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Research Report

The role of COX-2, caspase-1 and IL-17 in pericoronitis-related inflammation due to lower third molar impaction

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ABSTRACT

Background: *Inflammation of the pericorona due to lower third molar impaction (LTMI) is often diagnosed as pericoronitis. Expression of cyclooxigenase-2 (COX-2) and caspase-1 may be induced by lipopolysacharide (LPS) and cause pyroptosis with minimal inflammation. When LPS activates toll-like receptor (TLR-4), NOD-like receptors containing domain pyrin 3 (NLRP3) inflammasome will activate the release of pro-caspase-1 to caspase-1, followed by the secretion of interleukin (IL)-1β. IL-1β and IL-23 which induces CD4$^+$ Tcells (Th17) to produce IL-17 as a pro-inflammation cytokine.* ***Purpose:*** *This study aimed to identify the respective roles of COX2, caspase-1 and IL-17 in pericoronitis inflammation of the pericorona due to LTMI.* ***Methods:*** *Frozen section samples were produced through LTMI pericorona tissue biopsy using material provided by the Dental and Oral Clinic at Muwardi Hospital, Surakarta. The paraffin block produced was subsequently cut using a clean microtome with the resulting thin slices being placed on an object glass coated with polylysine. A diagnosis of pericoronitis was subsequently made by a pathologist. Immunohistochemical staining for COX-2, caspase-1 and IL-17 was carried out by indirect tyramide signal amplification (TSA) method. Photos were obtained by means of 100X, 200X, 400X and 1000X objective lensed microscopes to qualitatively assess the above mentioned protein expressions. T-Test was conducted in order to establish the difference in expression between the control group and pericoronitis due to LTMI.* ***Results:*** *The presence of a brownish yellow color indicated the expression of COX-2, caspase-1 and IL-17 in pericorona epithelial cells which visible expression categorized as moderate (30-70%). The mean expression of COX-2, caspase-1 and IL-17 was categorized as mild and there was no significant difference between the expression of the three proteins.* ***Conclusion:*** *COX-2, caspase-1 and IL-17 play an important role in the phyroptosis signal of LTMI pericoronitis in cases of low inflammation.*

Keywords: *caspase-1; COX-2, IL-17; inflammation; pericoronitis*

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INTRODUCTION

Severe inflammation of the gums can result in damage to the soft tissue around the teeth.[1,2] Pericoronitis is a polymicrobial infection of the soft tissues surrrounding the crown of a partially or incompletely erupted tooth. Pericoronitis generally occurs due to third molar impaction. The prevalence of pericoronitis, which constitutes an inflammatory process, is estimated to be between 8% and 59%.[3,4] Consequently, the condition needs to be appropriately treated immediately .[5] During pericoronitis, the inflammatory process is initiated by competent immuno cells present in tissues throughout the body. Several pro-inflammatory mediators, including: interleukin (IL), tumor necrosis factor and tumor growth factor, have been reported as forming part of the pericoronitis mechanism,[6–8] These mediators also comprise cyclooxigenase (COX)-2, caspase-1 and IL-17.

These COX-2 and endogenous and exogenous prostaglandin-2 (PGE-2) molecules are expressed by macrophage cells and triggered by the presence of lipopolysacarida (LPS) on bacterial cell surfaces. It has

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been stated that the stimulating effects of endogenous and exogenous PGE-2 leads to the cAMP-PKA-AKAP-dependent pathway resulting in the suppression of nuclear factor kappa beta (NF-κβ) expression, thereby continuing to suppress COX-2 expression.[9] In a depressed state, due the presence of pathogenic bacteria (LPS), cells will program their own death by expressing caspase.[10]

Caspases are expressed by both immune and non-immune cells and function as inactive zymogens consisting of the carboxy effector-terminal protease domain and the pro-domain amino-terminal referred to as the caspase-associated recruitment domain (CARD).[11] Caspase-1 actively converts pro IL-1β and pro IL-18 into its active form and initiates an inflammatory response. At the same time, gasdermin D will become active and lead to pyroptosis.[12–14] When LPS binds to toll-like receptor-4 (TLR-4), ATP signaling will continue in the NOD receptor protein and be forwarded to an inflammasome containing pyrin domain 3 (NLPR-3). With active NLPR-3, caspase-1 will be released and change to caspase-1. Furthermore, pro IL-1β will be changed to IL-1β by caspase-1. In addition, IL-23 will also be expressed, subsequently functioning as a paracrine for Th-17 cells in the production of IL-17.[12–14]

IL-17 is an important cytokine which is known to regulate various immunocompetent cells such as macrophages, neutrophils and/or epithelial cells during several pathological processes.[15] IL-17A, IL-17C and IL-17F also play a role in triggering tissue repair and epithelial cell responses to extracellular bacteria.[16] In another study, it was found that IL-17 responses would have implications for inflammatory events and cause tissue damage.[17,18] The aim of this study is to identify the correlations of COX-2, caspase-1 and IL-17 to the role of inflammation in pericoronitis resulting from lower third molar impaction (LTMI).

