The Roles of Periodontal Bacteria in Atherosclerosis

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Atherosclerosis (AS) is an inflammatory vascular disease that constitutes a major underlying cause of cardiovascular diseases (CVD) and stroke. Infection is a contributing risk factor for AS. Epidemiological evidence has implicated individuals afflicted by periodontitis displaying an increased susceptibility to AS and CVD.

atherosclerosis CVD periodontal pathogens Porphyromonas gingivalis Aggregatibacter actinomycetemcomitans Fusobacterium nucleatum plaque

1. Introduction

Atherosclerotic cardiovascular disease (CVD) is a major public health problem of all humankind. It is the primary contributor to death and disability and accounts for 1/3 of the deaths in the world [1][2]. Atherosclerosis (AS) is one of the most common causes of CVD. Stenosis, obstruction or rupture of blood vessels can lead to ischemic CVDs such as myocardial infarction, stroke, and limb ischemia [3]. AS is considered to be a chronic inflammatory disease of the arterial wall caused by a variety of stimulating factors, characterized by the formation, progression, and instability of atherosclerotic plaques. It often involves medium and large arteries. The development of AS is a long-term and slow accumulation process. It usually begins with the injury of the vascular endothelial barrier and is followed by cholesterol-rich lipoprotein accumulating subcutaneously. Vascular smooth muscle cells (VSMCs) migrate from vascular media to subendothelium, proliferate and synthesize extracellular matrix (ECM), resulting in intimal thickening, which is called diffuse intimal thickening (DIT). Subsequently, the resident VSMCs and blood monocyte-derived macrophages recruited in the subendothelial space uncontrolled uptake modified lipoproteins by scavenger receptors, transforming into lipid-rich cells called “foam cells” and leading to the formation and enlargement of AS plaques. With the death of cells and the disfunction of efferocytosis, the arterial plaque gradually becomes unstable, exhibits necrosis and calcification, or even ruptures and detaches to form a thrombus [4].

Traditional risk factors for AS include lifestyle factors, primarily smoking, dyslipidemia, hypertension, and altered glucose metabolism [5]. Studies in recent decades have revealed that infection plays an important role in AS. Beginning with Fabricant and colleagues, who induced AS in chickens by Marek’s disease virus infection and prevented atherosclerotic changes by vaccination [6], microbial infections such as herpes simplex virus [7], *Chlamydia pneumoniae* [8], *Porphyromonas gingivalis* (*Pg*) [9], *Helicobacter pylori* [10], influenza A virus [11], hepatitis C virus [12], cytomegalovirus [13], and HIV [14] have all been identified as risk factors for AS.

As one of the four major human bacterial reservoirs, more than 700 bacterial species exist in the oral cavity [15][16]. It is worth noting that these bacteria maintain an ecological balance within a healthy periodontium. However, in the presence of periodontal disease, microbial dysbiosis emerges, leading to a shift from Gram-positive anaerobic bacteria to Gram-negative anaerobic bacteria. Consequently, certain bacteria opportunistically acquire pathogenic capabilities, further exacerbating the pathogenesis of the disease [17][18]. Local or systemic infections of oral origin are prevalent in the human population; for example, periodontitis is the sixth most prevalent disease on a worldwide scale, with a global prevalence of 45–50% [19]. It not only contributes to the destruction of local tissues but is also related to the development of a variety of systemic diseases such as AS. The American Heart Association (AHA) acknowledges the correlation between periodontal disease (PD) and atherosclerotic cardiovascular disease, irrespective of known confounding factors [20]. Epidemiologic evidence shows that the incidence of AS in patients with periodontitis is 1.27 times higher than that in patients without periodontitis [21].

Oral bacteria can cause temporary bacteremia during some therapy like periodontal treatment, tooth extraction or during daily oral hygiene practices such as chewing, brushing, and flossing, especially in subjects with existing periodontitis and dental pulp infections. Periodontal pathogens can reach distant organs through the blood. Researchers have detected DNA of periodontitis pathogen from atherosclerotic plaques [22][23], providing direct evidence for the link between periodontitis and AS. The main periodontal pathogens detected in the plaques include *Pg*, *Aggregatibacter actinomycetemcomitans* (*Aa*), *Fusobacterium nucleatum* (*Fn*), *Prevotella intermedia* (*Pi*), *Tannerella forsythia* (*Tf*), *Treponema denticola* (*Td*), and *Campylobacter rectus* (*Cr*). In addition, several benign species associated with dental plaque on the tooth surface were detected in the plaques [24].

