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·综述·

铁死亡在牙周炎发生发展过程中的研究进展

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【摘要】 牙周炎是以牙周组织持续的炎症反应和进行性破坏为主要特征的慢性感染性疾病。铁死亡是一种可调控的，具有铁依赖性的新型程序性细胞死亡形式，在多种疾病中发挥着重要作用，其主要特征为铁代谢异常、抗氧化防御减弱以及脂质过氧化物堆积。近年来，越来越多的研究表明铁死亡与牙周炎发生、发展存在相关性。目前报道的发生于牙周膜成纤维细胞、牙周膜干细胞、人类永生化口腔上皮细胞、人牙龈成纤维细胞、牙髓干细胞、MLOY4骨细胞、小鼠下颌骨成骨细胞和巨噬细胞的铁死亡相关文献结果表明，牙周炎中广泛存在铁死亡现象。这一现象主要与铁离子代谢、脂质代谢、胱氨酸/谷氨酸逆向转运蛋白（cystine/glutamate antiporter system，system x_c^-）/谷胱甘肽（glutathione，GSH）/谷胱甘肽过氧化物酶4（glutathione peroxidase 4，GPX4）、烟酰胺腺嘌呤二核苷酸磷酸（nicotinamide adenine dinucleotide phosphate，NADPH）/铁死亡抑制蛋白1（ferroptosis suppressor protein 1，FSP1）/辅酶Q10（coenzyme Q10，CoQ10）、kelch样环氧氯丙烷相关蛋白-1（kelch-like ECH-associated protein-1，Keap1）/核因子E2相关因子2（nuclear factor erythroid2-related factor 2，NRF2）和p53等途径有关。目前研究表明，铁死亡在调节牙周软、硬组织破坏，炎症反应以及牙周病原菌参与全身性疾病进展中发挥了重要作用。尽管目前铁死亡在牙周炎中的作用机制有较多研究，但在牙周治疗的应用方面尚存在许多不确定性，相关药物仍需进一步开发探索。

【关键词】 牙周炎；铁死亡；活性氧；炎症反应；全身性疾病；牙周病原菌；铁离子代谢；脂质代谢；氨基酸抗氧化系统；谷胱甘肽过氧化物酶4；铁死亡抑制蛋白1
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Research progress of ferroptosis in the occurrence and development of periodontitis

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【Abstract】 Periodontal disease is a chronic infectious disease characterized by chronic inflammation and progressive destruction of the periodontal tissue. Ferroptosis, an iron-dependent form of programmed cell death, is primarily characterized by altered iron homeostasis, weak antioxidant defense, and accumulation of lipid peroxides and plays an important role in a variety of diseases. Recent research has shown the correlation between ferroptosis and the occurrence and development of periodontal disease. Through in-depth research of relevant literature on periodontal ligament fibroblasts, periodontal ligament stem cells, human immortalized oral epithelial cells, human gingival fibroblasts, dental pulp stem cells, MLOY4 cells, mouse mandibular osteoblast, and macrophages, we found that ferroptosis is widely suppressed in periodontal disease. This phenomenon is primarily related to lipid metabolism, iron metabolism, cysteine/glutamate

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transporter system x_c^-/glutathione/glutathione peroxidase 4, nicotinamide adenine dinucleotide phosphate/ferroptosis suppressor protein 1/coenzyme Q10, kelch-like ECH-associated protein-1/nuclear factor E2 related factor 2, and p53. Current research indicates that ferroptosis plays an important role in regulating the destruction of periodontal soft and hard tissues, inflammatory response, and periodontopathogen-induced progression of systemic diseases. Although there are several studies on the mechanism of ferroptosis in periodontal disease, there are many uncertainties in the application of ferroptosis in periodontal therapy. Therefore, further studies are required to explore and develop ferroptosis-related drugs for the treatment of periodontal disease.

