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The Close Association Of E Faecalis And NLRP3 Inflammasome In Pulpal Diseases.

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E Faecalis as a pathogen

Since Enterococcus Faecalis is the most frequently found microbial pathogen in root canals with persistent infection, its discovery seriously impairs any case's prognosis. [1,2] This species' capacity to infiltrate dentinal tubules and withstand intracanal medications is largely responsible for its survival.[3,4] A recent study has established the link between E. faecalis and extra-radicular infection in addition to intra-radicular infection.[3]

However, according to other findings, E faecalis is not the most common species and is not found in apical biofilms in patients with post-treatment apical periodontitis.[3,4] The aforementioned findings further demonstrate that it is unclear how E faecalis contributes to endodontic disorders. Therefore, it is necessary to improve knowledge, but in order to do so, it is important to discuss a clear molecular picture.

The inflammasome concept

The Pattern Recognition Receptor (PRR) is necessary for the innate immune response to target harmful microorganisms and other endogenous or foreign pathogens.[5,6]

The inflammasome is a newly found PRR that was first thoroughly characterized in 2002. Inflammasomes are "a huge molecular platform that initiates the activation of inflammatory caspases and processing of interleukin 1," according to Tschopp, who first suggested the idea in 2002. The nucleotide-binding oligomerization domain-like receptor (NLR), a pattern recognition receptor (PRR) that is known to be present in these big protein complexes that detect pathogenic damage, is becoming the focus of research.

The most well-known is the iNLRP3 inflammasome, is so named because the NLRP3 protein in the complex is also referred to as "pyrin domain-containing protein 3" and is a member of the family of nucleotide-binding and oligomerization domain-like receptors (NLRs). The NLRP3 inflammasome also includes procaspase-1 and the adaptor proteins apoptosis-associated speck-like protein (ASC).

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These three proteins interact to closely control inflammasome activity, ensuring that the immune system only activates when necessary.

NLRP3 and interleukin 1 precursors are only "barely visible" at very low levels in the cytosol. Numerous distinct stimuli can activate the NLRP3 inflammasome, causing it to oligomerize and further activate procaspase 1 to caspase 1. The development of IL-1 is finally stimulated by this activation, which results in inflammatory cascades.

Models of NLRP3 activation

Following activation by inflammatory stimuli, the NLRP3 inflammasome is typically present in immunological and inflammatory cells.[7,8] There are 2 phases of inflammasome activation. [8–10] First is the activation of NF-B-mediated signalling and up-regulate the transcription of inflammasome-associated molecules like inactive NLRP3, proIL-1, and proIL-18.[11–13]

The second stage of inflammasome activation is dominated by the inflammasome oligomerization. Procaspase-1 becomes caspase-1 as a result, and mature IL-1 and IL-18 are produced and secreted as well.[9,14,15]

The NLRP3 inflammasome is activated and assembled as a result of this process. According to this interpretation, it serves as the primary activation for the inflammasome's ability to secrete IL-1.[16–18]

The NLRP3 inflammasome may be activated by intracellular and endoplasmic reticulum (ER)-associated Ca2+ fluxes.[8,19,20]

In the next hypothesis, there is the production of reactive oxygen species (ROS), which then triggers the NLRP3 inflammasome to develop. These aggregates work through a process mediated by cathepsin B.

Other known triggers include internal disruption[21–23], mitochondrial damage or dysfunction brought on by mitochondrial Ca2+ overload, autophagic disorder[24–26], and thioredoxin-interacting protein (TXNIP).[27,28]

NLPR3 in Inflammation or Diseases

According to studies, the cytosol has very low quantities of the NLRP3 inflammasome. However, inappropriate NLRP3 inflammasome activation may result in a number of inflammatory diseases.[29,30] Increased production of cytokines by the NLRP3 inflammasome promotes the development and instability of atherosclerotic plaques.[31–33]

According to several studies[34–36], the severity of SLE in humans closely correlates with levels of IL-1, IL-18, and caspase-1.[37] Odd NLRP3 inflammasome activation has been linked to research in macrophages and colitis-prone mice models. [38–40]. According to Lewis et al.[41] (2011) and Villani et al.[42] (2009), variation in the NLRP3 gene is associated with the colitis in patients.[43–45] Familial bloodless vehicle-inflammatory syndrome, Muckle-Wells syndrome, and other unusual hereditary auto-inflammatory illnesses are all included in this condition.[46,47]

