Periodontal pathogen and cholesterol crystal induce NLRP3 inflammasome-mediated interleukin-1β secretion in human macrophages

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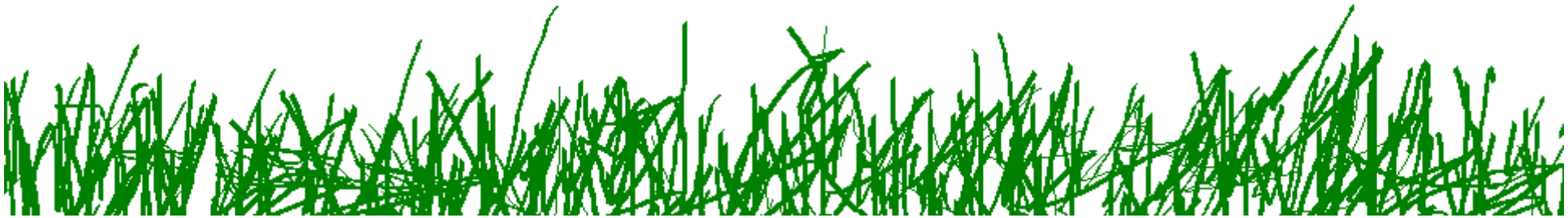
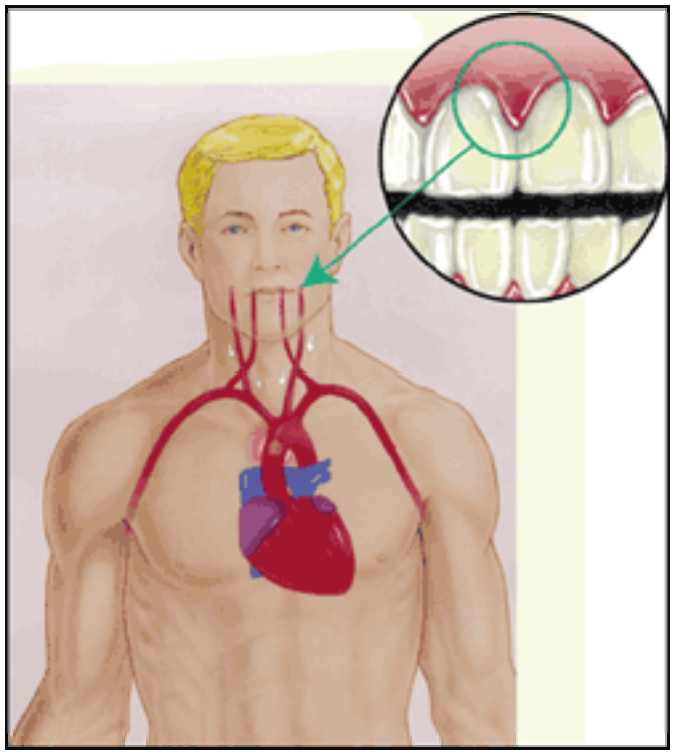


Oral cavity as a part of the body

- Human mouth **has long been recognized** as a infection and connected to the systemic health (Miller, 1890)
- European workshop 2010 : from epidemiologic study, there is a moderate significant association between periodontal disease and cardiovascular disease (Bouchard et al., 2010)



Periodontal disease-Atherosclerosis relationship

Distant chronic infection “**periodontitis**” is one of the candidates

Ulcerated inflamed periodontal pockets

↓

plaque micro-organisms and their products i.e. LPS

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blood vessels in the connective tissue

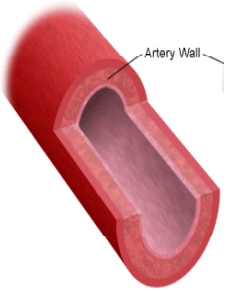
↓

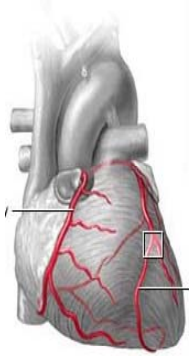
systemic circulation

↓

activate inflammatory & response of artery

(Gibson III et al., 2006)