2. *Porphyromonas gingivalis*

Pg is a dark, lytic, nonmotile, Gram-negative obligate anaerobes that derive energy from the fermentation of amino acids, which facilitates its survival in the subgingival sulcus and periodontal pockets. *Pg* is a main pathogen of periodontitis, and it forms the “red complex” with *Tf* and *Td*, which is responsible for the severe clinical manifestation of periodontal disease. *Pg* is one of the most common bacteria found in the subgingival biofilm of patients with periodontitis [25][26]. A retrospective study conducted in Germany involving 7804 adults diagnosed with periodontitis reported a detection rate of 68.2% for *Pg* in the biofilm of periodontal pockets [27]. *Pg* has a variety of virulence factors, such as lipopolysaccharide (LPS) on the bacterial outer membrane, which can activate the pathogen-related pattern recognition receptor signaling pathway, cause inflammatory response and the secretion of cytokines. Gingipains are trypsin-like cysteine proteinases generated by *Pg* that can cleave laminin, fibronectin, and collagen, activate complement pathways, and induce dysregulation of coagulation and fibrinolytic pathways.

Endothelial Barrier Disruption

Endothelial dysfunction is an early cardiovascular response to stimuli and is considered an “alarm” of AS. After entrance to the blood, *Pg* adheres to the cell surface of endothelial cells (ECs) via a variety of adhesins (including fimA and HagB) to interact with E-selectin, vascular cell adhesion molecule 1 (VCAM-1), intercellular cell adhesion

molecule 1 (ICAM-1), and other molecules on the cell surface [28][29][30]. It can also be internalized into ECs by lipid rafts on the cell membrane.

Pg can suppress the proliferation of vascular ECs and induce cell apoptosis, thus destroying the endothelial barrier [31]. It is evidenced that gingipains can cleave neural cadherin and vascular endothelial cadherin, and degrade integrin β1, making ECs disconnect from the ECM, and come to anoikis [32][33]. Systemic inflammation induced by *Pg* can also promote the endothelial–mesenchymal transition (EndMT) of ECs, thereby promoting the fibrosis of arterial plaques and destroying the permeability and integrity of the vessel wall [34]. *Pg*-activated ECs secrete angiotensin II and pro-inflammatory cytokines such as interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF), amplifying vascular inflammation and arterial hypertension [35].

Vascular oxidative stress is one of the pathological mechanisms of many cardiovascular diseases, including AS, hypercholesterolemia, hypertension, and diabetes mellitus [36]. Excessive or sustained reactive oxygen species (ROS) are the main characteristic of oxidative stress. *Pg* can promote ROS production in multiple ways. It is identified that *Pg* can motivate DNA methyltransferase 1 (DNMT-1) to methylate basic helix-loop-helix ARNT like 1 (BMAL1) promoter via activating TLRs-NF-κB signal axis, followed by the restrain of BMAL1 expression and release of circadian locomotor output cycles kaput (CLOCK). In turn, CLOCK phosphorylates P65 and further enhances the NF-κB signal, which aggravates oxidative stress and inflammatory response in human aortic ECs, thereby aggravating vascular endothelial injury and promoting the progress of AS [22]. *Pg* is also able to reduce the antioxidant mechanism and accelerate the oxidative damage of ECs through the NOS/BH4/Nrf2/GSK-3β pathway [37].

Monocyte Adherence and Aggregation

Monocyte recruitment to the endothelium is a crucial step in AS. Endothelium injury causes the subsequent chemotaxis and aggregation of monocytes to the subendothelium. *Pg* upregulates the expression of MCP-1, ICAM-1, VCAM-1, and E- selectin in ECs, and the expression of C-C chemokine receptor 2 (CCR2) and integrinαMβ2 in monocytes, promotes the adhesion and aggregation of monocytes to the endothelium [38][39][40][41][42]. The NF-κB pathway plays a vital role in this process. Restraint of the NF-κB pathway can abrogate ICAM-1 expression in ECs [43]. NOD1, an intracellular pattern recognition reporter, is overexpressed in *Pg*-infected ECs. After NOD1 recognizes *Pg*, the expression of ICAM-1 and VCAM-1 in ECs is up-regulated through the NF-κB signaling pathway [39]. Gas6 inhibits *Pg*-LPS-induced monocyte–endothelial cell interaction in vitro through the Akt/NF-κB pathway [44]. Macrophage migration inhibitory factor (MIF) secreted is augmented in *Pg*-infected ECs, which binds to CD74 and CXCR4 on the surface of ECs to form a receptor–ligand complex and activates ECs to express more ICAM-1 [45]. Exposure to *Pg* induces the increased expression of these adhesion molecules and attracts a large number of monocytes to accumulate in the subendothelium of the artery, which results in extensive secretion of inflammatory factors and exacerbates vascular and systemic inflammation [34][46].

