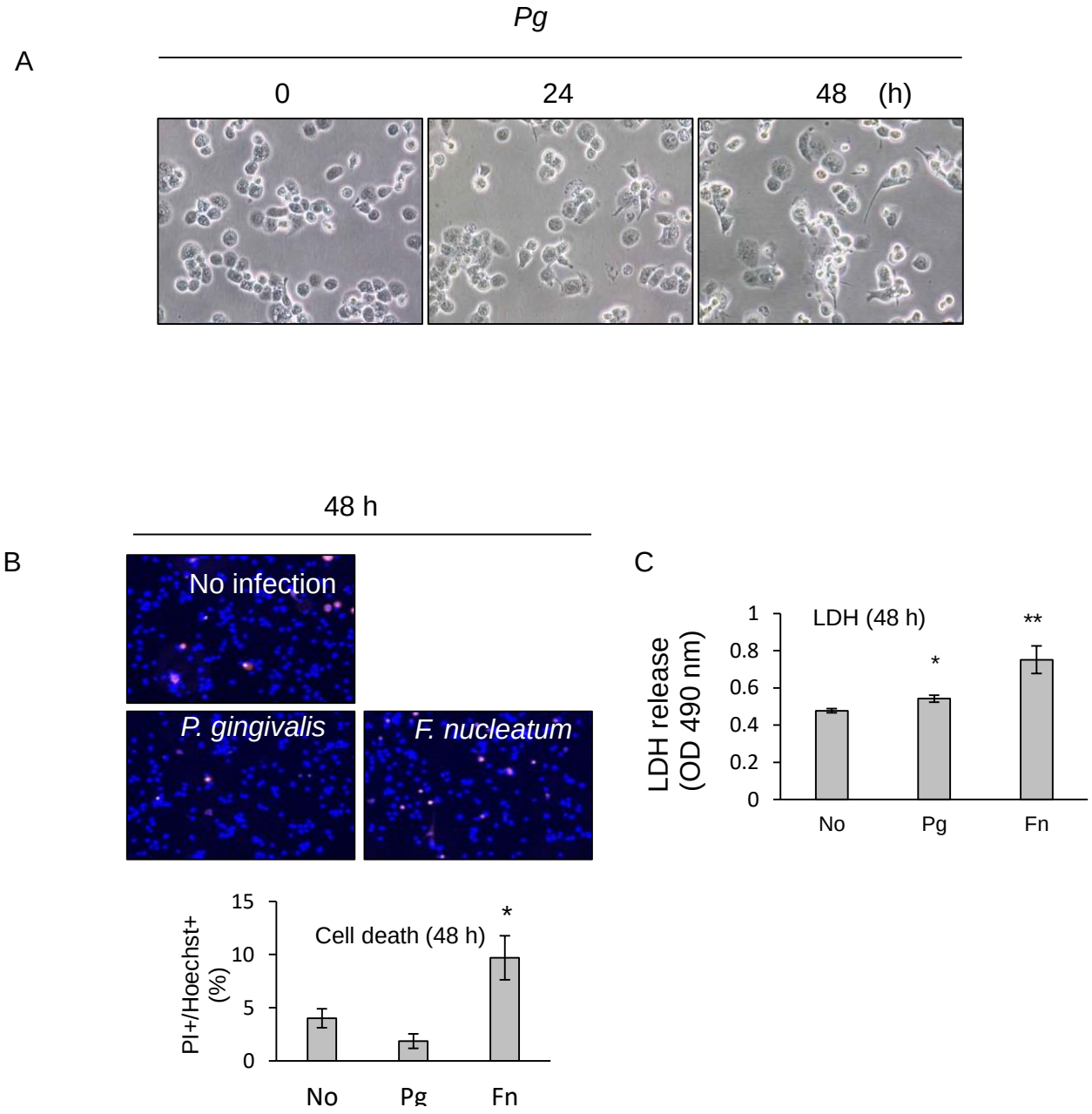
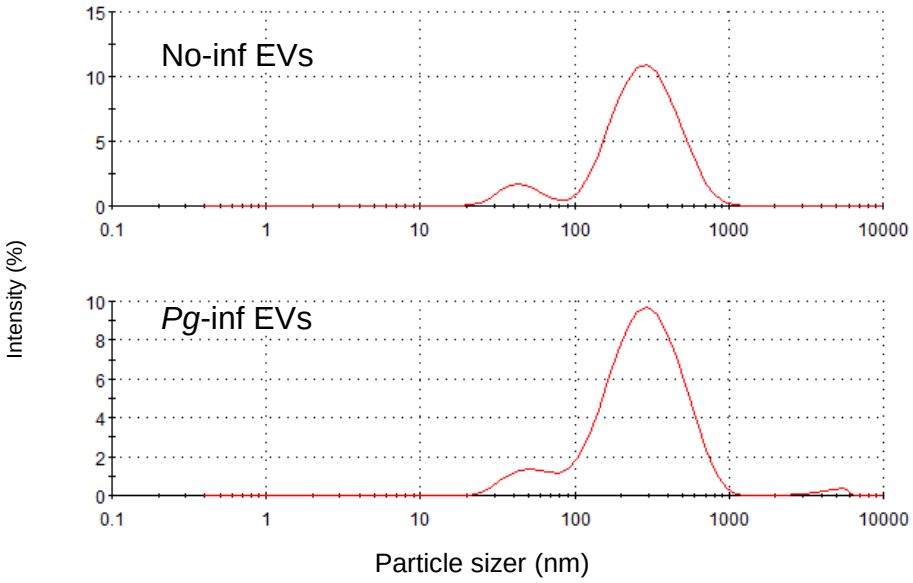