【Key words】 periodontitis; ferroptosis; reactive oxygen species; inflammatory response; systemic disease; periodontal pathogen; iron metabolism; lipid metabolism; amino-acid antioxidant system; glutathione peroxidase 4; ferroptosis suppressor protein 1

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2012年，Dixon等[1]发现了一种新型调节性细胞死亡形式并命名为铁死亡，其形态学特征不同于凋亡、坏死、自噬等死亡类型，主要表现为线粒体皱缩、膜密度增加、线粒体嵴模糊或消失、外膜破裂及细胞核形态正常，但缺乏染色质凝集等；生化方面主要表现为谷胱甘肽（glutathione，GSH）耗竭，谷胱甘肽过氧化物酶4（glutathione peroxidase 4，GPX4）活性下降，铁离子大量堆积，细胞无法清除由多不饱和脂肪酸（polyunsaturated fatty acids，PUFAs）与Fe^{2+}介导的活性氧（reactive oxygen species，ROS）聚集及脂质过氧化物的生成，从而使细胞发生膜破裂死亡[2]。目前，已有大量研究表明铁死亡在多种疾病的发生发展中起着关键作用，如炎症性疾病、缺血再灌注损伤、肿瘤、心肌梗死、胃肠道疾病、神经退行性疾病等[2-4]。同时，铁死亡在口腔疾病中也发挥重要作用，已有体内外研究证明，铁死亡相关基因和调控蛋白在牙髓炎、根尖周炎以及干燥综合征中的表达发生改变[5-8]。

目前，已有大量研究证明铁死亡与许多炎症性疾病相关[9]。牙周炎是以菌斑微生物为始动因素，导致牙周支持组织进行性破坏的慢性炎症性疾病。在牙周袋缺氧微环境下，细菌感染和宿主的免疫炎症反应会引起铁代谢异常，进而影响细胞内铁稳态，诱导氧化应激和脂质过氧化，加速细胞铁死亡。当口腔内菌群微生物与宿主之间的动态平衡被打破，牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P.g*）等牙周病原菌可损伤防御反应，进而引起免疫失调，诱导牙周炎症反应；口腔微环境紊乱可引发宿主免疫反应过度激活，免疫细胞被激活并释放大量促炎细胞因子，并最终破坏牙龈和牙槽骨[10]。目前，已有研究表明感染的牙周组织可引起免疫炎症反应，与远离口腔的远端器官相互作用，成为全身性疾病的重要危险因素[11]。

本文就铁死亡的定义、分子机制以及铁死亡在牙周炎发生发展中的作用等进行综述，以期为铁死亡相关口腔疾病进一步的临床研究和防治提供新思路。

1　铁死亡主要调控机制

1.1　铁代谢异常

铁代谢异常是导致铁死亡的关键因素。人体内，大部分铁以贮存铁的形式存在于铁蛋白（ferritin，FT）中，铁蛋白通过核受体共激活因子4（nuclear receptor coactivator 4，NCOA4）递送至自噬体，经自噬降解释放游离铁，促进细胞内铁蓄积，同时游离铁存储于细胞质中形成不稳定的铁池（labile iron of pool，LIP）[12]；细胞外Fe^{3+}与转铁蛋白（transferrin，TF）结合后，经细胞膜上转铁蛋白受体1（transferrin receptor 1，TFR1）复合物运输入细胞内，由前列腺六跨膜上皮抗原3（six-transmembrane epithelial antigen of the prostate 3，STEAP3）将其还原为Fe^{2+}，Fe^{2+}由二价金属转运体蛋白1（divalent metal-ion transporter-1，DMT1）运输并存储于细胞质内，也可以形成LIP[13-14]。正常生理状态下，细胞内铁代谢处于平衡状态。铁代谢紊乱时，细胞内的Fe^{2+}积累导致LIP异常增加，同时游离的Fe^{2+}催化Fenton反应（fenton reaction）产生大量ROS和脂质过氧化物，破坏细胞膜并最终诱导铁死亡发生[15]。

1.2　脂质过氧化

脂质过氧化物的过度积累是铁死亡的核心。当Fe^{2+}催化Fenton反应产生大量ROS堆积时，细胞膜或细胞器膜上的PUFAs的磷脂分子作为底物被其氧化，经过长链脂酰辅酶A合成酶4（long chain acyl-coenzyme A syntheatase 4，ACSL4）催化后，在溶血磷脂酰胆碱酰基转移酶3（lysolecithin acetyl trans-ferase 3，LPCAT3）的酯化作用下生成磷脂氢过氧化物，再由脂氧合酶和Fe^{2+}共同作用形成脂质过氧化物[16-17]。