MATERIALS AND METHODS

Ethical clearance was issued by the Ethical Commission of Research, Faculty of Medicine, Universitas Sebelas Maret, Muwardi Hospital, Surakarta (No. EC-98/VIII/2008).

Frozen sections were manufactured during a LTMI pericorona tissue biopsy performed at the Dental and Oral Clinic of Muwardi Hospital, Surakarta. The paraffin block produced was then cut using a clean microtome machine. Thin slices were placed on object glass previously coated with polylysine. A diagnosis of pericoronitis was arrived at by a pathologist. The immunohistochemical stain for COX-2, caspase-1 and IL-17 with monoclonal antibody (Santa Cruz Biotech, Amersham Pharmacia Biotech) at 1:500 was carried out by indirect tyramide signal amplification (TSA) method (NEN Life Science Products, Renaissence).[19,20] By using 100X, 200X, 400X and 1000X objective lensed microscopes (Nikkon), photos were obtained to qualitatively assess the abovementioned protein-protein expressions. T-Test was conducted in order to establish the difference in expression between the control group and pericoronitis due to LTMI.

RESULTS

Figure 1 shows the immunohistochemical staining using anti-COX-2, caspase-1 and IL-17 monoclonal antibodies. A brownish yellow color indicates the expression of COX-2, caspase-1 and IL-17 in pericorona epithelial cells (arrows). Visible expression is categorized as moderate (30-70%).

Table 1 contains the data relating to imunohistochemical staining which shows the expression of COX-2, caspase-1 and IL-17 in pericorona epithelial cells as the percentage of the power of expression (positive cells expressed from

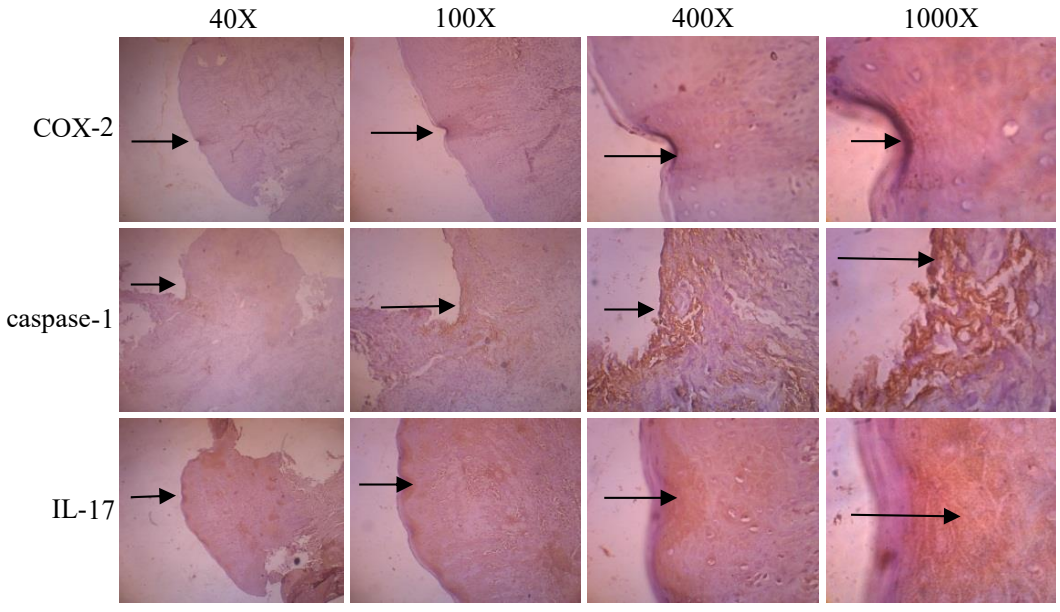

Figure 1. Comparison of the expression of COX-2, caspase-1 and IL-17-produced pericorona epithelial cells.

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one view as 100 cells). Visible expression is categorized as moderate (30-70%).