Foam Cell Formation

The formation of foam cells is a hallmark of AS. Macrophages serve as one of the primary sources of foam cells in plaque. *Pg* and its components, including outer membrane vesicles (OMVs), can boost the binding and phagocytosis of macrophages to low-density lipoprotein (LDL), and macrophage-mediated modification of LDL [47]. *Pg* can increase the expression of CD36, a scavenger receptor that mediates cholesterol uptake through the c-Jun-AP-1 pathway [48] or ERK/NF-κB [49], as well as lysosomal integral membrane protein 2 (LIMP2) involved in cholesterol transport [50][51], so as to intensify the lipid accumulation of macrophages. *Pg*-infected macrophages up-regulate fatty acid binding protein 4 (FABP4), an intracellular transport protein for fatty acids, presenting more intake of fatty acids [52]. Moreover, a notable positive association was observed between serum *Pg* antibody and FABP4 level in clinical periodontitis patients, suggesting that *Pg* can promote AS and other systemic diseases by affecting FABP4 [52].

Calcification and Angiogenesis in Plaque

In the advanced stages of AS, the presence of calcium deposition within plaques, known as calcification, is frequently observed. Calcified plaques contribute to luminal narrowing and impede blood flow. However, it is worth noting that there is a prevailing viewpoint suggesting that calcified plaques exhibit greater stability and reduced susceptibility to rupture compared to non-calcified plaques. VSMCs also constitute a large portion of the plaque. *Pg* promotes phenotypic transformation, apoptosis, and matrix vesicle release of VSMCs, and consequently intensifies inorganic phosphate-induced vascular calcification [53]. *Pg* boosted VSMCs proliferation and intimal hyperplasia, and the expression of vascular cell proliferative phenotypic markers S100 calcium-binding protein A9 (S100A9) and embryonic isoform of smooth muscle myosin heavy chain (SMemb) was observed higher on the surface of VSMCs of *Pg*-infected mice and in aneurysm specimens from *Pg*-infected patients [54][55].

In response to the oxygen and nutrient demands, new blood vessels gradually form within the growing plaque, while they are often structurally abnormal and fragile. Angiogenesis may cause leakage of blood cells and inflammatory cells into the plaque, or even rupture and lead to intraplaque hemorrhage. Microarray analysis revealed that gingipains influence the focal adhesion activation, ECM receptor interactions, and the actin cytoskeleton pathway of *Pg*-mediated VSMCs, suggesting an impact on VSMC motility, phenotype transition, and angiogenesis processes [56]. *Pg* and its gingipains have been demonstrated to facilitate the upregulation of the high angiopoietin 2 (Angpt2)/Angpt1 expression ratio in VSMCs, manifesting their potential involvement in promoting vascular neogenesis, SMC proliferation, and pro-inflammatory phenotypic changes. Conversely, fimbriae and LPS lack the ability to elicit similar effects [57].

Plaque Destabilization

There is currently a dearth of research regarding the association between *Pg* and plaque destabilization in AS. A study conducted in 2017 demonstrated that *Pg* can facilitate the imbalance between Th17 and Treg cells, and encourage intra-plaque inflammation by modulating T cell differentiation during the progression of AS. This contributed to an enlarged AS lesion area, accompanied by an escalation in macrophage content and a reduction in VSMC area, thereby fostering plaque instability [58]. *Pg* also triggered macrophages to secret MMP9, thereby

inducing the fragmentation of vascular type IV collagen, which weakened the structural support of the plaque and worsen its destabilized [59]. Be, the heightened vascular inflammation, also impairs plaque stability [60].

