血红素加氧酶-1在消化系统疾病中的作用

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摘要 血红素加氧酶-1(heme oxygenase-1, HO-1)是血红素分解代谢过程中的限速酶。HO-1及其降解产物(CO、胆绿素及Fe^{2+})能够通过各种途径调节机体免疫功能、抑制炎症反应和细胞凋亡, 在消化系统疾病中发挥潜在的保护作用。该文综述了*HO-1*基因的表达和调节及其在胃肠道和肝病中的作用。

关键词 血红素加氧酶-1; CO; 胆绿素; 消化系统

Roles of Heme Oxygenase-1 in Diseases of Digestive System

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Abstract Heme oxygenase-1 (HO-1) is a rate-limiting enzyme in the heme decomposition process. HO-1 and its degradative products (CO, biliverdin and Fe^{2+}) can regulate immune function, inhibit inflammatory reaction and cell apoptosis through a variety of ways, and play potential roles in the protection of gastrointestinal diseases. This review summarizes the mechanisms of *HO-1* gene expression and its regulation and the roles in the gastrointestinal and liver diseases.

Keywords heme oxygenase-1; CO; biliverdin; digestive system

血红素加氧酶(heme oxygenase, HO)是血红素氧化代谢过程中的限速酶。血红素水平受氧化应激相关因素调节, 如热休克、缺血、缺氧、活性氧(reactive oxygen species, ROS)和电离辐射等。HO可分为HO-1、HO-2和HO-3三个独立的亚型, 为不同基因编码产物, 但催化相同的生化反应。HO-1(32 kDa), 又称热休克蛋白-32(heat shock protein-32, HSP-32), 在很多组织中低水平表达。相关研究表明, 白细胞介素-1(interleukin-1, IL-1)、肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)、细菌脂多糖(lipopolysaccharide, LPS)、ROS和活性氮(reactive nitrogen species, RNS)等炎症因子都能够在体外诱导HO-1表达。HO-2(36 kDa)主要在神经和睾丸组织中表达, 能够维持细胞内环境的稳定。HO-3(33 kDa)是一种极少量的血红素降解酶, 只能从大鼠脑组织中分离出来[1]。

红细胞的平均寿命约为120 d, 单核巨噬细胞能够降解衰老的红细胞, 从而分离出血红素, 血红素在单核巨噬细胞微粒体内HO作用下氧化裂解为一氧化碳(CO)、胆绿素及Fe^{2+}, 发挥抗炎和抗氧化应激相关的细胞保护机制[2]。CO是重要的气体信号分子, 可上调环鸟苷酸(syclic guanosine monophosphate, cGMP), 导致血管舒张和抑制血小板聚集; 还能通过自分泌或旁分泌的方式与细胞内可溶性鸟苷酸

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环化酶(soluble guanylate cyclase, sGC)结合, 发挥抗炎和抗凋亡的作用[3]。CO的抗炎作用主要是通过p38/MAPK(mitogen-activated protein kinase)途径介导的[4]。p38/MAPK被氧化应激激活后, 能够诱导核转录相关因子2(nuclear factor E2-related factor 2, Nrf2)与*HO-1*基因启动子的抗氧化应答元件(antioxidant response element, ARE)结合, 从而启动*HO-1*的转录。通过此途径, 低浓度的CO能通过有丝分裂原激活蛋白激酶减少细胞凋亡。胆绿素是胆红素的前体物, 在耦合反应中经胆绿素还原酶迅速转化为胆红素, 而胆红素作为一种强抗氧化剂, 能够直接清除ROS并使自身转变为胆绿素[5]。胆绿素和胆红素在一定浓度下是内源性强抗氧化剂, 具有抗脂质过氧化和保护细胞免受氧自由基损伤的作用。Nakao等[6]发现, 胆绿素能够抑制诱导型一氧化氮合酶(inducible nitric oxide synthase, *iNOS*)、环氧化酶-2(cyclooxygenase-2, *COX-2*)、白细胞介素-6(interleukin-6, *IL-6*)和白细胞介素-1β(interleukin-1β, *IL-1β*)等基因表达, 还能够减少小肠移植模型大鼠空肠肌层中性粒细胞的浸润。此外, 胆绿素是芳香烃受体的内源性配体(aryl hydrocarbon receptor, AhR), 可预防由白细胞介素-22(interleukin-22, IL-22)诱导的实验性急性胰腺炎[7]。血红素代谢产物Fe^{2+}也参与多种基因调控, 如*iNOS*的基因调控, iNOS激活产生的高浓度NO能够导致组织损伤。Fe^{2+}可通过抑制iNOS表达, 进而降低NO水平。Fe^{2+}还可诱导铁蛋白的合成, 减少细胞内游离铁的蓄积, 从而减轻ROS导致的细胞损伤, 但其具体作用机制有待进一步研究。炎症发生后, 免疫反应能够产生T辅助细胞1(T helper 1, Th1)和免疫反应表现型的细胞因子(IL-1、TNF-α和IL-6), *HO-1*基因敲除小鼠模型由于β-干扰素(interferon β, *IFN-β*)基因表达缺陷容易导致脓毒血症[8]。此外, HO-1在胚胎发育中发挥重要作用, HO-1的缺失会导致胎儿和新生儿死亡率升高; 患有溶血性贫血、弥漫性血管内凝血、肾炎或无脾症的多数患儿, 出现贫血、红细胞碎片和铁蛋白沉积等症状, 幼年期表现为生长发育迟缓[9]。*HO-2*基因缺失的小鼠免疫调节系统正常, 但神经系统存在缺陷。

