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·综述·

半胱天冬酶调控牙周先天免疫相关细胞的研究进展

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【摘要】 牙周炎是一种慢性炎症性疾病，其发生发展与局部先天免疫应答失衡密切相关。半胱天冬酶家族在牙周先天免疫相关细胞（如牙龈上皮细胞、中性粒细胞、巨噬细胞、树突状细胞、自然杀伤细胞等）的炎症应答与死亡途径调控中发挥重要作用。这类蛋白酶对细胞功能具有双重调节作用：一方面，通过半胱天冬酶-3/7/9介导的细胞凋亡清除衰老或受损细胞，通过半胱天冬酶-1/4介导的细胞焦亡通路执行免疫防御、清除病原体，共同维持组织稳态；另一方面，通过过度激活半胱天冬酶-1/消皮素D通路及半胱天冬酶-4/6/8参与的炎症放大相关通路，促进白介素-1β、白介素-18等炎性因子释放，从而破坏上皮屏障、加剧牙周组织损伤。半胱天冬酶调控既有共性，亦表现出细胞特异性。在牙龈上皮细胞中，半胱天冬酶-1介导细胞焦亡与炎症激活，半胱天冬酶-3调控凋亡与增殖信号，半胱天冬酶-4参与分化调节及病原选择性免疫应答，三者协同响应生理与病理状态的变化。中性粒细胞则可通过半胱天冬酶-1/消皮素D信号通路驱动中性粒细胞胞外陷阱的释放，而不引发典型的细胞焦亡。在巨噬细胞中，半胱天冬酶-1与半胱天冬酶-8协同促进其向M1型极化；半胱天冬酶-3除作为凋亡执行者外，亦可在特定微环境中促进巨噬细胞向M2型转化。本文综述了半胱天冬酶在牙周先天免疫相关细胞中的具体作用机制，旨在为靶向调控半胱天冬酶治疗牙周炎提供新的理论依据。

【关键词】 半胱天冬酶；牙周炎；炎症；牙龈上皮细胞；中性粒细胞；巨噬细胞；先天免疫；焦亡；凋亡
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Research progress on the regulation of periodontal innate immune cells by caspases

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【Abstract】 Periodontitis is a chronic inflammatory disease, and its occurrence and development are closely related to the imbalance of local innate immune responses. The caspase family plays a crucial role in regulating inflammatory responses and cell death pathways in periodontal innate immune cells (such as gingival epithelial cells, neutrophils, macrophages, dendritic cells, and natural killer cells). These proteases exhibit a dual regulatory effect on cellular functions. On one hand, apoptotic pathways mediated by caspase-3/7/9 enable the programmed clearance of senescent or damaged cells, while pyroptosis pathways mediated by caspase-1/4 contribute to immune defense and pathogen elimination, collectively helping to maintain tissue homeostasis. On the other hand, excessive activation of the caspase-1/gasdermin D pathway, as well as inflammatory amplification pathways involving caspase-4/6/8, promotes the release of inflammatory

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cytokines such as IL-1β and IL-18, leading to the disruption of the epithelial barrier and exacerbation of periodontal tissue damage. Caspase regulation exhibits both commonality and cell specificity. In gingival epithelial cells, caspase-1 mediates pyroptosis and inflammation activation, caspase-3 regulates apoptosis and proliferation signaling, and caspase-4 participates in differentiation regulation and pathogen-selective immune responses, collectively adapting to physiological and pathological changes. Neutrophils can utilize the caspase-1/gasdermin D signaling pathway to drive the release of neutrophil extracellular traps without triggering typical pyroptosis. In macrophages, caspase-1 and caspase-8 synergistically promote polarization toward the M1 phenotype, while caspase-3 acts as an apoptosis executor to facilitate macrophage transition to the M2 phenotype in specific microenvironments. This article reviews caspase's specific mechanism of action in periodontal innate immune-related cells, aiming to provide a new theoretical basis for targeted regulation of caspase in the treatment of periodontitis.