Supplementary Figure 1. ***Pg* treatment did not induce host cell death in THP-1 cells.**
(A) The morphology of *Pg*-treated THP-1 cells. (B). The PI-positive cells were observed using microscopy in THP-1 cells at 48 h post *Pg* or *F. nucleatum* treatment (upper panel). The ratio of PI-positive cells in all Hoechst stained cells is shown in the lower panel. The data are given as the mean ± standard error of the mean. (n = 4). (C) Lactate dehydrogenase (LDH) release was measured in the same cells in B. The data are given as the mean ± standard error of the mean. (n = 4).



No-inf EVs

			diameter (nm)	%Intensity	Width (nm)
Z Average (d.nm)	198.2	**Peak 1:**	317.0	91.0	151.0
PdI:	0.332	**Peak 2:**	46.41	9.0	13.71
Intercept	0.959	**Peak 3:**	0.000	0.0	0.000

***Pg*-inf EVs**

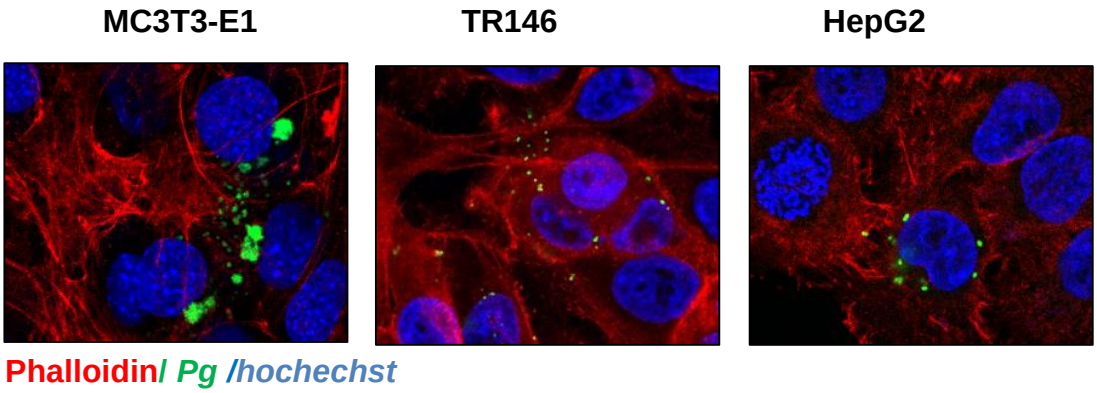
			diameter (nm)	%Intensity	Width (nm)
Z Average (d.nm)	199.8	**Peak 1:**	318.7	90.2	165.3
PdI:	0.370	**Peak 2:**	52.41	8.5	15.63
Intercept	0.928	**Peak 3:**	4455	1.3	899.7