Periodontal disease-Atherosclerosis relationship

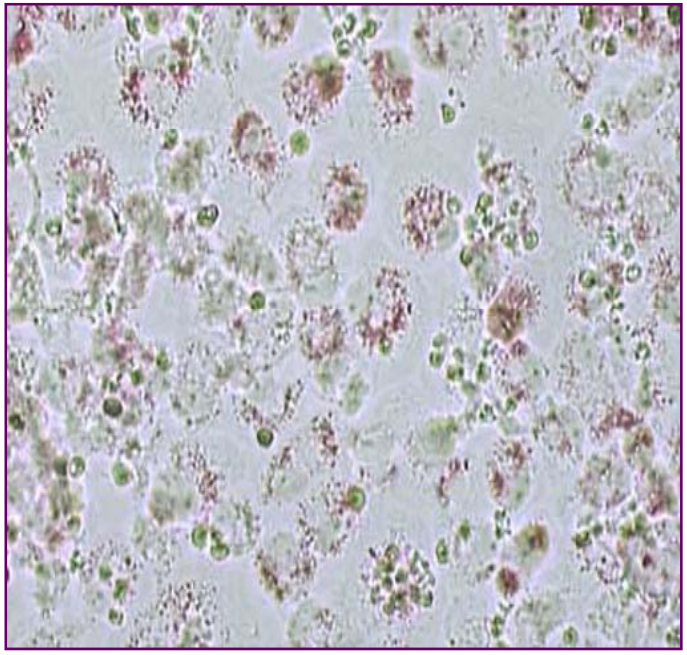
Supporting study :

- key periodontal pathogens such as *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* **could be detected** in **human atherosclerotic lesion**

  (Haraszthy et al., 2000)

- ***P. gingivalis*** **promoted foam cell formation** in the presence of **low density lipoprotein**

  (Giacona et al., 2004)



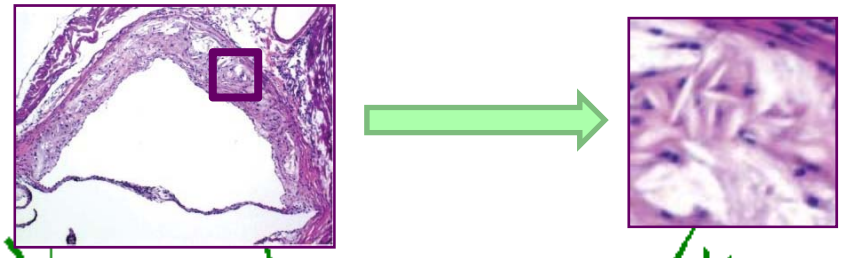
Cholesterol

Early study

- **Cholesterol** : hallmark of late stage of atherosclerotic lesions.
- It could only be observed in the mature atherosclerotic lesions or in the late stage of atherogenesis (Small, 1988)

Breakthrough knowledge

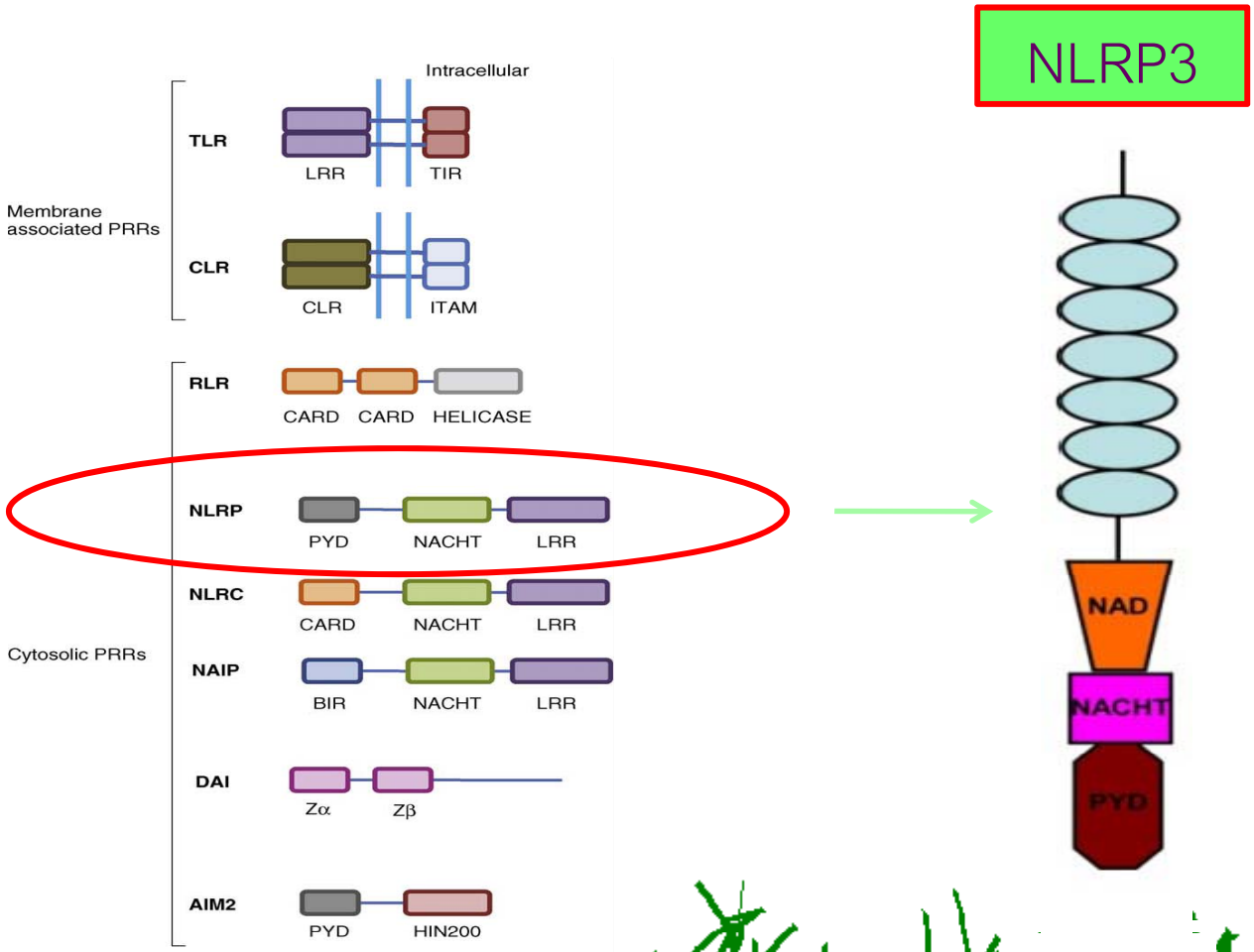
- Recent study (Duewell et al., 2010 Nature) demonstrated that **cholesterol crystals** can be detected at an early stage of the disease development in the atherosclerosis