3. *Aggregatibacter actinomycetemcomitans*

Aa, a Gram-negative facultent-anaerobic coccobacillus, is the predominant bacterium isolated from caries in adolescents and adults with stage Ⅲ or Ⅳ periodontitis [61] and can lead to premature tooth loss. *Aa* is also one of the major bacteria in the subgingival biofilm of patients with periodontitis [26]. Ramin Akhi et al. observed that the levels of salivary IgA antibodies to MAA-LDL (p = 0.034) and *Aa*-HSP60 (p = 0.045) increased with an elevated number of teeth with probing depths of 4–5 mm, which may suggest the cross-activation of the humoral immune may potentially mediate the association between PD and systemic disorders [62]. Pili is an important structure for *Aa* adhesion to the host. Isolated *Aa* pili contained a low molecular mass protein (about 6.5 kDa), called Flp, and a small amount of a 54-kda protein, called Fup [63]. Examination of the binding of Aa to hydroxyapatite surfaces coated with saliva exhibited a highly adhesive interaction that seemed to rely on the formation of glycoconjugates [64]. In an oral colonization model infected with the Flp mutant of *Aa*, the absence of soft tissue or plaque colonization, as well as the absence of bone loss, in the Flp mutant of Aa, provides compelling evidence supporting the critical role of Flp in *Aa*'s virulence [65].

Aa is known to generate two types of toxins, LtxA and cytolethal-distending toxins (Cdts). LtxA binds with lymphocyte function-associated antigen-1 (LFA-1; CD11a/CD18), the receptor for LtxA on leukocytes [66][67][68], to induce macrophages pyroptosis and activation of inflammasome to release inflammatory cytokines and induce secondary immune response [69]. *Aa* has a significant impact on inflammation as well as the aggregation and adhesion of monocytes by up-regulating ICAM-1 and VCAM-1 on ECs [70] and macrophages [71][72]. LtxA can also arrest the G2/M phase of the cell cycle in microvascular ECs, thus hindering cell proliferation and driving cell apoptosis [70]. LPS of *Aa* can induce TNF-α and IL-1β production, and restrain the expression of scavenger receptor class B type-I (SR-BI) and ABCA1 in macrophages, followed by augmented cholesterol accumulation [73]. Infection with *Aa* elevates serum and intramural levels of TH17 cell-related factors, such as IL-1β, IL-17, IL-6, TGF-β, and IL-1β, indicating a potential induction of TH17 activation and the promotion of vascular inflammation [74]. This evidence illustrates a certain correlation between *Aa* and CVD. Cdts, a heterotrimeric AB2 toxin, can be internalized into cells and induce cell-cycle retardation and apoptosis in lymphocytes and other cell types [75].

4. *Fusobacterium nucleatum*

Fn is a species of bacteria that belongs to the genus Fusobacterium. It is a Gram-negative anaerobic bacterium. *Fn* acts as a bridge bacterium, facilitating the adherence of other bacteria to form complex microbial communities. It exhibits various virulence factors that contribute to its pathogenicity, including adhesins such as adhesin FadA and Fap2 [76], outer membrane proteins like radial proteins D [76], hemagglutinins, secreted toxins like butyric acid [77], LPS, and some proteases.

Recent studies have elucidated that *Fn* can enhance EC permeability and reduce the abundance of EC adhesion molecule-1, leading to endothelial dysfunction [78]. *Fn* has been shown to impair ECs proliferation and induce apoptosis [79][80]. *Fn* and its GroEL *Fn* are capable to upregulate the expression of chemotactic factors, including MCP1 and IL-8, as well as cell adhesion molecules including ICAM-1, VCAM-1, and E-selectin in ECs [81]. *Fn* also disrupts lipid metabolism and transport processes. *Fn* fosters hepatic glycolysis and lipid synthesis through the PI3K/Akt/mTOR signaling pathway, thus uplifting plasma lipid concentrations and exacerbating AS in mice [82]. *Fn*-infected macrophages exhibit an activation of the PI3K-AKT/MAPK/NF-κB signaling pathway, propelling the inflammatory responses and cholesterol uptake, concurrently reducing lipid excretion, leading to lipid deposition [83].