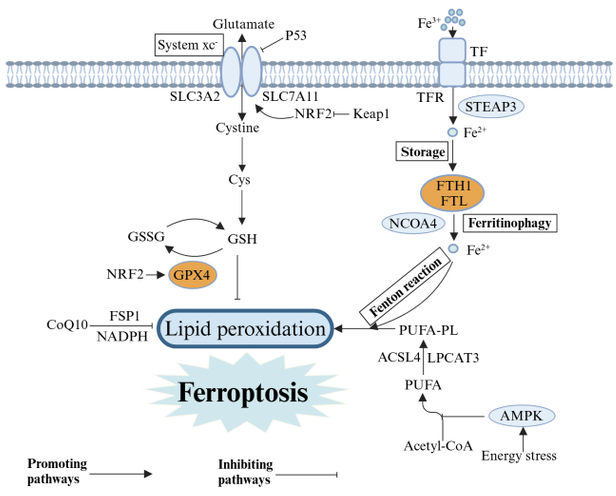
细胞内发生脂质过氧化反应不仅可以破坏脂质双分子层，进而影响细胞膜的结构与功能，同时酯化过程中可以降解具有细胞毒性的产物，导致细胞损伤并触发铁死亡[18-19]。

1.3　氨基酸抗氧化系统失调

氨基酸代谢在铁死亡中发挥着重要作用。氨基酸抗氧化系统包括胱氨酸/谷氨酸转运蛋白（cystine/glutamate antiporter system，system x_c^-）、GSH和GPX4。System x_c^-是位于细胞表面的氨基酸逆向转运系统，由溶质载体家族3成员2（solute carrier family 3 member 2，SLC3A2）和溶质载体家族7成员11（solute carrier family 7 member 11，SLC7A11）组成，SLC3A2用于维持蛋白稳定性，SLC7A11用于将胞外胱氨酸与胞内谷氨酸以1∶1的比例交换，将胱氨酸还原为半胱氨酸后与谷氨酸、甘氨酸以及合成酶在催化作用下，合成细胞内重要的抗氧化剂GSH[20]。GSH由半胱氨酸、谷氨酸、甘氨酸缩合形成，是GPX4的底物并为其提供电子供体来降解脂质过氧化物，从而抑制脂质过氧化引起的细胞膜损伤[21]。GPX4是细胞内的一种脂质过氧化物还原酶，在辅助因子GSH催化下将脂质过氧化物还原为正常脂质结构，从而维持脂质双分子层的稳态[22-23]。因此，维持System x_c^-的转运功能、增强GSH的合成并提高GPX4的表达和活性能够有效抑制氧化损伤和铁死亡的发生。

1.4　其他途径

除了上述途径会对细胞铁死亡的发生产生影响外，腺苷酸活化蛋白激酶（adenosine monophosphate activated protein kinase，AMPK）途径、kelch样环氧氯丙烷相关蛋白-1（kelch-like ECH-associated protein-1，Keap1）/核因子E2相关因子2（nuclear factor erythroid2-related factor 2，NRF2）通路、烟酰胺腺嘌呤二核苷酸磷酸（nicotinamide adenine dinucleotide phosphate，NADPH）/铁死亡抑制蛋白1（ferroptosis suppressor protein1，FSP1）/辅酶Q10（coenzyme Q10，CoQ10）信号通路以及肿瘤抑制因子P53（tumor suppressor p53，p53）通路也被证实参与调节铁死亡[24-27]（图1）。