【Key words】 caspases; periodontitis; inflammation; gingival epithelial cell; neutrophil; macrophage; innate immune; pyroptosis; apoptosis

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牙周炎是一种由牙菌斑微生物引发、宿主免疫介导的慢性炎症性疾病，其主要病理特征为牙周组织的持续炎症和进行性牙槽骨吸收，最终导致牙齿松动、脱落，严重影响患者的口腔健康和生活质量[1-3]。该疾病的发病机制为宿主免疫应答与口腔微生物相互作用及调控失衡，由于牙周组织长期暴露于复杂的口腔微生物环境，先天免疫系统作为抵御病原菌入侵的第一道防线，其非特异性防御机制对维持组织稳态和调控炎症反应至关重要[4-6]。牙龈上皮细胞不仅是重要的物理屏障，还与固有免疫细胞及组织细胞形成防御网络[7]。这些细胞通过识别病原体相关分子模式与损伤相关分子模式（damage-associated molecular patterns，DAMPs），激活固有免疫信号通路，启动炎症反应，清除入侵病原体及感染细胞。树突状细胞提呈抗原，增强局部免疫，维持口腔微生态稳态与组织内环境稳定[8-9]。先天免疫调控失调被认为是导致牙周炎慢性化和组织持续破坏的关键。近年来，半胱天冬酶（caspases）在调控炎症反应和细胞死亡过程中的作用日益受到重视[10-11]。半胱天冬酶在牙龈上皮细胞、牙周膜细胞、牙槽骨细胞以及牙周组织中的免疫细胞中均有表达，越来越多的证据表明，半胱天冬酶影响这些细胞的活化、炎性因子产生及抗菌等过程[12-13]。这些发现提示半胱天冬酶可能处于重要调控节点。本文梳理半胱天冬酶调节相关细胞功能的最新研究进展，探讨其作用机制，为阐明牙周炎的免疫病理机制，探索免疫调控的治疗策略提供新思路和理论依据。

1　半胱天冬酶概述

半胱天冬酶是一类半胱氨酸蛋白酶，通过切割特定底物蛋白，在调控细胞死亡和免疫反应中起重要作用的蛋白酶[14-15]。根据功能和激活机制不同，半胱天冬酶主要可分为凋亡相关半胱天冬酶和炎症相关半胱天冬酶两大类。

凋亡相关半胱天冬酶参与细胞凋亡[16]。在此过程中，启动型半胱天冬酶（如半胱天冬酶-8，-9，-10）激活后，切割并激活效应型半胱天冬酶（如半胱天冬酶-3，-6，-7）。活化的效应型半胱天冬酶切割相关底物，使细胞凋亡。其特征是形成凋亡小体，隔离DAMPs，此过程通常被视为非炎性或有抗炎属性[17-18]。相反，炎症相关半胱天冬酶主要介导炎症反应[14]。经典焦亡途径中，半胱天冬酶-1作为NOD样受体蛋白3（NOD-like receptor protein 3，NLRP3）等炎性小体的核心效应分子被激活，切割白细胞介素（interleukin，IL）-1β和IL-18的前体使其成熟，并切割消皮素D（gasdermin D，GSDMD）的第275位天冬氨酸[19-21]。在非经典焦亡途径中，半胱天冬酶-4/5和小鼠的同源蛋白半胱天冬酶-11能直接识别胞内脂多糖（lipopolysaccharides，LPS）并自我激活，继而切割GSDMD第276位天冬氨酸[21-23]。GSDMD被切割后，其N端结构域（GSDMD-NT）会寡聚化并在细胞膜上形成孔道，导致细胞焦亡，释放包括IL-1β、IL-18和DAMPs在内的细胞内容物，引发炎症。GSDMD孔道造成的离子流动进一步激活NLRP3炎性小体及半胱天冬酶-1，形成炎症放大环路[21，24]。此外，两类半胱天冬

酶在调控上存在交叉[10]。例如：Toll样受体4（toll like receptor 4，TLR4）信号可通过激活半胱天冬酶-8促进NLRP3炎性小体的活化及半胱天冬酶-1的激活[25]。此外，半胱天冬酶-1可通过切割帕金（parkin）蛋白抑制线粒体自噬，促进活性氧（reactive oxygen species，ROS）积累加剧炎症，并在特定条件下通过激活半胱天冬酶-3来调控凋亡与焦亡平衡[26]。

因此，半胱天冬酶通过其特定的激活模式、底物选择及相互间的交叉调控，影响着细胞死亡模式。在牙周炎症中，半胱天冬酶通过调控牙周先天免疫相关细胞的凋亡和焦亡途径参与炎症过程。

2　半胱天冬酶与牙龈上皮细胞

牙龈上皮细胞是抵御病原菌的物理屏障，兼具免疫功能，能感知并响应细菌入侵[12]。其屏障功能依赖于细胞间紧密连接和桥粒结构，还可通过模式识别受体介导炎症反应，如细胞表面TLR4受体能识别牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P.gingivalis*）的LPS并分泌促炎因子[27-28]。半胱天冬酶在其中可能存在双重调控机制：生理条件下，参与调节炎症与抗炎的动态平衡；病理状态下，其表达变化可能会促进局部炎症反应。