5. *Prevotella intermedia*

Pi, a Gram-negative bacterium, is a dominant bacterium of periodontitis and is predominant in adult patients with periodontitis [84][85]. Two genotypes, I and II, have been identified for *Pi* [86]. In 1992, Harou N N Shan et al. identified a new genetic group in the *Pi* strain, which was significantly different from genotype I in terms of DNA–DNA hybridization characteristics and peptidase and lipase activities. The new species was named *Prevotella nigrescens* (*Pn*) [87]. *Pi* and *Pn* can simultaneously exist in oral mucosa, the tongue, and tonsils, as well as in subgingival plaque in deep periodontal pockets [88][89]. Some studies have proposed that *Pn* strains are associated with healthy sites, whereas *Pi* strains are isolated from deeper sites of periodontal lesions and are thought to connect with periodontal breakdown [90][91][92]. In addition to periodontitis, *Pi* is also found to be abundant in colorectal cancer [93]. Moreover, *Pi* has been linked to subclinical hypothyroidism [94], infectious endocarditis [95], and other related conditions.

Currently, research on the impact of *Pi* on macrophages is limited. The pro-inflammatory effect of Pi on macrophages may aggravate the progression of AS. LPS is the major virulence factor of Pi. Similar to the LPS of *Pg*, the LPS of Pi differs greatly in the structure from LPS of Escherichia coli. Pi-LPS contains fewer and longer fatty acids than *E. coli*-type lipid A [96]. Pi-derived LPS can attract the production of macrophage inflammatory mediators such as nitric oxide (NO), IL-1β, and IL-6 through TLR4 signaling pathway [97]. In addition, a novel non-endotoxin protein, prevotella glycoprotein, was isolated from *Pi*, which is composed of carbohydrates and protein and is free of fatty acids [98]. PCG raises IL-8 production by human monocyte THP-1 cells and motivates human and mouse monocytes through CD14 and TLR2 but not TLR4-dependent pathways [99].

6. *Tannerella forsythia*

Tf is an anaerobic Gram-negative member of the *Cytophaga-Bacteroides* family. It was first isolated by the Forsyth Institute in the 1970s from subjects with advanced progressive periodontitis, and originally described as Fusiform Bacteroides [85]. According to the 16S rRNA phylogenetic analysis, it was reclassified to *Tf* [100][101]. *Tf* is one of the members of the “red complex”, and participates in the development of gingivitis and periodontitis. Multiple research studies have successfully detected *Tf* in the subgingival biofilm of patients using various techniques [26]. Several

potential virulence factors have been discovered in *T. forsythia*, including trypsin-like [102] and PrtH proteases [103], NanH [104], a leucine-rich repeat protein BspA [105], alpha-D-glucosidase, N-acetyl-beta-glucosaminidase [106], components of the bacterial S-layer, and methylglyoxal [107].

The mechanisms underlying the involvement of *Tf* in the promotion of AS remain inadequately understood. Existing research findings indicate that *Tf* and its components, including LPS and OMVs, can enhance the secretion of pro-inflammatory mediators by macrophages, including IL-1β, IL-6, TNF-α, and IL-8 [108][109][110], while S-layer-deficient *Tf* mutants yield a remarkably higher secretion level [109]. Similarly, infection of mice with *Tf* mutant strains lacking an intact S-layer glycan core has been shown to provoke robust Th17 cell responses and researchers considered that the surface glycosylation of *Tf* may contribute to its persistence within the host by restraining Th17 responses [111]. *Tf* and BspA can also induce THP-1 to form foam cells [112]. This evidence manifests that *Tf* may evade recognition by the innate immune system, elicit a chronic inflammatory response, and catalyze foam cell formation in AS plaque.

7. *Treponema denticola*

Td is a Gram-negative bacterium from the Spirochetes family. As a partner of the “red-complex” organisms, *Td* is commonly found in the oral cavity, especially in subgingival plaque. *Td* possesses several virulence factors, such as the major outer sheath protein (MSP), ortholog of oligopeptide transporter unit (OppA), factor H-like protein-1 binding proteins, coaggregation, dentilisin, lipooligosaccharide [113], peptidoglycan, and cystalysin, which assist *Td* in adhesion, locomotion, immune escape and destruction of host cells [114]. *Td* can activate human ECs by inducing IL-8 and MCP-1 expression [115], which facilitates the chemotaxis and aggregation of monocytes to the subendothelium.