Pulpitis and NLRP3 inflammasome

As is common knowledge, dental caries is an infectious microbiological condition that results in the demineralization of enamel and dentin. If unchecked, pulpitis results from the invasion of the dentinal tubules and subsequent damage to the pulpal tissues. The pulp's innate defence mechanism, which is the initial line of defence, is known to be activated by this bacterial invasion.[48]

The innate immune system is made up mostly of two cell types, odontoblasts and fibroblasts. When carious bacteria and/or bacterial products are detected, the Toll-like receptors (TLRs) in the odontoblasts produce chemokines such interleukin-8 (IL-8) and IL-1beta.[49] According to a 2015

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study by Jian W et al, the NLRP3/caspase-1 pathway is associated with the innate immune response of human dental fibroblasts.[50]

This bolsters Song Z et al claims that NLRP3 is present in human dental pulp cells, which they made in their clinical investigation. The study's findings demonstrated that pulp tissue from healthy persons had lower levels of NLRP3 than pulp tissue from inflammatory pulp cells.[51]

The aforementioned findings unequivocally demonstrated that dental fibroblasts contain NLRP3. However, the groundbreaking research by Zhang A shown that the NLRP3 inflammasome is active during inflammation in human dental fibroblasts.[52]

E Faecalis and NLRP3 inflammasome

This thorough review did a search to discover the impact of E. faecalis on the NLRP3 inflammasome because it is the most prevalent pathogen and challenging to eradicate in the case of infected root canals. To find publications about Enterococcus Faecalis and the NLRP3 inflammasome, researchers examined the databases of Pubmed/Medline, Scopus, and EBSCOhost. The final search strategy reached after using the Boolean operator keywords was (E Faecalis) AND (NLRP3 inflammasome).

The impact of E. faecalis on NLPR3 inflammasome activation in pulpal disorders was the subject of three papers with similar characteristics, which have been methodically summarised in table 1.

Table 1: NLRP3 infllammasome and E faecalis

Author	Journal Name And Year	Bacteria Analyzed	Cell Culture Used	Control Group	Elisa Test Done And Results	Immunoblotting Done And Results	RTPCR Done And Results	Conclusion
Yang HH et al	J Endod 2014	E faecalis	THP1 cells a human monocytic cell line were differentiated into macrophage like cells.	yes synthetic bacteria (Pam3CSK4) was used as a positive control	yes and increased levels of IL-1 beta via Toll receptor 2 via NLRP7 inflammasome	yes , increased levels of caspase 1 and IL-1beta	done for IL-1 beta and GADPH	1. increased IL-1 beta was detected by ELISA 2. E faecalis induces IL- 1 beta secretion in macrophages 3. E faecalis induces pyrotosis
Wang L et al	J Endod 2016	E faecalis	RAW 264.7 cells (mouse macrohpage cell line)	yes	yes and increased levels of IL-1 beta and NLRP3	yes , increased expression of NLRP3, caspase 1 and IL-1 beta	done. Increased levels of NLRP3 , Caspase 1 , IL-1 beta and GAPDH compared to control group	high expression of NLRP3 and IL-1 beta is linked to E faecalis
Ran S et al	Microb Pathog 2021	E faecalis	THP1 cells a human monocytic cell line were differentiated into macrophage like cells.	yes synthetic bacteria (Pam3CSK4)	yes and increased levels of IL-1 beta	done. Results showed increased levels of NLRP3 IL-1beta and caspase 1	done, increased levels of IL-1 beta, NLRP3 , caspase 1 , ASC	1.e faecalis incrased IL-1 beta secretion 2.efaecalisincreases expression of NLRP3, IL-1 beta, caspase 1 3. E . Faecalis induces NLRP3 and caspase 1 activation.

NLRP3 inflammsome in Saliva and GCF

The NLRP3 inflammasome has been discovered in early studies to be present in saliva in addition to human tooth pulp cells and fibroblasts. Isaza-Guzman D. et al works from 2017 has clearly demonstrated that patients with chronic and severe periodontitis have been discovered to have elevated levels of the NLRP3 inflammasome in their saliva.[53] They continued by saying that this might pave the way for a brand-new periodontitis biomarker.[4]

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According to a study by Yu L et al.[54], NLRP3 has been discovered in gingival crevicular fluid (GCF) in cases of periodontitis.
The importance of employing biomarkers in GCF as a diagnostic tool to spot modest disease changes has been highlighted by Bibi T et al.

CONCLUSION

In this era of problems during diagnosis of pulpal diseases there is a clear paradigm shift towards Molecular diagnostics which advocates the use of biomarkers as the diagnostic tools. One such marker is NLRP3 inflammasome that could pave the way for accurate diagnosis and predictable treatment of pulpal diseases

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