2.1　生理状态下的稳态维持作用

生理状态下，半胱天冬酶协同维持免疫平衡与组织稳态。例如：半胱天冬酶-1介导前体IL-33切割发挥促炎作用；半胱天冬酶-3和半胱天冬酶-7则会切割IL-33使其失活，这可能作为一种负反馈调节，限制过度炎症[29-30]。半胱天冬酶-4稳定表达于健康牙龈上皮细胞，负向调控转化生长因子α（transforming growth factor α，TGF-α）与白细胞抑制因子[31]，参与细胞分化与分层，限制过度增殖并调节组织重塑；半胱天冬酶-3不仅介导细胞凋亡，还切割α-连环蛋白，破坏其与14-3-3蛋白及Yes相关蛋白（Yes-associated protein，YAP）所形成的复合物，使YAP核转位并驱动促增殖基因的表达[32]，这可能会促进牙龈上皮细胞生长和组织修复。半胱天冬酶-3活性降低则抑制YAP功能，导致细胞增殖受阻，牙龈组织萎缩[32-33]。

2.2　病理状态下的功能紊乱与炎症转化

牙周炎患者牙龈上皮中，半胱天冬酶-1明显升高，*P.gingivalis*的LPS增强半胱天冬酶-1的募集，激活焦亡途径，释放促炎因子（如IL-1β、IL-18），激活核转录因子通路，破坏上皮钙黏素等介导的上皮细胞连接，导致上皮屏障完整性丧失和炎症扩散[34]。而半胱天冬酶-4的蛋白表达呈现了升高或降低两种不同的变化趋势[34-35]。这可能反映了半胱天冬酶-4不同阶段调控机制变化：在细菌侵入早期，半胱天冬酶-4可能通过参与维持上皮屏障，增强局部固有免疫反应，抑制细菌侵入[31]；但长期慢性炎症使不健康的牙龈上皮半胱天冬酶-4表达下调，导致趋化因子（如IL-8、化学趋化因子配体9/10）的增加，加重中性粒细胞聚集，促进炎症。同时，半胱天冬酶-4表达下调减弱了对TGF-α和白细胞抑制因子的负调控作用，导致二者水平升高，引发龈上皮代偿性增殖[35]。此外，半胱天冬酶-4对不同牙周病原微生物的免疫调节具有选择性。例如，半胱天冬酶-4参与对放线杆菌的防御，增强*P.gingivalis*细胞壁诱导的IL-8和IL-18表达，而对具核梭杆菌无显著影响。半胱天冬酶-4的表达水平虽与牙龈指数、菌斑指数等临床指标呈负相关，但与反映牙周炎进展及活跃程度的其他指标间未发现显著关联[35-36]。

局部微环境改变也可通过半胱天冬酶影响牙龈上皮功能。烟草刺激通过半胱天冬酶-3诱导牙龈上皮细胞凋亡[37-38]。高血糖则可触发半胱天冬酶-1活化，诱导细胞衰老，并干扰线粒体自噬的动态调控[39-40]。此外，研究表明，短暂的高血糖可能增强自噬，上调凋亡抑制机制。例如，杆状病毒凋亡抑制蛋白重复序列蛋白6（baculoviral IAP repeat containing 6，BIRC6）可促进半胱天冬酶-9酶原的泛素化及蛋白酶体降解[41]，从而抑制半胱天冬酶-9活性。然而，长期持续的高血糖会导致自噬功能障碍，同时伴随着细胞应激（如氧化应激）的加剧，最终可能解除对凋亡的抑制，导致半胱天冬酶-9等凋亡相关分子的激活。

综上所述，半胱天冬酶家族通过调控炎症反应、免疫应答、组织修复与屏障完整性，在牙龈上皮细胞功能中扮演着关键角色。其中，半胱天冬酶-1与半胱天冬酶-4在牙周炎上皮中的表达与功能改变尤为显著，但其具体作用机制尚未完全阐明，有待进一步深入研究。

3　半胱天冬酶与中性粒细胞

在牙周组织中，中性粒细胞通过吞噬作用、脱颗粒及形成中性粒细胞胞外陷阱（neutrophil extracellular traps，NETs）来捕获和抑制病原体[42]。它

