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Association Of Inflammasomes In Pathogenesis Of Periodontal Disease: A Review

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Abstract

A key function of the innate immune system is in flammasome activation. Inflammasomes are multimeric protein structures composed of a sensor molecule (the PRR), typically the adapter molecule apoptosis-associated speck-like protein containing a caspase-recruitment domain (CARD), and the protease caspase-1. There are multiple inflammasomes that are formed, which are named for their sensor pattern recognition receptors that induces its activation. Inflammasome-mediated processes are important during microbial infections and also help in regulating both metabolic processes and mucosal immune response. Inflammasomes are widely activated in myeloid cells, including monocytes, macrophages, dendritic cells and neutron philsthey can also be activated in keratinocytes, gingival and dermal fibroblasts, and mucosal epithelial cells. This article reviews the functions and importance of inflammasomes related to pathogenesis of periodontal diseases.

Keywords

Inflammasomes, Periodontitis, NLR family, Pyrin.

Introduction

The innate immune response is the body's first line of defense against pathogens. The innate immune system recognizes pathogens, including bacteria and viruses by engagement of the germ line encoded pattern recognition receptors (PRR). There are five families of PRR swhich are able to sense vast families of microbial components, referred to as pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP), they are host cell components produced during inflammation or environmentally derived [1,2]. Although PRRs are predominately expressed by innate immune cells, many of the PRRs are also found on other cells including epithelial, endothelial and cells of the adaptive immune system. PRR engagement by its legend induces downstream signaling cascades that induce multiple effects, including activation of innate immune cells and cytokine/chemokine production for the recruitment of immune cells to the site of infection or tissue damage. There are multiple inflammasomes that are formed, which are named for their sensor pattern recognition receptors that induces its activation. Inflammasomes are widely recognized to be activated in myeloid cells, including monocytes, macrophages, dendritic cells and neutrophils, they can also be activated in keratinocytes, gingival and dermal fibroblasts, and mucosal epithelial cells. In response to PAMPs or DAMPS, some PRRs assemble inflammasomes for the activation of cellular caspases that, in turn induce the maturation of the pro inflammatory cytokines interleukin-1β and interleukin-18 together with the induction of inflammation-induced programmed cell death (pyroptotic).

It is still not clear how many sensors are capable of forming inflammasomes, with strong literature support for over 10 different inflammasomes, including NLRP1, NLRP3, NLRP6, NLRP12, pyrin, NAIP/NLRC4, RIG-I AIM2, IFI16, NLRC3, NLP6 [5,7]which are recently reviewed. The study of periodontal disease represents a excellent model to study the role of infammasomes due to the abundance of MAMPs and DAMPs and the elevated proportion of macrophages in the tissue microenvironment.

This review will mainly therefore will focus on discussing a potential role of NRRP1, NLRP3, NOD1 &NOD2, Pyrinin relation to pathogenesis of periodontal disease and the role of the cytokines matured during inflammasome activation.

Inflammasomes

The term ‘inflammasome’ was coined by the late Jurg Tschopp and his research team in 2002 [8]. Inflammasomes are nucleotide-binding-domain-like receptors containing multi protein complexes functioning as a molecular platform and are activated by exposure to cellular danger or stress signals, which trigger the maturation and secretion of pro-inflammatory cytokines, such as interleukin-1beta and interleukin-18 [8].

Inflammasome activation is a highly inflammatory process that is often initiated during pathogen infections (in communicable diseases) or during sterile inflammation by detection of proinflammatory debris (in noncommunicable diseases).Inflammasome activation induce the maturation of the proinflammatory cytokines interleukin-1β and interleukin-18 through their cleavage by caspase-1. Recognition of mature interleukin-1β and interleukin-18 by their receptors has pleiotropic actions, which also includes (a) recruitment of neutrophils and other innate immune cells, (b) activation of B cells and antibody