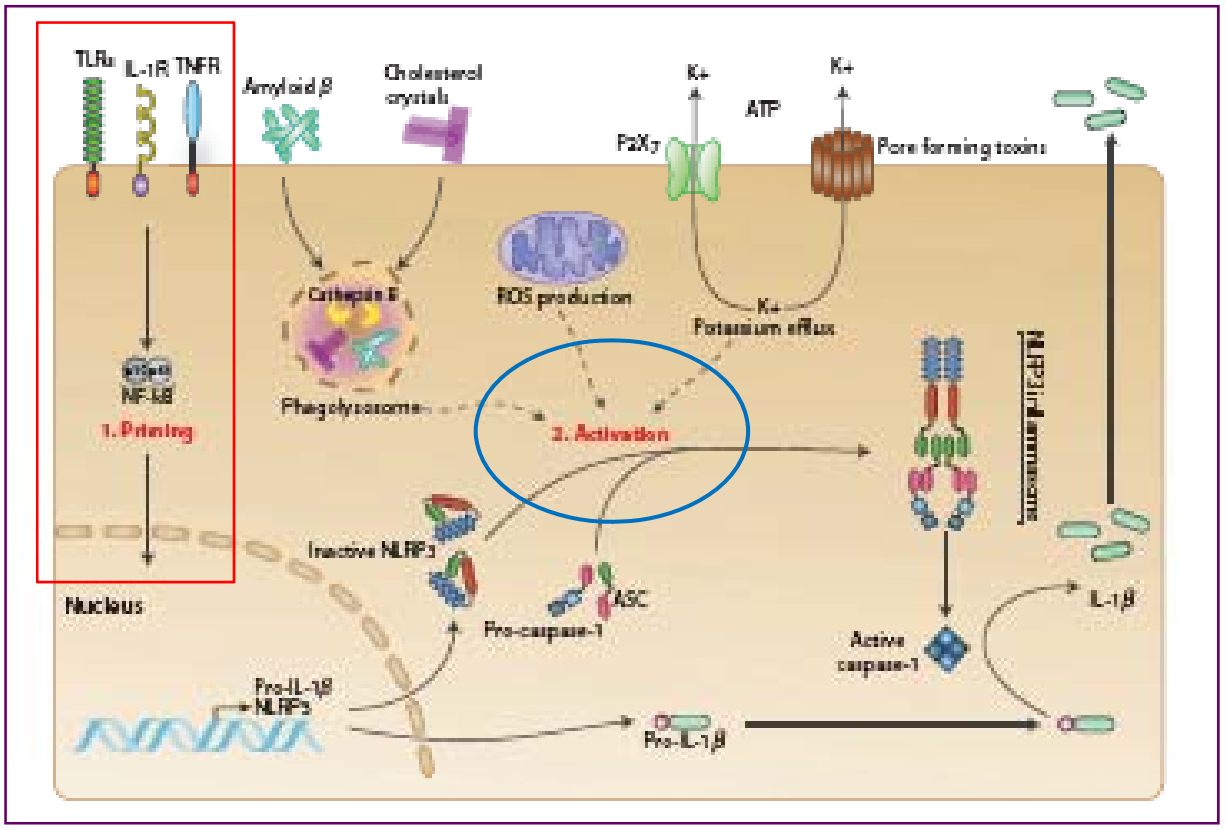
From Duewell Study…

- A novel link between cholesterol crystals and inflammation in atherosclerosis lesion was shown by their ability to activate caspase-1- activating **"nucleotide-binding domain leucine-rich repeated containing family, pyrin domain containing 3" (NLRP3)** in form of INFLAMMASOMES
- results in cleavage and secretion of *Interleukin-1 (IL-1) family cytokines*, in human and mouse macrophages (Rajamaki et al.,2010; Duewell et al.,2010).

NOD-like receptors



NLRP3 inflammasome activation



(Horvath et al., 2011)

Interleukin-1β

- Important proinflammatory cytokines
- Triggers inflammation