The data analyzed with a pair t-test is shown in Table 2–5. From this analysis, it can be concluded that the expression of COX-2, caspase-1 and IL-17 proteins are difference beetwen control/healthy and pericoronitis. And the expression of COX-2, caspase-1 and IL-17 as a pro-inflammation cytokine was low (30%-70%) due to Cox-2–PGE-2 feedback system through suppressed NF-κβ proteins (as a central integritor for proteins expression).

DISCUSSION

Inflammation is stimulated by chemical mediators released by injured cells for the purpose of blocking the spread of infection and initiating healing of damaged tissue. Inflammation is strictly regulated by the body where inadequate inflammatory processes can cause damage or persistent infection, while excessive inflammation potentially results in chronic or systemic inflammatory disease.[21–24]

Table 1. Comparison of the expression of COX-2, caspase-1 and IL-17-produced pericorona epithelial cells

	Expression (%)
Cox-2	38.94
casp-1	41.05
IL-17	33.68

Table 2. Paired samples correlations

		N	Correlation	Sig.
Pair 1	Cox-2	38	.914	.000
Pair 2	casp-1	38	.926	.000
Pair 3	IL-17	38	.906	.000

Table 3. Paired samples statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Cox-2	25.0000	38	15.46574	2.50887
Pair 2	casp-1	26.3158	38	16.13642	2.61767
Pair 3	IL-17	22.6316	38	13.54357	2.19706

Table 4. Paired sample test

		Paired differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Cox-2	23.50000	15.00405	2.43398	-28.43171	-18.56829	-9.655	37	.000
Pair 2	Casp-1	24.81579	15.66862	2.54179	-29.96594	-19.66564	-9.763	37	.000
Pair 3	IL-17	21.13158	13.08635	2.12289	-25.43295	-16.83020	-9.954	37	.000

Table 5. Paired sample t-test of COX-2–caspase1, COX-2–IL-17 and caspase1–IL-17

		Paired differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	COX-2–casp-1	-.21053	1.35724	.31137	-.86470	.44364	-.676	18	.508
Pair 2	COX-2–IL-17	.42105	1.16980	.26837	-.14277	.98488	1.569	18	.134
Pair 3	casp-1–IL-17	.63158	1.01163	.23208	.14399	1.11917	2.721	18	.014

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COX)converts arachidonic acid into prostaglandin-H2. Two forms of COX have been identified, namely; COX-1 which is expressed constitutively and COX-2 which is expressed due to growth factors, oncogenes, cytokines and endotoxins.[25,26] LPS is a component of the cell wall of Gram-negative bacteria whose extreme sensitivity activates the inflammatory response via TLR-4. Macrophages activated by LPS show high COX-2 expression.[27]

Caspase-1 is a component of inflammasome which is released when inflammation is active. Caspases-4, -5 and -11 also activate inflammatory NLRP3 in response to LPS. Finally, caspases-4, -5 and -11 are also referred to as caspase-1 activators to promote caspase-1 division.[28–32] The maturation of pro IL-1β and pro IL-18 to IL-1β and IL-18 promoted by caspase-4 has also been proposed,[33,34] but further studies are required to confirm this result. Activation of caspases-4, -5 and -11 has also been shown to lead to pyroptosis.[35] Biochemically, it has been revealed that caspases-4, -5 and -11 will directly trigger the formation of a gasdermin D substrate that leads to the event of pyroptosis by activating non-canonical NLRP3 inflammation.[36] Caspase-1 also triggers gas D mirror to mediate pyroptosis by canonical inflammation.[37–39] In infectious diseases, expression of caspases-1 and -11 regulates the protective response by releasing IL-1β and IL-18 in specific contexts. It can be argued that caspase-1 activation and IL-18 release through NLRP3 inflammation contribute to colorectal cancer protection.[40–42]

Simultaneously, IL-23, IL-1β and IL-18 will induce the expression of IL-17A by Th17 lymphocyte cells, γδ T cells and iNKT cells.[43–46] The direct effect of IL-17A on other cells remains to be explored. To test the hypothesis that IL-18 and IL-1β can stimulate IL-17A secretion in cells has been demonstrated in mice.[47]

The majority of pathological conditions include pyroptosis which can, therefore, be used to identify an infection, hereditary auto-inflammation syndrome and inflammatory bowel disease.[48–51] In a mouse subject suffering from septic shock, the presence of pyroptosis is probably the crucial determinant of mortality resulting from excessive LPS.[52] In conclusion, COX-2, caspase-1 and IL-17 play a significant part in pyroptosis signaling of pericoronitis LTMI with low inflammation.

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