Supplementary Figure 2. **Measurement of particle size of EVs.**
The diameter of EVs from the *Pg* infected THP-1 cells (*Pg*-inf EVs) or noninfected THP-1 cells (No-inf EVs) were measured using a Zetasizer. The means of the particle diameter of the No-inf EVs and *Pg*-inf EVs were 198.2 nm and 199.8 nm, respectively

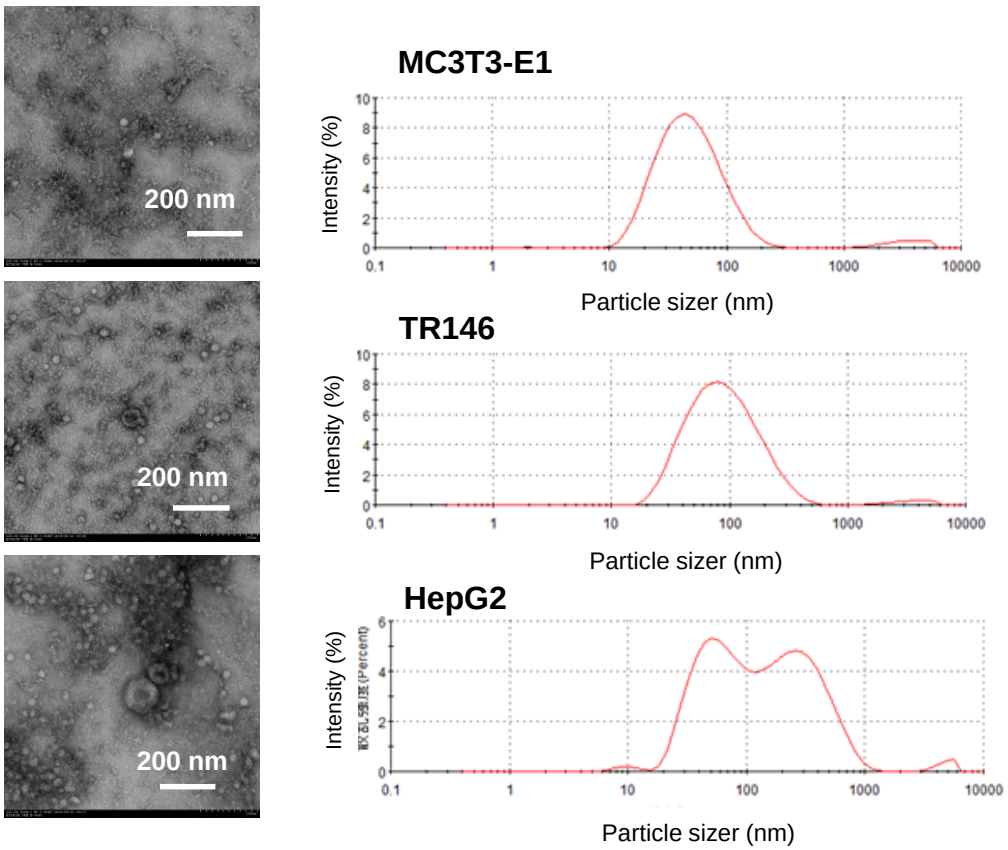
	Description (Mascot score, Accession)				
	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
a	**Histone H2B type-1** (2266, H2B1D_HUMAN)	**Histone H3, 1t** (442, H31T_HUMAN)	**Histone H2A type 1-H** (361, H2A1H_HUMAN)	**Histone H2A type 1-A** (203, H2A1A_HUMAN)	**Histone H2A. V** (190, H2AV_HUMAN)
b	**Histone H2A type 1-H** (1698, H2A1H_HUMAN)	**Histone H2B type-1-C/E/F/G/I** (948, H2B1C_HUMAN)	**Histone H4** (285, H4_HUMAN)	**Single-stranded DNA-binding protein, mitochondrial** (246, SSBP_HUMAN)	**Vesicle-associated membrane protein 3** (172, VAMP3_HUMAN)
c	**Histone H4** (2226, H4_HUMAN)	**Histone H2B type-1-C/E/F/G/I** (1607, H2B1C_HUMAN)	**Histone H2B type-3-B** (1531, H2B3B_HUMAN)	**Desmoplakin** (568, DESP_HUMAN)	**Histone H2A type 1-C** (467, H2A1C_HUMAN)