- Macrophage : major source (Taylor, 2010)
- Level of IL-1β correlate with disease severity

(Libby, 2002)

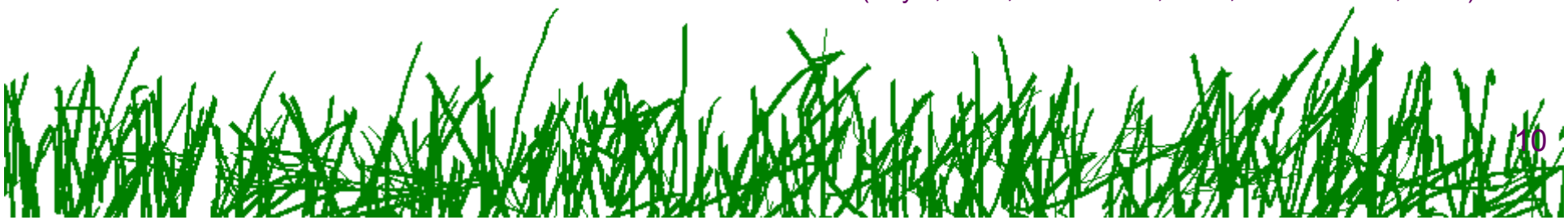
- Requires 2 separate signals for production

(Martinon et al., 2009)

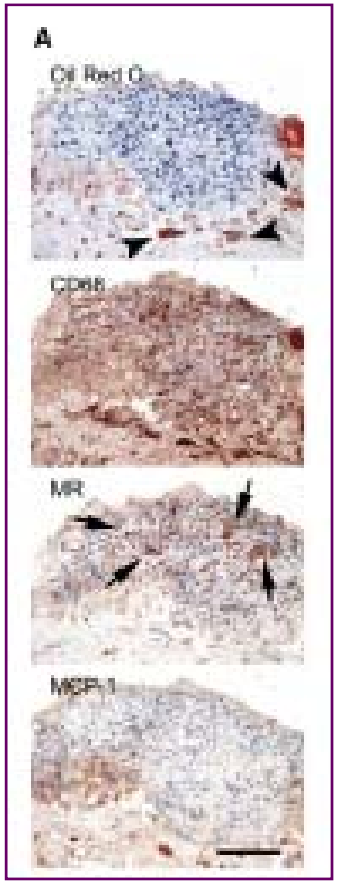
M1 vs M2 macrophage

Characteristics	M1 macrophage	M2 macrophage
Synonym	Classically activated macrophage	Alternatively activated macrophage
Th polarization	Th1	Th2
Stimulating factor	GM-CSF	M-CSF
Morphology	Round shape	Elongated shape
Cell surface markers	$CD14^+$, $CD16^-$, $CD36^-$,$CD163^-$	$CD14^+$, $CD16^+$, $CD36^+$,$CD163^+$

(Boyle, 2005; Waldo et al., 2008; Verreck et al., 2006)