System x_c^-: cystine/glutamate antiporter system. SLC7A11: solute carrier family 7 member 11. SLC3A2: solute carrier family 3 member 2. GSH: glutathione. Cys: cysteine. GPX4: glutathione peroxidase 4. GSSG: glutathione. PUFA: polyunsaturated fatty acid. ACSL4: long chain acyl-coenzyme A syntheatase 4. PUFA-PL: PUFA - containing phospholipids. LPCAT3: lysolecithin acetyl trans-ferase 3. LOX5: lipoxygenase. TF: ferritin. TFR: transferrin receptor 1. STEAP3: six-transmembrane epithelial antigen of the prostate 3. FTH1: ferritin heavy chain 1. FTL: ferritin light chain. NCOA4: nuclear receptor coactivator 4. P53: tumor suppressor P53. AMPK: adenosine monophosphate activated protein kinase. Keap1: kelch-like ECH-associated protein-1. NRF2: nuclear factor erythroid 2-related factor 2. NADPH: nicotinamide adenine dinucleotide phosphate. FSP1: ferroptosis suppressor protein 1. CoQ10: coenzyme Q10. Acetyl-CoA: acetoacetyl coenzyme A

Figure 1　Regulatory mechanisms associated with ferroptosis

图1　铁死亡相关调控机制

2　铁死亡调节牙周炎

2.1　铁死亡调节牙周软组织破坏

在体外实验中，Zhao等[28]用丁酸盐刺激牙周膜成纤维细胞（periodontal ligament fibroblasts，PDLFs），发现铁死亡调控蛋白ACSL4表达增加，GPX4、NCOA4、TFR1表达减少，细胞内GSH含量降

低，抑制PDLFs的生长和增殖，而加入铁死亡抑制剂Ferrostatin-1（Fer-1）逆转了这一效应，同时细胞活力升高，牙龈上皮屏障损害减少。Wang等[29]分别用*P.g*-LPS、铁死亡诱导剂Erastin处理牙周膜干细胞（periodontal ligament stem cells，PDLSCs）建立模型，观察到铁死亡抑制基因GPX4、SLC7A11 mRNA表达明显下调，铁死亡促进基因ACSL4 mRNA表达上调，细胞活力降低，GSH含量减少，而加入铁死亡抑制剂Fer-1或敲除长链非编码RNA中LINC00616后逆转了这一效应，初步证明了*P.g*可诱导PDLSCs铁死亡，降低细胞活力与分化能力。同样，Shi等[30]用*P.g*感染人类永生化口腔上皮细胞（human immortalized oral epithelial cells，HIOECs），发现铁死亡标志物GPX4和SLC7A11的蛋白表达显著降低，铁蛋白轻链（ferritin light chain，FTL）表达升高，胞质紧密粘连蛋白1（zonula occludens-1，ZO-1）、钙粘蛋白1（cadherin 1，CDH1）和闭合蛋白（occludin，OCLN）表达降低，而加入甲磺酸去铁胺（deferoxamine mesylate，DFO）可以逆转这一效应，初步证明了*P.g*可诱导HIOECs铁死亡参与上皮屏障的破坏。

在体内实验中，Xing等[31]建立牙周炎小鼠模型，发现铁死亡标志物ACSL4、TFR1 mRNA和蛋白的表达升高，GPX4 mRNA和蛋白的表达降低，牙龈组织内GSH含量减少，上皮钉突增长，牙龈正常结构破坏。同样，研究人员构建大鼠牙周炎模型，发现牙龈组织中铁死亡调控蛋白SLC3A2、SLC7A11和GPX4蛋白的表达降低，FTL表达升高，上皮连接蛋白ZO-1、CDH1和OCLN表达下降，采用micro-CT和组织学检查发现牙周附着丧失量逐天递增，而加入铁死亡抑制剂Fer-1逆转了这一效应，同时缓解了牙周软组织损伤[30, 32]。