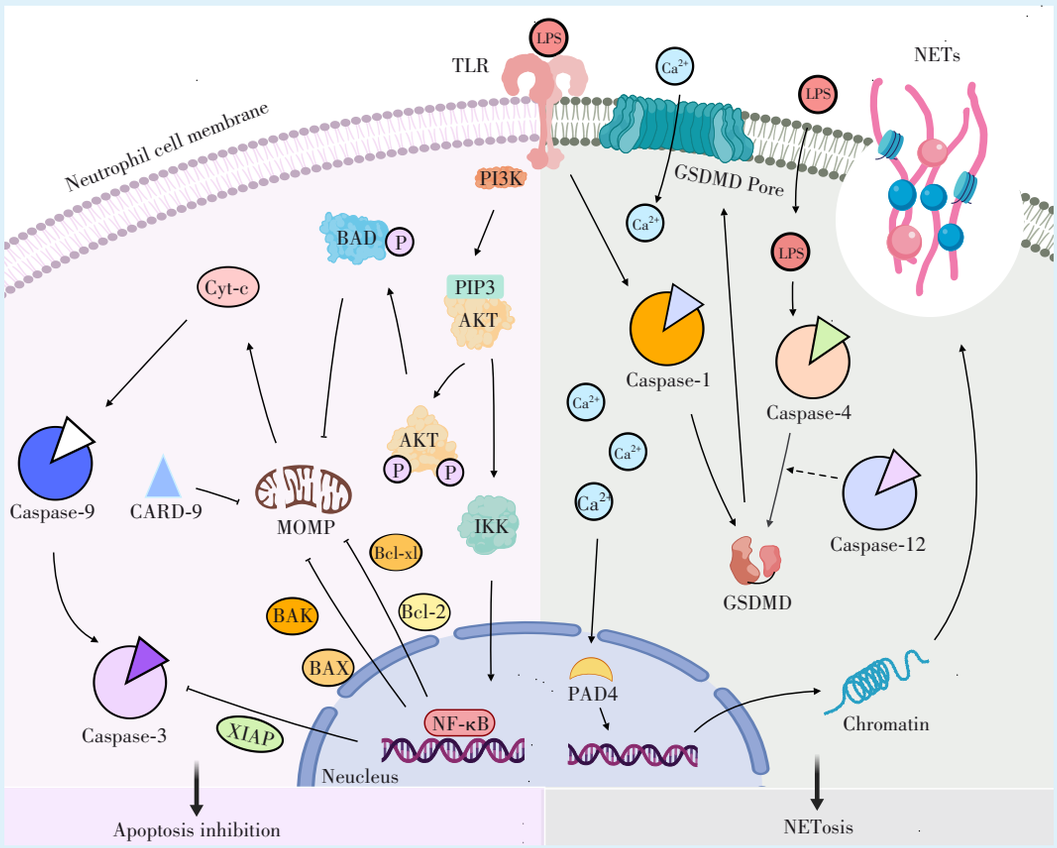
们响应趋化信号，跨内皮迁移至牙周组织以对抗牙周病原微生物[43]。中性粒细胞寿命短暂，其及时凋亡并被巨噬细胞清除是炎症消退的关键。该凋亡过程由半胱天冬酶-9/半胱天冬酶-3级联反应介导：凋亡刺激可激活促凋亡的BH3相互作用域死亡激动蛋白（BH3 interacting domain death agonist，BID），进而诱导B细胞淋巴瘤-2（B-cell lymphoma 2，Bcl-2）相关X蛋白/Bcl-2同源拮抗杀手蛋白（B-cell lymphoma 2-associated X protein/Bcl-2 homologous antagonist/killer，BAX/BAK）寡聚化，导致线粒体外膜透化，释放细胞色素c，形成凋亡体，激活半胱天冬酶-9酶原，进而激活下游效应半胱天冬酶（如半胱天冬酶-3、-7），执行凋亡程序[44]。相反，半胱天冬酶募集结构域蛋白9（caspase recruitment domain-containing protein 9，CARD9）则可通过维持线粒体功能、抑制ROS生成，进而抑制半胱天冬酶-9的活化，从而负向调控中性粒细胞的凋亡[45]。在牙周炎中，口腔细菌产物（如LPS）可显著延迟中性粒细胞凋亡[46]。其机制可能与磷脂酰肌醇3-激酶/蛋白激酶B（phosphatidylinositol 3-kinase/protein kinase B，PI3K/AKT）、核转录因子κB（nuclear transcription factor-κB，NF-κB）等信号通路有关[47]，通过抑制半胱天冬酶-3酶原的活化，并上调Bcl-2蛋白及B细胞淋巴瘤-X型（B-cell lymphoma-extra large，Bcl-xL）蛋白，使细胞凋亡延迟。半胱天冬酶-3功能被抑制后，中性粒细胞寿命异常延长，持续释放ROS、蛋白酶（如基质金属蛋白酶8/9）及促炎细胞因子[48]，使其功能由防御保护转为持续促炎，从而加剧牙周组织炎症。此外，中性粒细胞能有效规避半胱天冬酶-1介导的细胞焦亡，与其他细胞不同，中性粒细胞产生的GSDMD-NT优先定位于胞内细胞器（如嗜天青颗粒和自噬体）而非胞膜，这种定位差异引发了中性粒细胞弹性蛋白酶的释放以及自噬依赖的IL-1β持续分泌[49]。可能与中性粒细胞调控凋亡相关颗粒样蛋白和半胱天冬酶-1的表达调控有关，导致其组装的炎性小体在规模、结构或组成上小于巨噬细胞等其他细胞的炎性小体，较小的炎性小体导致激活后的半胱天冬酶-1活性较低，无法有效裂解下游底物。基于此，中性粒细胞在激活炎性小体后不容易发生焦亡。中性粒细胞的这种特性可能会更高效地介导炎症反应。