production and (c) differentiation of T cells[1,3,4]. Additionally, activation of the inflammasome induces pyroptosis in immune cells. Pyroptosis is a highly inflammatory form of lytic programmed cell death that occurs frequently upon infection with intracellular pathogens and is likely to form part of antimicrobial response.Interleukin-1 (IL-1), a proinflammatory cytokine, consists of IL-α and IL-1β. IL-1β induces inflammatory mediator production, osteoclast formation, matrix metalloproteinase expression, and matrix-producing cell death in periodontal tissues, resulting in the destruction of alveolar bone and periodontal connective tissue [3]. Thus, IL-1β plays crucial roles in the onset and progression of periodontal disease. IL-1β is produced extracellularly after pro-IL-1β is processed by caspase-1 to become activated by the intracellular multiprotein complex known as the inflammasome. The word "inflammasome" was first used to describe platforms for inflammatory caspase activation 2. IL-18 is also produced as pro-IL-18 and processed by caspase-1 tobecome activated by the inflammasome. The inflammasome is composed of the "nucleotide-binding domain leucine-rich repeat-containing receptor" (NLR), adaptor protein "apoptosis-associated speck-like protein containing a caspase-recruitment domain" (ASC), and procaspase-1 3.

Several members of the nucleotide-binding-domain-like receptor gene family participate in the assembly of inflammasomes, and the main members demonstrated to form inflammasomes in cells are NLR family, pyrin domain containing 1 (NLRP1), NLR family, pyrin domain containing 3 (NLRP3) and NLR family, CARD domain containing 4 (NLRC4) [9,10]. NLRP3 is the most comprehensively characterized inflammasome and has been shown to be associated with several auto inflammatory and nonautoimmune chronic conditions. NLRP3 has lately become an important target molecule in understanding how various pathogens and related danger signals could help in the inflammasome complexes in order to redirect host immune responses. Inflammasomes can control the mediation of proinflammatory responses in a diverse group of chronic diseases, such as gout, cancer and bacterial and viral infections

Role of Inflammasomes in Periodontal Diseases

Periodontitis (PD) is a common infectious disease of the periodontium which can affect almost about 20–50% of the population in the world [11,12]. The disease initially starts with bacterial invasion in the periodontal tissue which induces the activation of immune response [13] through the presence of pathogens which leads to the imbalance in the host immune response resulting in progressive periodontal tissue damage. Also genetic and epigenetic factors contribute to the exaggeration of periodontal disease such as individual differences in the host immune response, tissue abusive habits, gender, poor oral-hygiene and systemic diseases as diabetes mellitus, rheumatic diseases, metabolic syndrome[11].Genetic variants that influence the susceptibility and the severity of periodontitis arise from changes that occur in the genes and in the biological molecules that they encode [13,14] including cytokines [15-20]. Cytokines are soluble mediators produced by resident cells (epithelial and fibroblasts) and phagocytes in the early chronic phases of periodontal inflammation and by T and B lymphocytes in established and advanced lesions in the periodontium[21]. However, the unbalanced production of pro and anti-inflammatory cytokines induces severe damage in the periodontal tissue [22]. Interleukin (IL)-1, IL-8 and tumor necrosis factor (TNF)-α are produced by fibroblasts, promote neutrophils chemotaxis in the inflamed periodontal site.

IL-1 can also enhance the expression of the receptor-activator of nuclear factor-kappa B (NF-κB) ligand (RANKL) on osteoblasts. RANKL is an osteoclastogenic factor that up regulates alveolar bone loss.

TNF-α in synergism with IL-6 promotes osteoclast differentiation and IL-6 can stimulate the stromalcells to produce RANKL. Thus, these cytokines also promote bone resorption in PD [23]. Usually the proinflammatory cytokines increase in the gingival crevicular fluid (GCF) of periodontal disease individuals compared to those without periodontal disease[24]. In contrast, IL-4 and IL-10 have suppressive properties and can attenuate the tissue destruction in periodontitis. Nevertheless, they were found in lower concentrations in the biological fluids of periodontitis patients [25]. Among the cytokines involved in the pathogenesis of periodontitis, IL-1β, an inflammatory cytokine, can be highlighted for its contribution in stimulating the recruitment and differentiation of osteoclasts in the tissues. Thus, IL-1β contributes to bone resorption in periodontal destruction. IL-1β levels were higher in the serum, GCF, saliva and gingival tissue of periodontitis patients, and this cytokine could be a potential marker in the management of the disease [26,27]. The decreased levels of this cytokine were found in the GCF after non-surgical periodontal therapy [28, 29, 30], but not in all cases [31,32].