2.2　铁死亡调节牙周硬组织破坏

在体外研究中，发现在*P.g*-LPS处理MLOY4骨细胞构建的牙周炎模型中，铁死亡标志物GPX4和SLC7A11 mRNA和蛋白的表达下调，4-羟基壬烯醛（4-hydroxynonenal，4-HNE）、TFR1、ACSL4、前列腺素内过氧化物合成酶2（prostaglandin endoperoxide synthase 2，PTGS2）mRNA的表达上调，骨细胞调节因子硬化蛋白（sclerostin，SOST）和调控核因子κB受体配体（receptor activator for nuclear factor-κB ligand，RANKL）mRNA和蛋白的表达升高，而加入铁死亡抑制剂Fer-1、Liproxstatin-1（Lip-1）或白藜芦醇（6.25 μg/mL）后逆转了这一效应，初步证明了*P.g*可促进MLOY4骨细胞铁死亡，进而导致牙周组织破骨吸收[33-34]。研究人员用铁死亡诱导剂Erastin处理小鼠下颌骨成骨细胞，发现铁死亡标志物GPX4、SLC7A11、NRF2、FPN mRNA和蛋白的表达显著减少，TFR1 mRNA和蛋白的表达升高，同时检测到成骨细胞调节基因Runt相关转录因子2（runt-related transcription factor 2，RUNX2）、成骨细胞特异性转录因子（osterix，OSX）和骨钙素（osteocalcin，OCN）mRNA的表达显著降低，GSH含量以及矿化结节数量减少，而加入铁死亡抑制剂Fer-1或IL-17（50 ng/mL）后逆转了这一效应，证明铁死亡参与调节牙周骨组织代谢[35-36]。同样，Liu等[37]在牙髓干细胞（dental pulp stem cells，DPSCs）中导入慢病毒载体ZDHHC16建立炎症模型，发现铁死亡调控蛋白GPX4表达下调，抑制GSH活性水平，同时检测到RUNX2、OCN、OSX、碱性磷酸酶（alkaline phosphatase，ALP）mRNA的表达下调，抑制成骨分化，证明铁死亡参与调节骨组织代谢。

在体内实验中，发现在牙周炎小鼠模型中铁死亡标志物ACSL4、PTGS2、4-HNE和TFR1 mRNA和蛋白的表达增加，而GPX4、SLC7A11和NRF2 mRNA和蛋白的表达降低，且通过CEJ-ABC距离分析可见牙槽骨丧失，牙槽骨中铁死亡标志物GSH含量减少，而加入铁死亡抑制剂Fer-1、IL-17、Lip-1、DFO或姜黄素[50、100、200 mg/(kg·d)]后可以逆转这一效应，牙槽骨破坏减少[30-31, 33, 35, 38]。Li等[34]建立糖尿病牙周炎小鼠模型，检测到铁死亡标志物GPX4和SLC7A11蛋白的表达降低，通过CEJ-ABC距离分析可见牙槽骨丧失，同时观察到牙槽骨中的骨细胞数量明显减少，而局部注射白藜芦醇（6.5 μg/mL）后逆转了这一效应，牙槽骨丧失量减少。同样，Fu等[32]建立大鼠牙周炎模型，发现铁死亡调控蛋白SLC3A2、SLC7A11和GPX4的表达下降，通过micro-CT和组织学检查观察到牙槽骨吸收增加，而加入铁死亡抑制剂Fer-1后可以逆转这一效应，同时炎症导致的骨吸收减少。

同样，生物信息学分析也进一步证实了铁死亡可以调控牙周骨组织的代谢。相关研究通过构建铁死亡相关基因免疫网络分类模型，证明了ALOX5、SLC2A14、XBP1、FTH1、SLC7A11、GCLC、CYBB和MAP1LC3A等是铁死亡的核心基因[39]。

2.3　铁死亡调节牙周炎症反应

在体外实验中，Xing等[31]用铁死亡诱导剂Erastin处理人牙龈成纤维细胞（human gingival

fibroblasts，HGFs）建立炎症模型，发现铁死亡标志物GPX4 mRNA和蛋白的表达下降，ACSL4 mRNA和蛋白的表达水平上升，细胞内GSH含量减少，炎性细胞因子白细胞介素-1β（interleukin 1β，IL-1β）、白细胞介素-6（interleukin 6，IL-6）和肿瘤坏死因子-α（tumor necrosis factor α，TNF-α）mRNA表达增强。同样，相关研究[40-41]用*P.g*-LPS刺激HGFs构建炎症模型，发现铁死亡标志物过氧化物酶6（peroxiredoxin 6，PRDX6）、TFR1和NRF2 mRNA和蛋白的表达降低，炎性细胞因子IL-6、IL-1β、TNF-α、PTGS2和TNF-α mRNA和蛋白的表达升高，细胞内GSH含量减少，而加入铁死亡抑制剂Fer-1或抑制PRDX6-aiPLA2活性后，削弱了上述这些变化，缓解了LPS诱导的牙周炎症反应。