Macrophage phenotypes

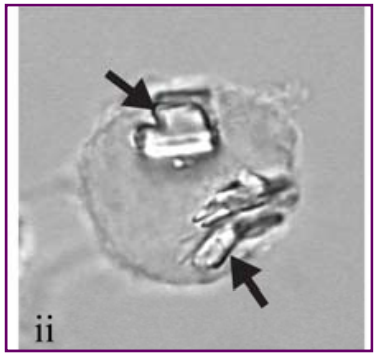


(Brocheriou et al., 2011)

M1

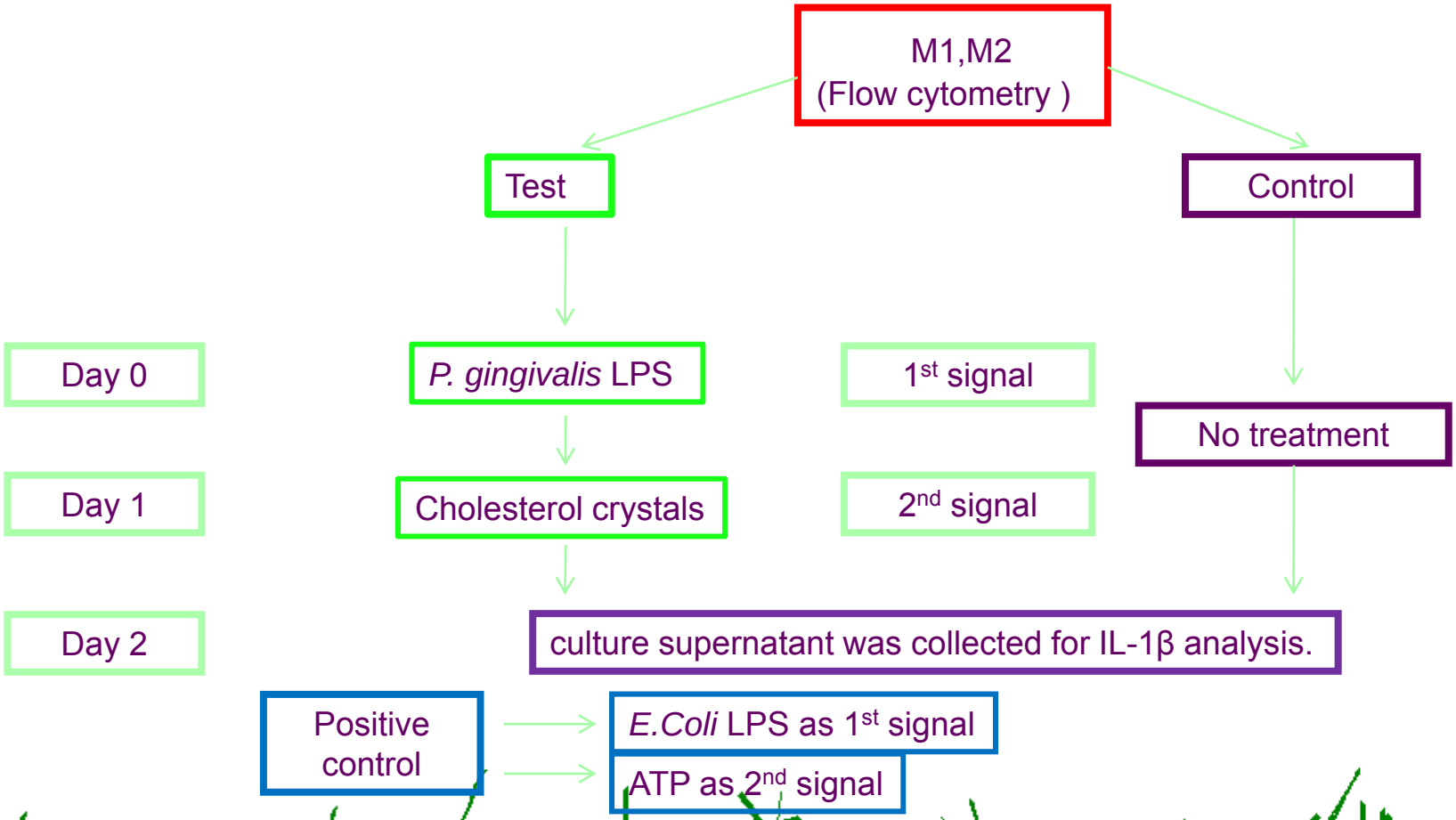
(Duewell et al., 2010)