The maturation of IL-1β and its subsequent secretion are dependent on an oligomeric assembly of multiprotein complex called inflammasome. Inflammasome complex mainly consists of cytosolic pattern recognition receptors (PRRs), apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) and pro-caspase-1 [33]. PRRs such as nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and absent in melanoma 2 (AIM2)-like receptors (ALRs) are activated by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Upon sensing the stimuli, the pro-caspase-1 is activated to cleave the IL-1β into its bioactive form. Up regulation of the inflammasome may lead to an increase in IL-1β production [38].

However a unique approach defined disease as periodontal complex traits (PCTs) by supplementing clinical data with biological intermediates of microbial burden (eight periodontal pathogens) and the local inflammatory response by interleukin 1β (IL-1β) in the gingival crevicular fluid (GCF)[1].This approach led to identification of genetic loci significantly associated with several unique biologically informed PCTs.

Three main PCTs were identified 1: **PCT1,** called the Socransky trait, is characterized by the presence of a high number of periodontal pathogens and a moderate amount of GCF-IL-1β; **PCT3,** named the Aggreg atibacteractinomy cetemcomitans (Aa) trait, is characterized by high amounts of IL-1β and dominated by the periodontal pathogen Aa; and **PCT5,** named the Porphyromonasgingivalis (Pg) trait, is dominated by the periodontal pathogen Pg. In addition to the unique biological characterization, the loci significantly associated with each PCT were also distinct.

The Socransky trait was associated with SNPs that interfered with genes encoding interferon gamma inducible protein 16 (IFI16) and absent in melanoma 2 (AIM2), proteins that form inflammasomesand lead to increased levels of mature IL-1β upon a microbial challenge.

The Aggregatibacteractinomy cetemcomitans (Aa) trait correlated with polymorphisms in genes that affect the processing of prostaglandin and IL-17.

The Porphyromonasgingivalis (Pg) trait was associated with SNPs in genes that influence the

epithelial barrier function, including the gene encoding plakophilin2 (PKP2), which is present within desmosomes of epithelial cells. Any functional impairment in the epithelial boundary adjacent to the subgingival biofilm has the potential to highly increase the risk for disease. Other traits include PCT6, which is most strongly associated with clinically determined disease and has the highest plaque levels and the highest association with smoking and Type 2 diabetes mellitus[1]. Complex traits PCT7-PCT11 are associated with health and lower clinical plaque scores and have microbial community structures dominated by low counts of Gram-negative periodontal microorganisms Prevotellanigrescens, Treponemadenticola, Tannerella forsythia, and Prevotellaintermedia. Intriguingly, most of the loci associated with each of these biological traits had not previously been explored in the pathogenesis of periodontal disease [1].

NLR family (Nucleotide-Binding Domain Leucine-Rich Repeat-Containing Receptor)

NLRP1

NLR family members all share a central nucleotide-binding domain (NBD) and most members have a C-terminal leucine-rich repeat (LRR) domain and a variable N-terminal domain.

The NLR family can be subdivided into NLRP or NLRC based on whether the N terminus contains a pyrin or caspase activation and recruitment domain (CARD), respectively. Certain members of the family, including NLRP1, NLRP3, and NLRC4, have been well established as NLRs capable of forming inflammasomes, whereas other members, like NLRP6 and NLRP12, are still considered putative inflammasome sensors. It remains to be seen if other members of the NLR family are capable of forming or regulating inflammasome assembly in response to some unknown stimuli. Several inflammasomes have been described: NLR family pyrin domain-containing 1 (NLRP1), NLRP2, NLRP3, NLR family CARD domain-containing 4 (NLRC4) and AIM2 [34].