牙周炎中NETs的形成明显增加[50]。半胱天冬酶调控NETs释放涉及以下两个途径：第一，当病原体的毒力因子通过质膜转运到胞浆，会激活半胱天冬酶-1/GSDMD焦亡途径使钙离子内流，进而活化细胞内的瓜氨酸化酶，其中，肽基精氨酸脱亚胺酶4（peptidyl arginine deiminase 4，PAD4）发挥重要作用[51-52]。PAD4能催化组蛋白（特别是组蛋白H3）精氨酸残基发生瓜氨酸化，降低其正电荷，削弱其与带负电DNA之间的静电相互作用，使核小体结构稳定性下降，染色质松解[53-54]，DNA释放到细胞质中，与抗菌肽、弹性蛋白酶等相互结合，形成NETs[53]。第二，通过非经典炎症小体通路激活GSDMD，使细胞核膜通透性增高，促进中性粒细胞胞外陷阱相关细胞死亡（neutrophil extracellular trap associated death，NETosis），释放NETs[55-56]。有研究提出，内质网应激过程中的半胱天冬酶-12可能通过与其他蛋白相互作用，间接影响半胱天冬酶-4/11和GSDMD的结合，增强切割活化作用，但其具体机制尚未明确[57]。这些通路共同促进NETs形成，发挥抗菌作用（图1）。NETs在发挥抗菌作用的同时，亦可形成炎症反馈环路：一方面，NETs能够触发NLRP3炎症小体活化，通过半胱天冬酶-1促进IL-1、IL-18等促炎因子释放[58]；另一方面，NETs中的组蛋白可作为DAMPs，激活巨噬细胞上的TLR4，诱导其释放促炎细胞因子如IL-1β和IL-6，间接促进Th17细胞存活和增殖，加重炎症反应[59]，通过细胞外信号调节激酶/克鲁佩尔样因子4（extracellular signal-regulated kinase/recombinant kruppel-like factor 4，ERK/KLF4）轴抑制龈上皮细胞角化，导致牙龈炎性破坏和牙槽骨丧失[60]。此外，半胱天冬酶-11在清除胞内病原菌中发挥重要作用，且其作用可能独立于NETs形成[61]，这提示半胱天冬酶在抗菌防御和炎症诱导间关系的复杂性。

因此，靶向半胱天冬酶以调控中性粒细胞的存活时间或死亡方式，或为牙周炎的治疗提供新策略。未来研究亟待阐明半胱天冬酶信号在NETs形成与清除失衡中的具体调控机制，从而发现精准的治疗靶点。

4　半胱天冬酶与巨噬细胞

巨噬细胞由单核细胞分化成熟而来，是牙周组织中的重要免疫细胞[62-63]。半胱天冬酶在调控其分化成熟、极化及炎症反应中发挥重要作用。其中，半胱天冬酶-8通过切割受体相互作用蛋白激酶1（receptor-interacting protein kinase 1，RIPK1），



AKT: protein kinase B; BAD: Bcl-xl/Bcl-2 associated death promoter; BAX: Bcl-2-associated X protein; BAK: Bcl-2 homologous antagonist/killer; Bcl-xl: B-cell leukemia/lymphoma protein X-linked long; Bcl-2: B-cell lymphoma-2; CARD-9: caspase recruitment domain-containing protein 9; Cyt-c: cytochrome c; GSDMD: gasdermin D; IKK: IκB kinase; LPS: lipopolysaccharide; MOMP: mitochondrial outer membrane permeabilization; NETosis: neutrophil extracellular trap associated death; NETs: neutrophil extracellular traps; NF-κB: nuclear transcription factor-κB; PAD4: peptidyl arginine deiminase 4; PIP_3: phosphatidylinositol(3, 4, 5)-trisphosphate; TLR: toll-like receptor; XIAP: X-linked inhibitor of apoptosis protein; PI3K: phosphatidylinositol 3-kinase

