Mediators and receptors in the resolution of inflammation: drug targeting opportunities. *Br J Pharmacol*. 2009;158(4):933–5. doi:10.1111/j.1476-5381.2009.00484.x.
5. Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat Rev Immunol*. 2016;16(1):51–67. doi:10.1038/nri.2015.4.
6. Serhan CN. Resolution phases of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Annu Rev Immunol*. 2006;25:101–37. doi:10.1146/annurev.immunol.25.022106.141647.
7. Romano M. Lipoxin analogs and lipoxin formation in vivo. *Prostaglandins, Leukotrienes Essential Fatty Acids*. 2005;73(3-4):239–43. doi:10.1016/j.plefa.2005.05.011.
8. Maderna P, Godson C. Lipoxins: resolutionary road. *Br J Pharmacol*. 2009;158(4):947–59. doi:10.1111/j.1476-5381.2009.00386.x.
9. Kasuga K, Yang R, Porter TF, Agrawal N, Petasis NA, Irimia D, et al. Rapid appearance of resolvin precursors in inflammatory exudates: novel mechanisms in resolution. *J Immunol*. 2008;181(12):8677–87. doi:10.4049/jimmunol.181.12.8677.
10. Park J, Langmead CJ, Riddy DM. New advances in targeting the resolution of inflammation: implications for specialized pro-resolving mediator GPCR drug discovery. *ACS Pharmacol Transl Sci*. 2020;3(11):88–106. doi:10.1021/acsptsci.9b00075.
11. Xu H, Chen J, Ge J, Xia K, Tao S, Su Y, et al. Resolvin E1 ameliorates pulpitis by suppressing dental pulp fibroblast activation in a chemerin receptor 23-dependent manner. *J Endod*. 2019;45(9):1126–1134.e1. doi:10.1016/j.joen.2019.05.005.
12. Azuma MM, Gomes-Filho JE, Ervolino E, Cardoso CBM, Pipa CB, Kawai T, et al. Omega-3 fatty acids reduce inflammation in rat apical periodontitis. *J Endod*. 2018;44(4):604–8. doi:10.1016/j.joen.2017.12.008.
13. Van DTE, Luiz EB, Scarparo RK, Dondoni L, Böttcher DE. Intracanal delivery of Resolvin E1 controls inflammation in necrotic immature rat teeth. *J Endod*. 2014;40(5):678–82.
14. Siddiqui YD, Omori K, Ito T, Yamashiro K, Nakamura S, Okamoto K, et al. Resolvin D2 induces resolution of periapical inflammation and promotes healing of periapical lesions in rat periapical periodontitis. *Front Immunol*. 2019;10:307. doi:10.3389/fimmu.2019.00307.
15. Van Dyke T, Hasturk H, Kantarci A, Freire MO, Nguyen D, Dalli J, et al. Proresolving nanomedicines activate bone regeneration in periodontitis. *J Dent Res*. 2015;94(1):148–56. doi:10.1177/0022034514557331.
16. Xin Y, Yin M, Zhao L, Meng F, Luo L. Recent progress on nanoparticle based drug delivery systems for cancer therapy. *Cancer Biol Med*. 2017;14(3):228–41. doi:10.20892/j.issn.2095-3941.2017.0052.
17. Fukushima KA, Marques MM, Tedesco TK, Carvalho GL, Gonçalves F, Caballero-Flores H, et al. Screening of hydrogel-based scaffolds for dental pulp regeneration-a systematic review. *Arch Oral Biol*. 2018;98:182–94. doi:10.1016/j.archoralbio.2018.11.023.
18. He W, Kapate N, Shields CW, Mitragotri S. Drug delivery to macrophages: a review of targeting drugs and drug carriers to macrophages for inflammatory diseases. *Adv Drug Deliv Rev*. 2019;doi:10.1016/j.addr.2019.12.001.
19. Wang B, Wang J, Shao J, Kouwer PHJ, Bronkhorst EM, Jansen JA, et al. A tunable and injectable local drug delivery system for personalized periodontal application. *J Control Release*. 2020;324:134–45. doi:10.1016/j.jconrel.2020.05.004.

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