Evidence for the ability of NLRP1a to induce inflammasome activation comes from a genetic model, wherein mice harboring a mutation in the NLRP1a gene (Q593P) develop a caspase-1– and IL-1β–mediated systemic inflammatory disease (Masters et al., 2012). These mice also exhibit a change in myelopoiesis, such that the number and function of hematopoietic progenitor cells are markedly altered in a caspase-1– dependent but IL-1R signaling–independent manner. Thus, a significant loss of hematopoietic progenitors is observed because of aberrant inflammasome activation and cell-intrinsic pyroptosis.NLRP1 was the first inflammasome described but how exactly it is activated is still unclear [39,40]. Lilue J et al in their study showed that although the human genome encodes for a single NLRP1 protein, mice express eight paralogs, Nlrp1a-f and Nlrp1b2[41]. Additionally, murine Nlrp1b has five different alleles that respond differentially to stimuli. The human NLRP1 domain structure deviates from the typical tripartite domain structure and contains an N-terminal pyrin domain, followed by a nucleotide-binding domain, leucine-rich repeats, function to find domain (FIND) and C-terminal CARD. The mouse domain structure lacks the N-terminal pyrin domain. Proteolytic cleavage in FIND must occur for NLRP1 to recognize its stimulus, although both portions remain associated. Anthrax lethal toxin is sensed by multiple murine Nlrp1b alleles. This toxin is a protease and N-terminally processes Nlrp1b, leading to its activation in mice. Although human NLRP1 is neither cleaved nor activated by lethal toxin, experimental cleavage of its N-terminal sequence is sufficient to activate NLRP1[42]. This suggests that human

NLRP1 may detect pathogen infection by an as yet unknown protease. Toxoplasma gondii activates some alleles of rat Nlrp1b. Although polymorphisms in human NLRP1 are linked to congenital toxoplasmosis, there is no evidence that T. gondii activates NLRP1 inflammasome[43].

NLRP 3

NLRP3 was first shown to be associated with hereditary autoinflammatory syndromes called cryopyrin-associated periodic syndromes, which are characterized by skin rashes and episodes of fever (Hoffman et al., 2001). In fact, over 90 diseases associated mutations have since been observed in humans in and around the NBDs that render NLRP3 constitutively active(Masters et al., 2009). NLRP3 is an inflammasome-forming NLR that responds to a wide range of infectious and endogenous ligands and is implicated in the pathogenesis of several autoinflammatory diseases, including arthritis, gout, diabetes, obesity, and Alzheimer's disease (Guo et al., 2015).

The triggers that have been shown to induce NLRP3 activation include pathogen-derived ligands such as microbial cell wall components, nucleic acids, and pore-forming toxins; environmental crystalline pollutants like silica, asbestos, and alum; and endogenous danger signals like ATP, serum amyloid A, and uric acid crystals (Man and Kanneganti, 2015).NLRP3 is the better characterized member and mainly to be involved in the innate immune reaction of infectious, inflammatory and chronic diseases [35,36].

NLRP3 consists of the NLRP3 scaffold, the ASC adaptor, and procaspase-1[51]. Two steps are required to activate the NLRP3 inflammasome[52]. The first step is initiated by microbial ligands or endogenous cytokines and is needed to induce upregulation of NLRP3 protein expression [53]. NF-rB activation and reactive oxygen species (ROS) are required for this step. The second step is activation of NLRP3 by microbial stimuli or endogenous molecules [52]. NLRP3 is activated by several microbial-derived ligands, including toxins [53]. The endogenous signals triggering NLRP3 activation include the danger signal ATP, fatty acids, particulate matter, necrosis, and necroptosis (reviewed by Hao et al.[52,53]. Also K efflux, lysosome function, endoplasmic reticulum (ER) stress, intracellular calcium, ubiquitination, micro RNAs, and particularly ROS have been proposed (reviewed by Abais et al.)[53]. ROS may serve a 'kindling' or triggering factor for activation of the NLRP3 inflammasome as well as 'bonfire' or 'effector' molecules leading to pathological processes [53].In monocytes and dendritic cells, TLR stimulation is adequate to induce caspase-1 activation and IL-1b production but not in macrophages (reviewed by Hao et al).[52]Overexpression of NLRP3 in the gingival tissue and increased salivary levels of NLRP3 were observed in periodontal disease patients [37].

The NLRP3 inflammasome reacts to structurally and chemically diverse stimuli, including pathogen infections, tissue damage and metabolic changes. Although NLRP3 is activated during a variety of infections and inflammatory diseases, no direct agonist for NLRP3 has been found.Cellular stressors that are able to activate the NLRP3 inflammasome lead to multiple upstream signaling events that are critical for NLRP3 activation. These signaling events include: (a) K+, Ca2+ and Cl− ion fluxes, (b) lysosomal disruption, (c) mitochondrial damage or dysfunction, (d) production of reactive oxygen species, (e) release of oxidized-mitochondrial DNA (ox-mt DNA) and (f) metabolic changes.