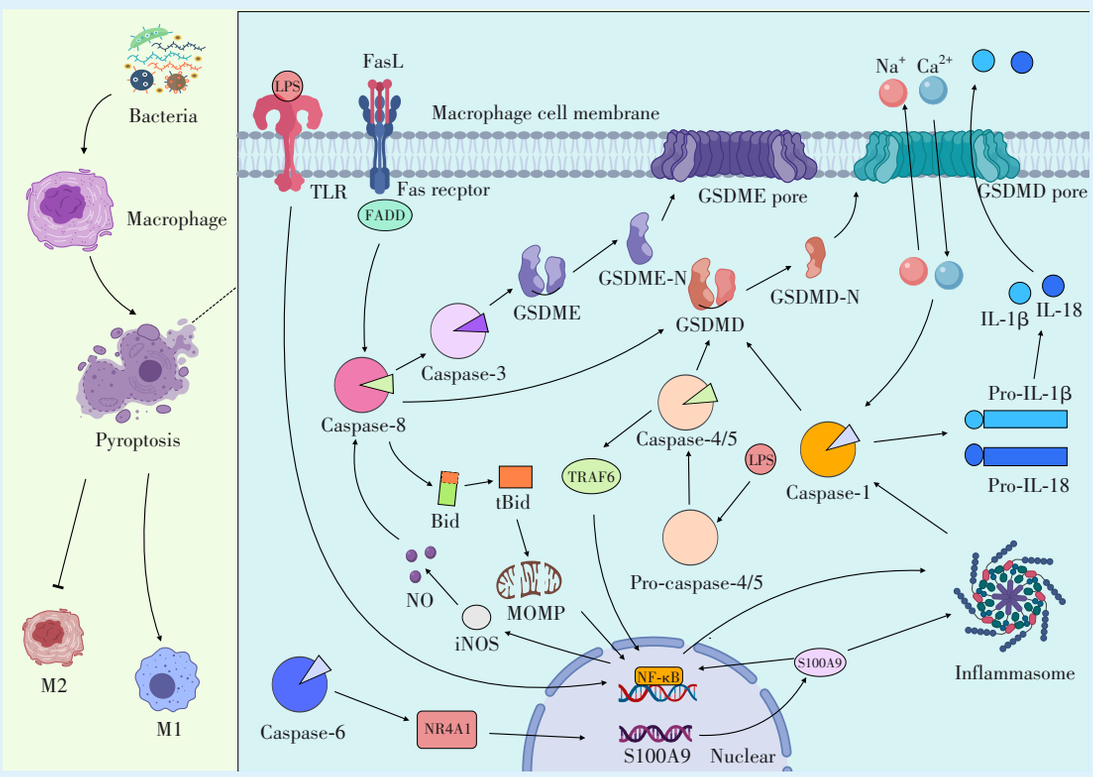
Figure 1　Schematic diagram of the mechanism of caspase-mediated inhibition of neutrophil apoptosis and promotion of NETosis

图1　半胱天冬酶介导的抑制中性粒细胞凋亡与促进NETosis的机制示意图

灭活其激酶活性并抑制程序性坏死途径[64-65]，从而在维持单核/巨噬细胞存活和分化过程中起重要作用。另一方面，在分化过程中，PI3K/AKT通路受抑制导致ROS积累，进而激活凋亡信号调节激酶1-c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）通路，促进半胱天冬酶-3的活化，并触发DNA酶，导致特定的DNA链断裂。这种亚致死性的DNA损伤可能作为一种信号机制，驱动巨噬细胞的成熟[66]。

半胱天冬酶通过促进巨噬细胞向M1型极化并放大炎症反应，在牙周炎的免疫应答中发挥重要作用。在巨噬细胞中，*P. gingivalis*主要激活NLRP3/半胱天冬酶-1炎症小体通路，具核梭杆菌则倾向于非经典炎症小体通路的激活[67-69]。这些通路均触发细胞焦亡，使炎性因子释放[70]。LPS使半胱天冬酶-4与肿瘤坏死因子受体相关因子6（tumor necrosis factor receptor-associated factor 6，TRAF6）结合基序发生相互作用[71-72]，可能作为TRAF6信号复合体支架，促进TRAF6下游信号分子的招募与激活，激活NF-κB信号通路。半胱天冬酶-6促进核受体亚家族4A组成员1（nuclear receptor subfamily 4 group A member 1，NR4A1）蛋白向核内转运，NR4A1蛋白通过结合S100钙结合蛋白A9（S100 calcium-binding protein A9，S100A9）启动子区域促进转录[73]，S100A9蛋白可能作为DAMP，促进炎症小体组装活和半胱天冬酶-1活化[74]。半胱天冬酶-8可间接降低Bcl-2蛋白的表达，打破细胞生存/凋亡平衡，促进促炎因子的表达[75]。诱导型一氧化氮合酶可以催化L-精氨酸生成一氧化氮，激活半胱天冬酶-8的同时降低促生存蛋白MCL-1的表达，加剧炎症反应[76]。当病原