8. *Campylobacter rectus*

Cr is a Gram-negative anaerobic bacterium. It was initially named and identified in 1981 as *Wolinella recta*, and was reclassified as *Campylobacter* in 1991 based on phylogenetic analysis [116]. It is common in the oral cavity and gastrointestinal tract and mainly participates in oral and periodontal infections, but it is also detected in cases of severe infection outside the gastrointestinal tract [117].

Similar to other oral bacteria, *Cr* possesses potent TLR4 stimulating activity, effectively triggering the macrophage TLR4 signaling pathway and inducing IL-6 secretion [118]. Currently, there is a lack of evidence of how *Cr* affects AS, and further research is needed (**Figure 1**).

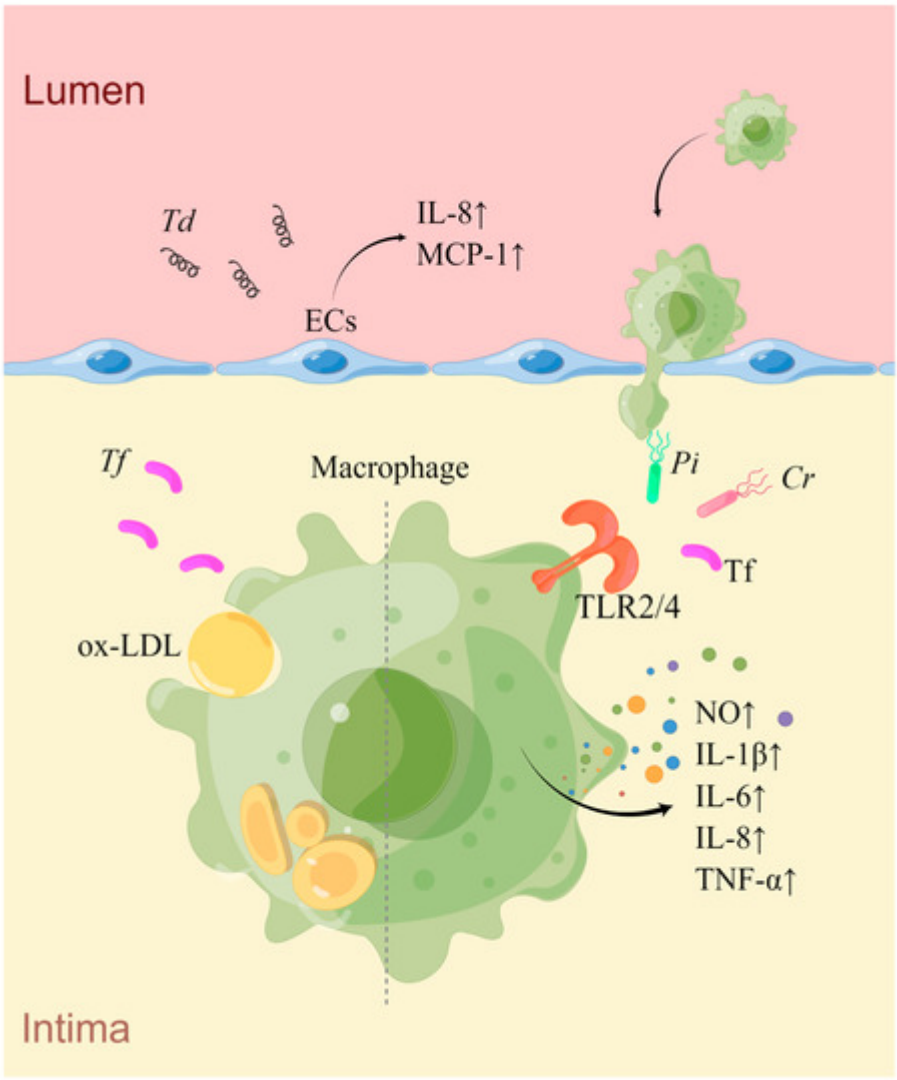

Figure 1. An overview of the mechanisms of *Pi*, *Tf*, *Td*, and *Cr* in AS. *Td* infection induces the secretion of IL-8 and MCP1 by ECs, promoting the adhesion and aggregation of monocytes towards the sub-endothelial space. *Pi*, *Cr*, and *Tf* can activate macrophages via the TLR2/4 signaling pathway, leading to increased production of inflammatory mediators. Additionally, *Tf* can also promote macrophage-derived foam cell formation induced by ox-LDL (drawn by Figdraw).

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