Additionally, mitochondrial antiviral signaling protein, an adaptor protein in RNA sensing pathways are considered to be important for NLRP3 inflammasome activation during infections by several different RNA viruses and after stimulation with the synthetic RNA poly I:C[44-47] The location of the mitochondrial antiviral signaling protein in the mitochondrial outer membrane protein substantiates a role for NLRP3 sensing of mitochondrial perturbations.

The NLRP3 inflammasome has an additional protein that is unique to it and not found to be associated with other inflammasomes. It was recently recognized that NIMA-related kinase 7 (NEK7), a serine-threonine kinase known to be involved in mitosis, is also essential for NLRP3 inflammasome activation.[48-50]The upstream signaling events that induce inflammasome activation also induce NEK7-NLRP3 interaction. Upon sensing cellular stress, NLRP3 oligomerizes at its nucleotide-binding domains in a helical manner. NLRP3 oligomerization clusters the pyrin domain of NLRP3, inducing pyrin domain-pyrin domain-mediated ASC polymerization.

NOD1 and NOD2

The importance of NOD2 in inflammatory diseases is mostly supported by the association of mutations in NOD2 and the increased risk for developing Crohn's disease, an autoinflammatory disorder of the gastrointestinal tract.NOD receptors not only help in microbial and damage sensing but they also promote activation of NLRP3 and NLRP1 inflammasomes[54,56].The most common polymorphisms in association with Crohn's disease are located in the leucine-rich repeat domain of NOD2 and include R702W, G908R and L1007fsinsC.[24,55,56]

Individuals with these variants have an increased risk for developing Crohn's disease. Data indicate that these mutations mostly damage the mucosal barrier function due to a insufficiency in bacterial clearance and activation of toll-like receptors and Th1 immune responses [57,58] Recent studies suggested that these defects may also alter the recognition of endoplasmic reticulum stress-inducedNOD1/NOD2 activation and further contribute to the development of Crohn's disease [54,57]

Crohn's disease and ulcerative colitis are classified under the inflammatory bowel diseases. Although the pathogenesis are distinct, both diseases have various similarities, including the chronic devitalizing inflammation of the gastrointestinal tract that is partially driven by defects in the innate immune system in response to gut bacteria. It is been suggested that inflammatory bowel disease and periodontal disease share similar immunopathogenic pathways, in that both diseases show tissue-destructive mucosal inflammation directed against commensal microbiota[1].

In recent studies healthy and diseased human gingival tissues showed increased levels of NOD1 and NOD2 in epithelial cells and inflammatory cells, with no difference reported among different periodontal conditions [59,60,61].In a preclinical study Nod2−/− and Rip2−/− (downstream kinase of Nod1 and Nod2) mice showed a significant reduction of experimental alveolar bone resorption and osteoclastogenesis, supporting NOD2 as a driver of periodontal bone loss [62]. This result is contradictory to the findings of a collaborative effort developed by the authors in which Nod2−/− mice showed no difference in the amount of bone loss compared with controls [63]. This could be attributed to the different types of model used to study experimental periodontitis (injection of heat-killed Aggregatibacteractinomycetemcomitans into murine gingival tissues in their study vs ligature model developed by Jiao et al)[63]. Although the inflammatory

infiltrate in the gingival tissues did not seem to be affected by Nod2, the osteoclastogenesis was significantly reduced in mice lacking Nod2 in the gavage model [1]. Neither study evaluated the effect of Nod2 in the mucosal barrier function of the gingival tissues, as reported to be the main effect on the development of Crohn's disease [1] .In the ligature model of periodontitis, Nod1 (rather than Nod2) drives the alveolar bone resorption, with decreased bone loss (approximately one-third less compared with wild-type), decreased interleukin-β levels, decreased osteoclast numbers and decreased neutrophil migration observed in mice lacking Nod1 and Ripk2 (a mediator of NOD1 and NOD2 signaling)[63]. In summary, the current data demonstrate potential involvement of NOD1 and NOD2 in the pathogenesis of periodontitis.