菌使Fas信号过度激活时，Fas受体与其配体结合，招募Fas相关死亡结构域蛋白（fas-associated protein with death domain，FADD），募集半胱天冬酶-8参与GSDMD的切割，也可通过半胱天冬酶-3切割GSDME，将细胞死亡模式从凋亡切换为焦亡[20, 77]（图2）。半胱天冬酶-1/11介导的焦亡有助于释放胞内细菌以便清除，但过度激活会加剧炎症反应和组织损伤[78-79]。牙周炎小鼠模型中，缺失半胱天冬酶-11虽可减轻炎症损伤，但也削弱了宿主对病原菌的抑制能力[80]，这凸显了半胱天冬酶在牙周炎中调控炎症反应和组织稳态的双面性。



Bid: BH3-interacting domain death agonist; tBid: truncated Bid; GSDMD: gasdermin D; GSDME: gasdermin E; FADD: fas-associated protein with death domain; FasL: fas ligand; LPS: lipopolysaccharide; IL: interleukin; MOMP: mitochondrial outer membrane permeabilization; iNOS: inducible nitric oxide synthase; TLR: toll-like receptor; TRAF6: tumor necrosis factor receptor-associated factor 6; S100A9: S100 calcium-binding protein A9; NF-κB: nuclear transcription factor-κB; NR4A1: nuclear receptor subfamily 4 group A member 1; M1: M1 macrophage; M2: M2 macrophage

Figure 2　Diagram of the mechanism of caspase-mediated macrophage pyroptosis and polarization

图2　半胱天冬酶介导巨噬细胞焦亡及极化的机制图

另一方面，半胱天冬酶参与巨噬细胞的抗炎（M2）极化及炎症消退过程[81]。炎症过程中产生的抑炎因子（如IL-10、IL-37）通过直接或间接途径抑制NLRP3/半胱天冬酶-1通路，进而抑制焦亡及促炎因子释放[82-83]。例如，IL-10可通过激活信号转导子与转录激活子3（signal transducer and activator of transcription 3，STAT 3）信号通路，诱导抗炎蛋白表达，进而抑制NLRP3/半胱天冬酶-1的活性，减少炎症反应[84]，也促进了巨噬细胞向M2表型极化，加速组织修复[85-86]。在炎症消退阶段，半胱天冬酶-3扮演着多重角色：其一，介导已完成任务的效应巨噬细胞凋亡，从而及时终止炎症反应[87]；其二，最新研究发现，半胱天冬酶-3能直接切割并降解由炎症性半胱天冬酶活化的GSDMD-NT片段，抑制焦亡途径[88]。值得注意的是，M1和M2巨噬细胞对凋亡诱导的敏感性存在差异：促炎的M1型细胞更容易被诱导凋亡；而修复型的M2型细胞则可能通过高表达Bcl-2等抗凋亡蛋白来维持存活，确保其组织修复功能的持续[89-90]。

总之，巨噬细胞在牙周炎中扮演着“双刃剑”角色，兼具防御与破坏、促炎与抑炎的双重潜能。半胱天冬酶通过调控巨噬细胞分化、极化、死亡方式和炎症反应参与牙周炎过程，但具体作用机制仍需进一步验证。

5　半胱天冬酶与其他先天免疫细胞

树突状细胞是专业的抗原呈递细胞，细菌感染时会通过激活半胱天冬酶依赖的细胞焦亡、凋亡途径限制细菌的复制[91]，不同亚群对炎性小体反应存在差异，有些亚群可能倾向于避免细胞焦亡以诱导免疫反应[92]。*P.gingivalis*通过菌毛激活AKT/哺乳动物西罗莫司靶蛋白（mammalian target of rapamycin，mTOR）通路，抑制半胱天冬酶-3活化，导致感染的树突状细胞凋亡受阻，使其存活时间异常延长，持续滞留在组织中，过度释放IL-1β、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）等促炎因子[93]，可能加剧局部炎症反应和牙槽骨破坏。