Wang等[42]用具核梭杆菌感染PDLSCs，发现其中铁死亡标志物TFR1和TF mRNA和蛋白表达持续上调，GPX4 mRNA和蛋白表达逐渐下调，促炎细胞因子IL-1β、IL-6和TNF-α表达显著增加，表明具核梭杆菌可通过加剧细胞内铁超载和抑制脂质氢过氧化物解毒来诱导PDLSCs铁死亡，进而加重牙周炎症。同样，Wu等[43]用TNF-α处理PDLSCs建立牙周炎模型，发现铁死亡标志物GPX4、NRF2、NADPH mRNA和蛋白的表达显著降低，Keap1 mRNA和蛋白的表达显著增加，同时促炎细胞因子IL-6和IL-8 mRNA和蛋白的表达升高，抗炎细胞因子IL-10 mRNA和蛋白的表达降低，细胞内GSH含量减少，而加入抗菌肽Bomidin后，削弱了上述这些变化以及由TNF-α引起的炎症水平。

杜雪纯等[44]用*P.g*-LPS处理RAW264.7细胞构建炎症模型，发现铁死亡标志物ACSL4和TFR1 mRNA和蛋白的表达显著增加，GPX4 mRNA和蛋白的表达减少，而加入姜黄素后可以逆转这一效应，初步表明*P.g*-LPS可诱导RAW264.7细胞铁死亡，同时上调巨噬细胞中Toll样受体4（Toll-like receptor 4，TLR4）表达并调节炎症反应，进而加重牙周炎症反应。同时，Li等[34]在高糖环境下用*P.g*-LPS处理MLOY4骨细胞构建炎症模型，发现铁死亡标志物GPX4和SLC7A11 mRNA和蛋白的表达下调，促炎细胞因子IL-6、TNF-α和IL-1β mRNA和蛋白的表达升高，抗炎细胞因子IL-4和IL-10 mRNA的表达降低，而加入铁死亡抑制剂Fer-1或白藜芦醇（6.25 μg/mL）后，削弱了上述这些变化并同时缓解了牙周炎症状态。

在体内实验中，相关研究[33, 38, 43]发现在牙周炎小鼠中可检测到铁死亡标志物GPX4、NRF2、NADPH mRNA和蛋白的表达下调，ACSL4、SLC7A11和Keap1、TFR1、4-HNE、PTGS2 mRNA和蛋白的表达上调，促炎细胞因子IL-6、IL-1β、IL-8 mRNA和蛋白的表达升高，抗炎细胞因子IL-10 mRNA表达降低，牙周组织内GSH含量减少，而加入铁死亡抑制剂Fer-1、lip-1、姜黄素或抗菌肽Bomidin可以逆转这一效应，缓解牙周组织中的炎症反应[32]。同样，Fu等[32]构建牙周炎大鼠模型，检测到铁死亡标志物SLC3A2、SLC7A11和GPX4蛋白的表达随时间增长逐渐降低，炎性细胞因子IL-1β和TNF-α蛋白的表达增加，而加入铁死亡抑制剂Fer-1后逆转了这一效应，缓解了牙周炎症反应。

同样，生物信息学分析也进一步证实了铁死亡可以调控牙周炎症反应。研究人员构建了铁死亡相关基因免疫网络分类模型，证明了ALOX5、XBP1、IL-1β、IL-6、NFE2L2、SLC2A3、NCOA4、SLC1A5和HSPB1等是铁死亡的核心基因[39, 45-51]。

2.4　牙周病原菌诱导铁死亡调节系统性疾病进展

Xiong等[52]通过体内、体外实验，发现铁死亡基因ACSL4、PTGS2、SOCS1和NCOA4 mRNA表达水平上调，GPX4 mRNA表达下调，表明*P.g*可诱导肺组织细胞铁死亡，从而促进慢性阻塞性肺病。