Supplementary Table 1. **EVs proteins are identified by mass spectrometry.**
Three bands corresponding to the low-molecular-weight proteins shown in figure 2A (a–c) were identified as multiple core histones including histone H2A, H2B, H3, and H4 using Nano-LC-MS/MS.

A

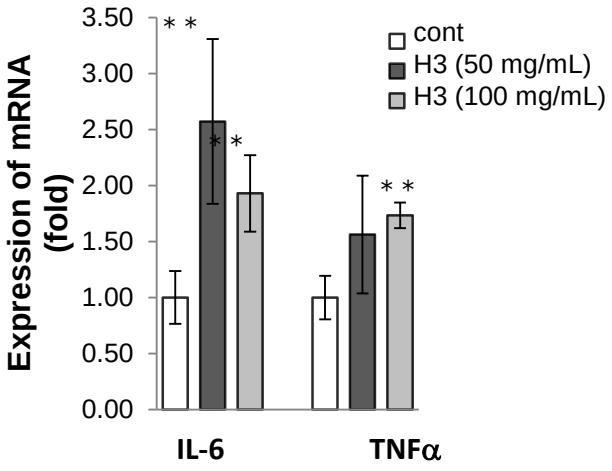


B

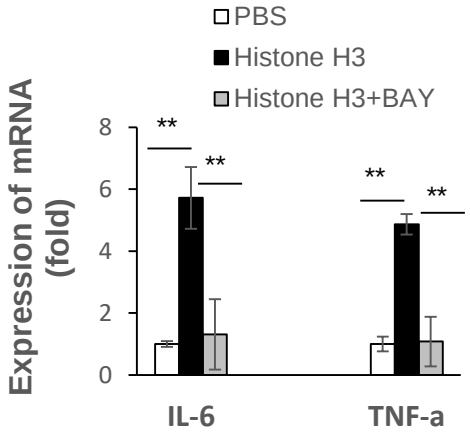


Supplementary Figure 3. **Analysis of EVs released from *Pg*-infected non-phagocytic cells.** Mouse osteoblasts (MC3T3), human gingival epithelial cells (TR146), and human hepatocytes (HepG2) were infected with green fluorescent-labeled *Pg* for 4 h. (A). The invaded *Pg* inside the cells was observed using confocal microscopy. (B). The non-phagocytic cells shown as A were infected with *Pg*, and then EVs were isolated from the cultured media at 48 h post-infection. The diameter of the EVs was measured using a Zetasizer. The mean particle diameter was 40.92 nm in MC3T3-E1 cells; 64.84 nm in TR cells; 83.89 nm in HepG2 cells.