Additional studies involving NOD receptors, DAMPs and epithelial barrier integrity are needed to clarify further the role of these receptors in periodontal disease.

Pyrin

Pyrin is associated with an autoinflammatory disorder called familial Mediterranean fever and was only recently identified as an inflammasome-forming protein. Pyrin was first implicated in inflammasome activation from a mouse model expressing familial Mediterranean fever mutation–containing pyrin; these mice exhibited an ASC and IL-1–mediated autoinflammatorydisorder (Chae et al., 2011). A more recent study provided definitive proof by showing that the pyrininflammasome assembles in response to Rho-modifying toxins produced by various bacterial species, including Clostridium difficile (TcdB), Vibrio parahemolyticus (VopS), Histophilussomni (IbpA), Clostridium botulinum (C3), and Burkholderiacenocepacia (Xuet al., 2014).Five (M694V, V726A, M680I, M694I and E148Q) out of 68 acknowledged MEFV mutations have been reported to be the most common[64.65]

The spatial arrangement and relocalization of pyrin and NLRP3 inflammasome components during activation are mainlydriven by microtubulin dynamics [66,67]. Colchicine is highly effective and specific treatment for familial Mediterranean fever and NLRP3 inflammasome that works by binding to tubulin and preventing microtubule polymerization. In addition colchicine also activates RhoA and suppresses pyrininflammasome activation[68].

Few studies have been conducted which evaluated the periodontal condition of individuals with familial Mediterranean fever. The type of classification selected for familial Mediterranean fever is reported to affect the periodontal clinical findings[69,70]. Individuals with familial Mediterranean fever (n = 81) were shown to have significantly higher clinical measures of periodontal disease severity compared with systemically healthy controls (n = 85), although the clinical magnitude of difference was small (mean, SD probing depth in systemically healthy controls was 2.73 ± 0.86 vs 3.00 ± 0.93 mm in familial Mediterranean fever, P = .044; mean clinical attachment level in systemically healthy controls was 2.96 ± 1.10 vs 3.15 ± 1.22 mm in familial Mediterranean fever, P = .032). Moreover several salivary oxidative stress parameters were significantly higher in individuals with familial Mediterranean fever compared with systemically healthy controls (up to six times higher, mean, SD 8OHdG in healthy controls was 12.78 ± 19.88 pg/mL vs 82.80 ± 82.09 pg/mL in familial Mediterranean fever, P = .001).[69] These studies showed that periodontal disease in individuals with familial Mediterranean fever may have oxidative stress regulation as a stronger underlying biological consideration when

compared with systemically healthy individuals. It is also possible that particular genetic mutations of MEFV may be more detrimental to the oral microflora environment. Of all the MEFV gene mutations, individuals with the M694V mutation showed a higherprevalence of severe familial Mediterranean fever development with early emergence, frequent attacks and need for treatment with higher colchicine doses and frequent amyloidosis occurrence in untreated patients[72-74]. Mostly individuals with familial Mediterranean fever with this same pyrin mutation, M694V, were reported to be~3.5 times more likely to present with periodontitis than individuals with other pyrin mutations.[72,75] These studies provide clinical indications that pyrin proteins can be important in the pathogenesis of periodontal disease.

Conclusion

Inflammasome activation is mainly associated with basic cellular functions. In addition to removal of damaged cells, inflammasomes are also involved in cell repair, metabolism, and proliferation. Various molecules are believed to be involved in the maintenance of cellular homeostasis have been demonstrated to act as critical regulators of inflammasome function and vice versa.

The uncovered functions of new inflammasomesin cell metabolism and proliferation require further investigation.Many interactions between inflammasomesand the innate immune system are still unknown. It is now becoming clear that the inflammasome and its constituents are more likely to be crucial in the initiation of periodontal disease and several chronic systemic diseases associated with periodontitis. The involvement of inflammasome components in periodontal health and subtypes of disease are in the early stages of exploration and more studies are required to create evidence based knowledge. Efforts should also be made to see how inflammasomes can affect the ecology of the dental plaque, calculus and oral microbiota.

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