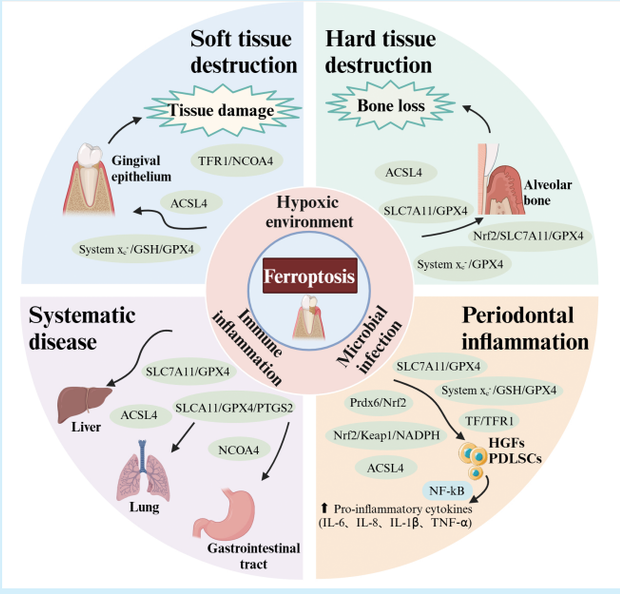
Yao等[53-54]分别用*P.g*感染L-02细胞非酒精性脂肪性肝病与酒精性脂肪性肝病体外模型，用小鼠灌饲*P.g*来建立非酒精性脂肪性肝病与酒精性脂肪性肝病体内模型，发现铁死亡标志物GPX4、SLCA11表达显著减少，ACSL4、NCOA4、PTGS2表达显著升高，同时促炎因子IL-6、IL-17表达显著上升，抗炎因子IL-10表达降低，而加入铁死亡抑制剂Fer-1或NF-κB信号抑制剂后可以逆转这一效应，证明了*P.g*诱导肝脏组织炎症，促进细胞铁死亡，导致非酒精性脂肪性肝病进展。同样，Yao等[55]分别在酒精刺激条件下用*P.g*感染L-02细胞以及小鼠灌饲*P.g*和酒精来建立体外、体内模型，发现相较于单纯的酒精作用，酒精和*P.g*联合作用下铁死亡标志物NCOA4、PTGS2 mRNA和蛋白的表达显著增加，GPX4 mRNA和蛋白的表达降低，而加入铁死亡抑制剂Fer-1后可以逆转这一效应，表明了*P.g*可以诱导细胞铁死亡，从而促进酒精性脂肪性肝病，引起肝脏损伤。

3　小结与展望

综上所述，相关研究已经证明了铁死亡参与

牙周炎的进程[56]。铁死亡可以通过以下4点参与牙周炎进程的调控(图2):①参与牙周软组织代谢的调节;②参与牙周硬组织代谢的调节;③参与调节牙周炎症反应;④参与调节牙周病原菌诱导的系统性疾病。铁死亡在牙周炎的治疗中可能具有潜在作用,为牙周炎的新治疗策略提供依据。

目前,已有相关研究报道,传统中药可以通过调节铁死亡的表达及活性来参与疾病的治疗,如白藜芦醇可以改变LPS诱导的心肌细胞铁死亡的抑制作用,从而改善内毒素血症小鼠的心肌损伤[57];姜黄素可以抑制葡萄糖诱导的心肌细胞铁死亡,从而缓解糖尿病诱导的心脏病[58]。本课题组认为中药的天然化合物可以通过调节铁死亡来预防和控制牙周炎,但相关药物的开发仍需进一步的基础和临床研究。



FT: ferritin. TFR1: transferrin receptor 1. ACSL4: long chain acyl-coenzyme A syntheatase 4. System x_c^-: cystine/glutamate antiporter system. GSH: glutathione. GPX4: glutathione peroxidase 4. SLC7A11: solute carrier family 7 member 11. PRDX6: peroxiredoxin 6. PTGS2: prostaglandin endoperoxide synthase 2. NADPH: nicotinamide adenine dinucleotide phosphate. Keap1: kelch-like ECH-associated protein-1. NRF2: nuclear factor erythroid 2-related factor 2. IL-1β: interleukin-1β. IL-8: interleukin-8. IL-6: interleukin-6. TNF-α: tumor necrosis factor α. HGFs: human gingival fibroblasts. PDLSCs: periodontal ligament stem cells

Figure 2　Role of ferroptosis in the occurrence and development of periodontitis

图2　铁死亡在牙周炎发生发展过程中的作用

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