M2

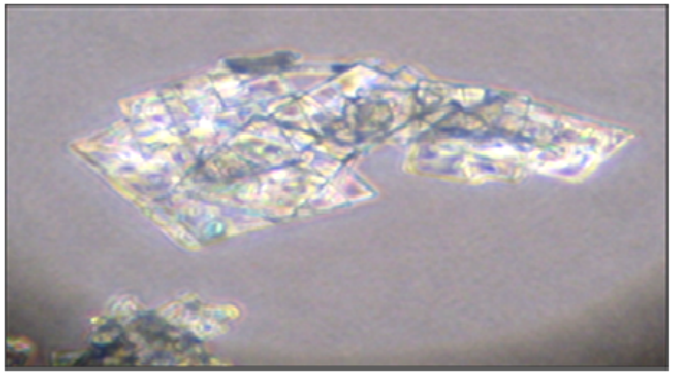


(Rajamaki et al., 2010)

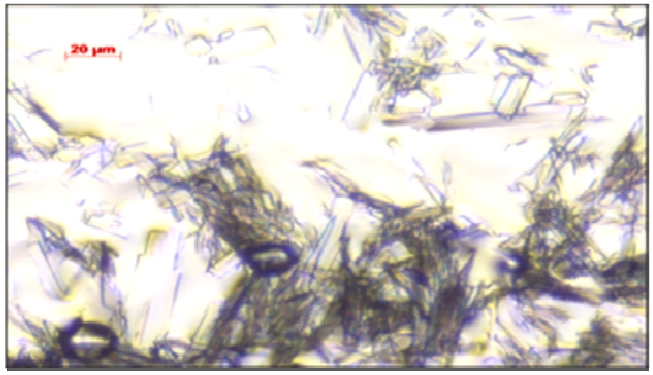
From our research…



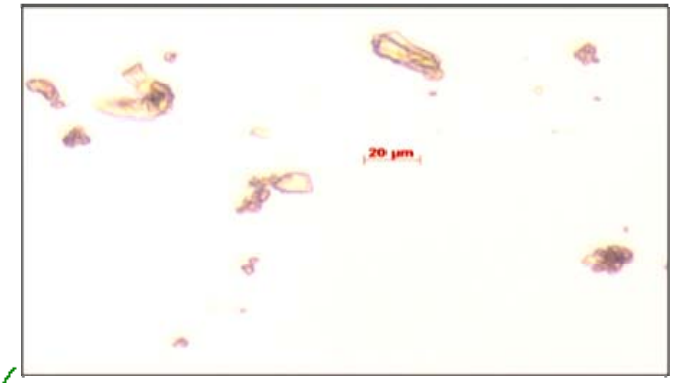
Cholesterol crystals



A: Cholesterol crystal powder

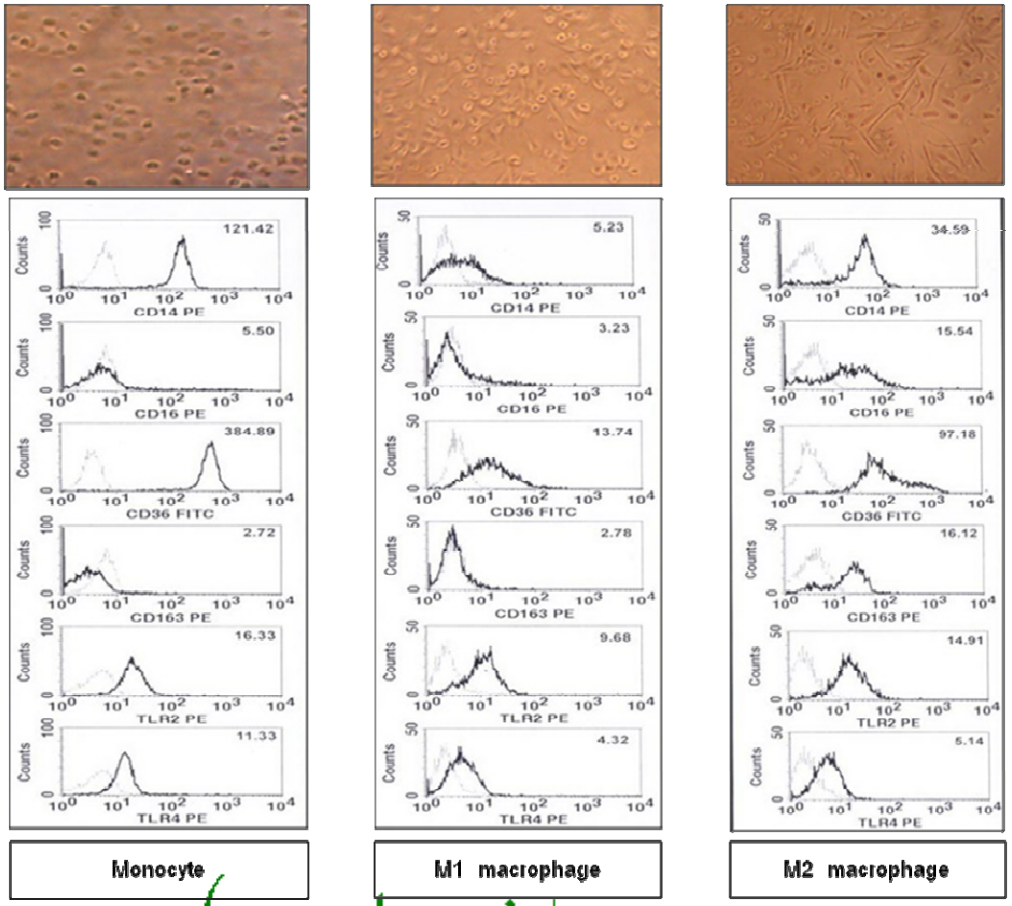


B: 6th recrystalllization