A

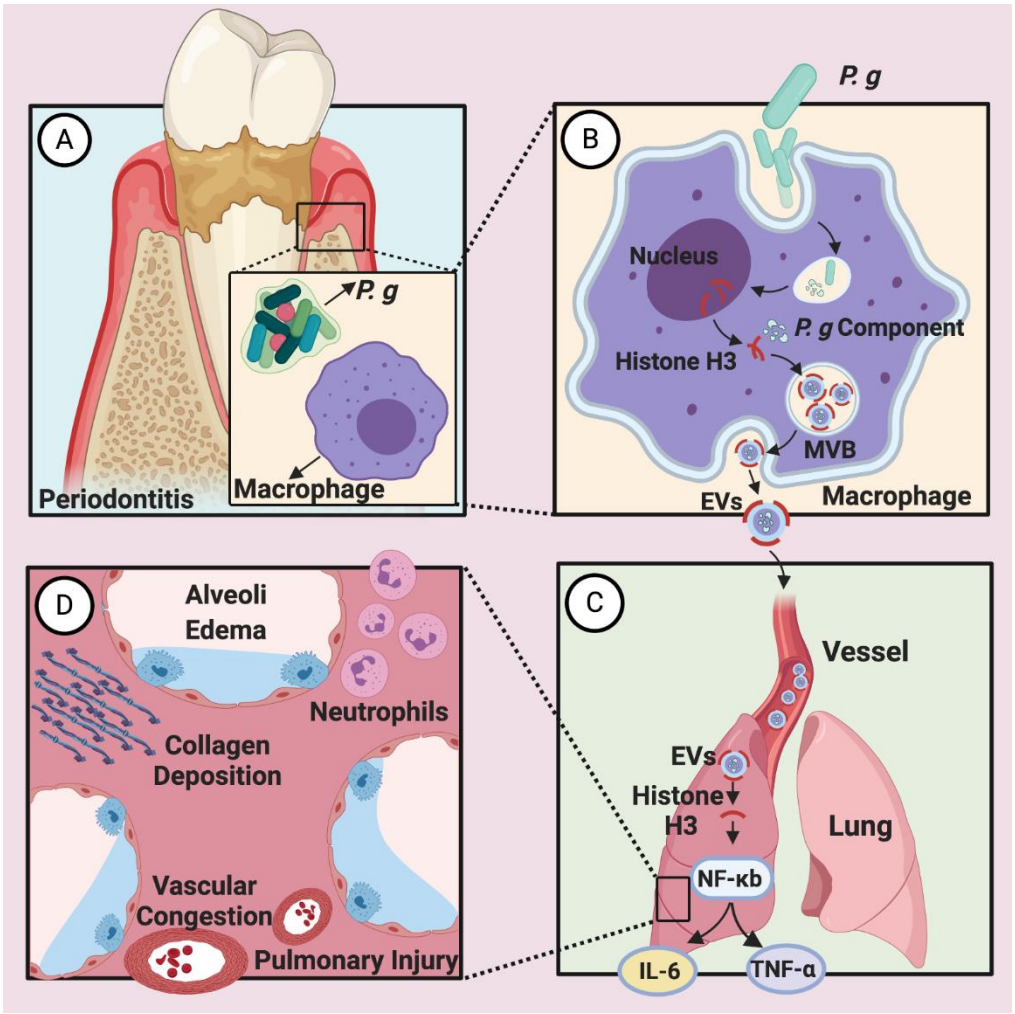


B



Supplementary Figure 4. **Recombinant histone H3 increased inflammatory cytokines via the NF-κB pathway in A549 cells.**

(A). A549 cells were treated with recombinant human histone H3 for 4 h, and then mRNA expressions were analyzed using real-time PCR. (B). The mRNA expressions were analyzed using real-time PCR in recombinant histone H3-treated A549 cells in the presence of NF-κB inhibitor, BAY. The data are given as the mean ± standard error of the mean (n = 4). * $p < 0.05$, ** $p < 0.01$ compared with each control group.



Supplementary Figure 5. **Our proposal model.**
In periodontitis, macrophages are infected with *Pg*, periodontal bacteria (A), and released extracellular vesicles (EVs) which included histone H3 (B). These EVs translocated to the lungs through blood circulation, and there histone H3 induced cytokines by NF–κB pathways (C), resulting in pulmonary injury such as edema, vascular congestion and collagen deposition (D).