在牙周炎环境中，自然杀伤细胞与感染细胞结合后，会释放穿孔素和颗粒酶[94]。穿孔素在靶细胞膜上形成孔道，使颗粒酶能够进入靶细胞内。其释放的颗粒酶B可切割并激活半胱天冬酶-3和半胱天冬酶-7，启动半胱天冬酶依赖的凋亡途径，还可激活半胱天冬酶-8和半胱天冬酶-10，启动外源性凋亡途径[95]。研究表明，在细胞受到病原体攻击，并发生穿孔素或GSDMD介导的胞膜损伤时，半胱天冬酶-7可激活酸性鞘磷脂酶，通过将鞘磷脂转化为神经酰胺来促进质膜修复，从而延迟细胞溶解[96]。此修复可能为感染细胞争取凋亡时间，增强免疫清除效果。

相较于中性粒细胞与巨噬细胞，半胱天冬酶在牙周炎背景下调控树突状细胞与自然杀伤细胞的相关研究较少，具体机制缺少深入研究（表1）。

表1　半胱天冬酶在牙周不同先天免疫相关细胞中的作用

Table 1　Roles of caspases in different innate immunity-related cells in the periodontium

Cell type	Caspase type	Functions
Gingival epithelial cells[31, 33-34]	Caspase-1	Mediated pyroptosis; pro-inflammatory defense.
	Caspase-3	Mediated apoptosis; limits periodontal inflammation.
	Caspase-4	Regulates cell growth; early defense, chronic pro-inflammatory effects; differentially modulates pathogen-induced inflammation.
	Caspase-7	Mediated apoptosis; limits periodontal inflammation.
	Caspase-9	Suppressed under transient hyperglycemia, but long-term activation promotes apoptosis.
Neutrophils[44, 48-51, 55-57]	Caspase-1	Regulates pyroptosis, pro-inflammatory defense; promotes NETs formation.
	Caspase-3	Mediated apoptosis; limits periodontal inflammation.
	Caspase-4	Promotes NETs formation.
	Caspase-9	Mediates apoptosis; inhibits periodontal inflammation.
	Caspase-12	May enhance caspase-4 cleavage activity.
Macrophages[67-69, 76, 78, 80]	Caspase-1	Mediates pyroptosis; modulates cell polarization.
	Caspase-6	Promotes inflammasome activation.
	Caspase-8	Promotes apoptosis; enhances inflammation.
Dendritic cells[93]	Caspase-3	Maintains immune homeostasis.
Natural killer cells[95-96]	Caspase-3	Synergizes with granzyme B to promote target cell apoptosis.
	Caspase-7	

NETs: neutrophil extracellular traps

6　总结与展望

半胱天冬酶在牙周固有免疫中扮演着重要角色，包括调控细胞凋亡、炎症反应、抗菌防御和组织修复。通过影响相关细胞存活、增殖、极化及死亡方式，影响牙周炎进程。半胱天冬酶功能具有双面性：一方面，其促炎作用通过激活炎症小体、诱导细胞焦亡和促炎因子释放，放大牙周炎症反应；另一方面，其抗炎作用通过抑制过度炎症、促进组织修复和维持免疫稳态，为牙周炎症的消退和组织修复提供保障。因为半胱天冬酶的这种特性，基于半胱天冬酶的治疗策略需更加精准和动态化。例如，半胱天冬酶-1抑制剂可通过焦亡通路抑制牙周膜干细胞焦亡，抑制破骨细胞分化[97-98]。然而，这种抑制策略可能削弱半胱天冬酶在抗菌防御和组织修复中的作用。例如，半胱天冬酶-1缺失会导致沙门氏菌感染加重[99]，这提示需要在抑制过度炎症和保留正常免疫功能间寻找平衡。目前开发的半胱天冬酶调节剂因其毒副作用，还主要用于实验研究[100]。而一些低毒且有半胱天冬酶调控潜力的天然产物（如多酚类化合

物),或更具应用前景[101-102]。未来研究需深入探究半胱天冬酶在牙周不同细胞类型以及不同炎症阶段中的变化规律。例如,可聚焦中性粒细胞中半胱天冬酶激活状态与病原菌清除效率之间的内在关联,以及不同半胱天冬酶对巨噬细胞极化方向的影响等。在炎症方面,探究半胱天冬酶在炎症始发期、进展期和缓解期的表达模式演变及功能变化,为开发更有效的治疗策略提供理论基础。

总之,半胱天冬酶在牙周固有免疫相关细胞中存在复杂的双向调控机制。未来应深入探索半胱天冬酶调控机制并将其转化为靶向治疗策略,为牙周炎提供新干预方向。

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