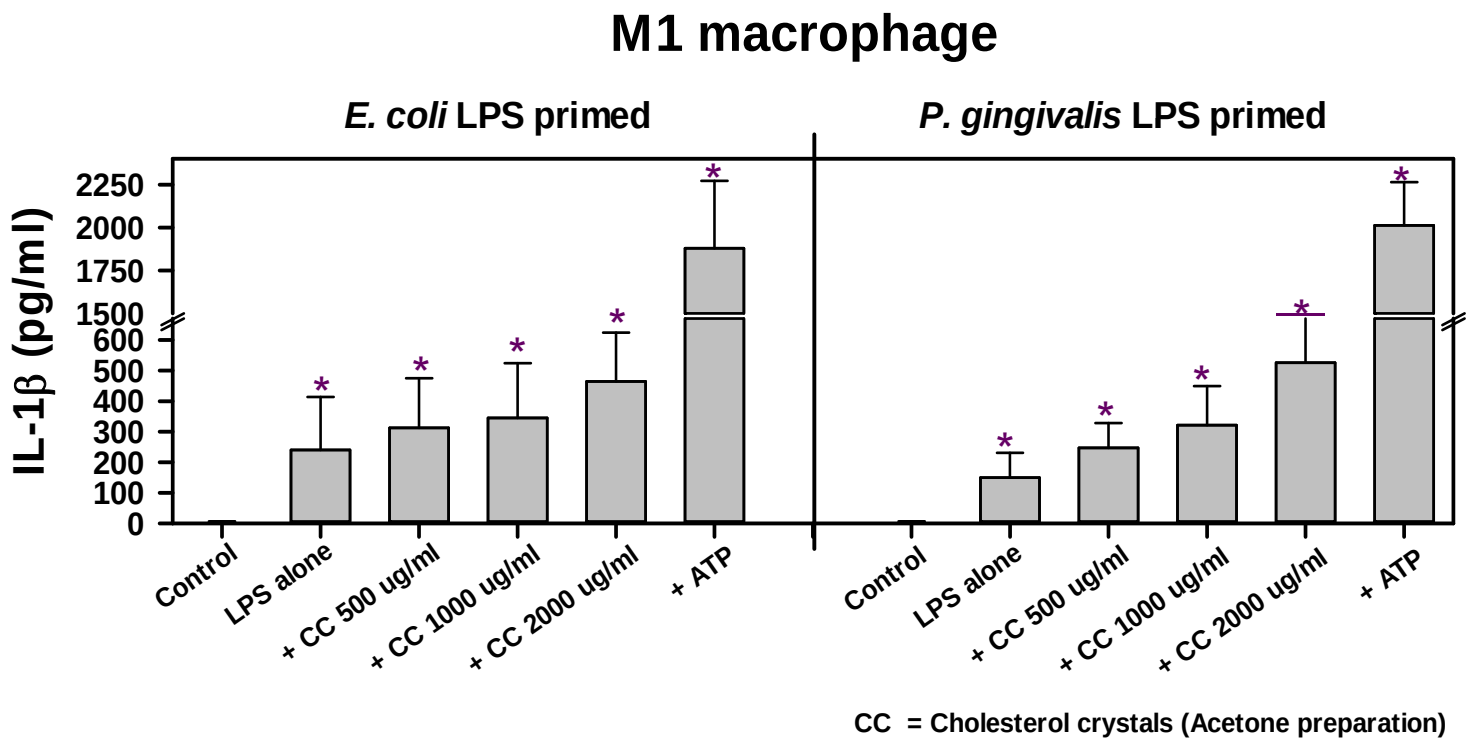


C: Grinded cholesterol crystals

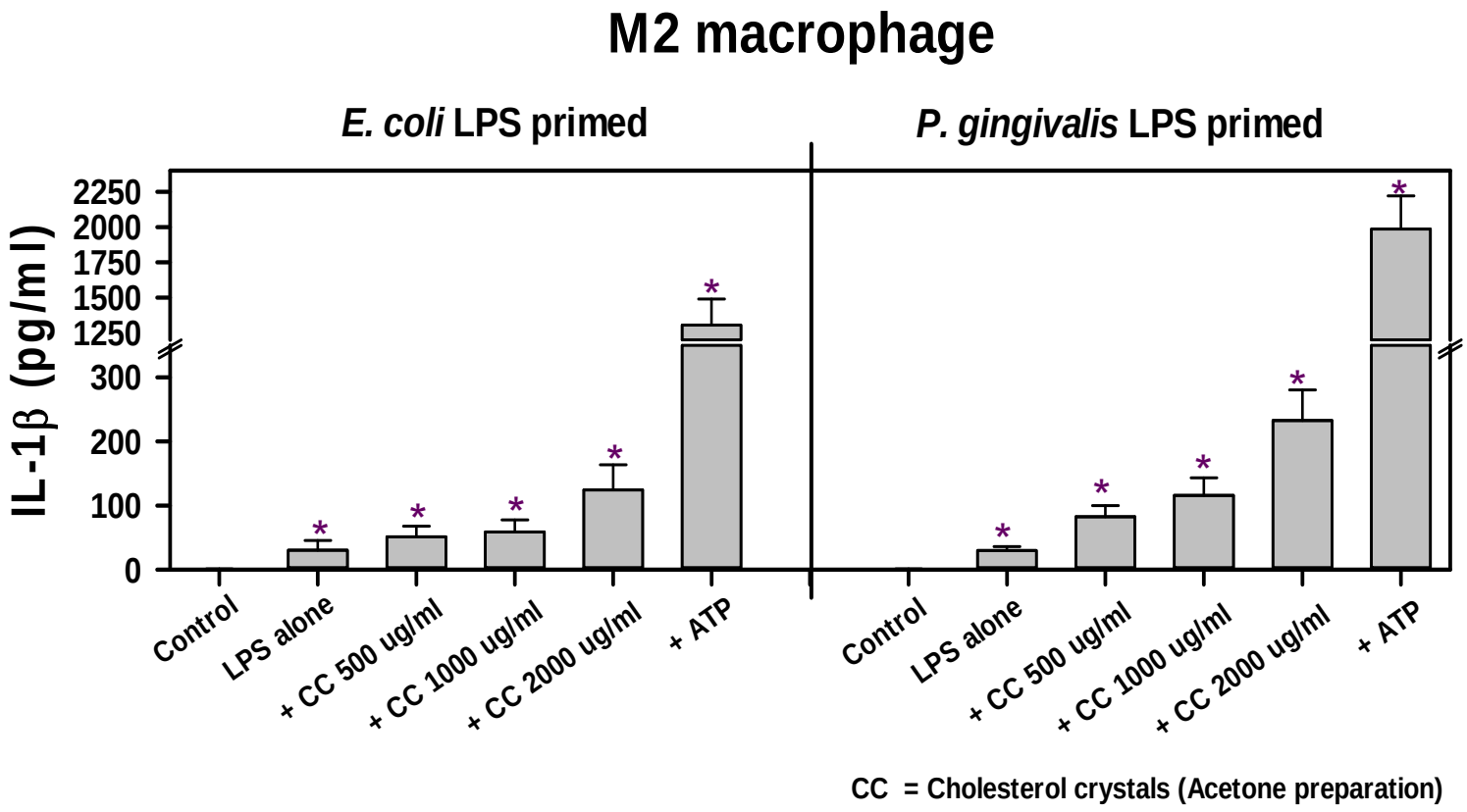
Monocyte and Macrophage Phenotypes



Cytokine production from M1 macrophage



Cytokine production from M2 macrophage



Conclusion

"*P. gingivalis* LPS and cholesterol crystals induced dose-dependent

IL-1ß secretion from both M1 macrophage and M2 macrophage

via NLRP3 inflammasome activation and no significant differences

in IL-1ß production at each concentration of cholesterol crystals

were observed between two types of macrophages "

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