1 HO-1的表达

HO-1在肝脏枯否氏细胞、脾脏巨噬细胞和树突状细胞(dendritic cell, DC)中高表达[10]。LPS刺激后, 这些细胞HO-1表达增加并且参与抑制多种炎性基因的表达[11]。在DC中使用HO-1诱导剂能够改变DC的成熟状态及其与其他细胞的互作[12], 例如DC中HO-1的高表达能够导致$CD4^+$ T细胞的增殖能力减弱[13]。HO-1在髓系祖细胞分化过程中表达增加, 提示在髓系祖细胞分化为巨噬细胞过程中, HO-1发挥了重要作用[14]。在组织水平, HO-1在肝、胃、小肠和结肠黏膜中均有表达[15]。在胃溃疡、放射性肠炎、炎性肠病和肝纤维化中, HO-1表达水平都有增加[1]。

2 HO-1的调节

*HO-1*基因的转录主要受Nrf2和血红素结合蛋白筛查因子1(BTB and CNC homology 1, Bach1)调控。细胞氧化应激反应中的重要调控因子1(Kelch-like ECH-associated protein 1, Keap1)/Nrf2/HO-1信号通路在细胞抗氧化损伤和抗炎过程中发挥重要作用。生理状态下, Nrf2与细胞质分子伴侣蛋白Keap1偶联并被锚定在细胞质中, Nrf2处于相对失活状态。当细胞暴露于ROS时, Keap1的构象发生改变, Nrf2从二聚体上解离并转移入核与*HO-1*基因启动子AREs结合, 进而调控下游抗氧化基因*HO-1*等表达, 清除多余的ROS, 发挥抗应激作用。生理状态下, Bach1在核内与*HO-1*基因启动子AREs紧密结合, 抑制*HO-1*基因表达。当细胞暴露于ROS时, Bach1能与胞内血红素结合并引起Bach1构象的改变, 使其从AREs分离并降解[16]。

此外, HO-1还受其他的信号通路调控, MAPK信号通路通过磷酸化Ser-188参与HO-1的诱导[17]。前列腺素能通过磷脂酰肌醇-3激酶(phosphatidylinositol-3 kinase, PI3K)/蛋白激酶B(serine/threonine kinase, Akt)信号通路促进HO-1的表达[18]。抗炎细胞因子IL-10通过p38/MAPK途径诱导*HO-1*基因表达。而HO-1与IL-10存在正反馈调节, 在活化的巨噬细胞中, HO-1及其产物CO能够诱导IL-10表达, 从而抑制iNOS的表达和NO的产生, 进一步增强IL-10的抗炎效应。同时, HO-1和IL-10还能够协同抑制炎症因子TNF-α的表达[4]。

3 HO-1与上消化道的疾病

3.1 HO-1在胃食管反流疾病中的作用

食管下括约肌(lower esophageal sphincter, LES)松弛功能失调能够引起胃食管反流疾病。HO-1

可能在LES功能的维持中发挥作用。Kruel等[19]在鼠的食管反流动物模型中研究发现, 十二指肠内容物反流引起的反流性食管炎引发了较强的氧化应激, HO-1可能在反流性食管炎和食管癌的发生中起关键作用。临床上, 在食管十二指肠吻合术(esophagoduodenal anastomosis, EDA)中常通过辅助手段上调HO-1的表达水平[19]。

3.2 HO-1在胃溃疡中的作用

非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAID)具有解热、镇痛、抗炎和抗风湿等作用, 长期服用容易导致食管炎和胃溃疡等疾病。Uc等[20]对NSAID药物介导的胃溃疡模型研究发现, 溃疡组织中IL-6和TNF-α表达量增加。在溃疡模型中使用HO-1的诱导剂钴原卟啉(cobalt protoporphyrin, CoPP)后, HO-1的表达增加, 可减少胃黏膜中性粒细胞浸润和炎症因子的表达, 抑制细胞凋亡。相反, Aburaya等[21]研究发现, HO-1抑制剂锡中卟啉(tin mesoporphyrin, SnMP)的使用会导致胃黏膜病变加重, 细胞凋亡增加。Cheng等[22]研究证明, 在NSAID酮洛芬介导的胃溃疡模型中, 使用儿茶素(一种膳食多酚抗氧化剂)可激活Nrf2诱导*HO-1*基因表达, 达到抑制上皮细胞氧化损伤的目的。Song等[23]研究表明, 异泽兰素在小鼠体内或体外培养的食管上皮细胞中通过Nrf2、胞外信号调节激酶(extracellular signal-related kinase, ERK)和PI3K/Akt信号通路可有效诱导*HO-1*基因表达, 从而减轻NSAID的细胞损伤作用。大量的研究表明, 聚普瑞锌剂、异泽兰素和兰索拉唑等药物都可以介导HO-1的上调, 在消化道上部疾病中都能够发挥细胞保护作用[24]。

3.3 HO-1在糖尿病性胃轻瘫中的作用

糖尿病容易引起植物神经功能紊乱、胃动力下降, 导致糖尿病性胃轻瘫。糖尿病性胃轻瘫常伴随胃排空延迟, HO-1在糖尿病性胃轻瘫的治疗中发挥重要作用。氯化血红素可导致胃HO-1$^+$CD206$^+$巨噬细胞增殖, 还会引起促炎症型M1巨噬细胞向创伤愈合诱导型M2巨噬细胞转型[25]。HO-1$^+$CD206$^+$巨噬细胞的减少和氧化应激能够导致胃肠间质细胞(interstitial cells of Cajal, ICC)中酪氨酸激酶低表达, 从而导致糖尿病性胃轻瘫出现胃排空延迟[26]。Takagi等[27]在非肥胖型糖尿病(non-obese diabetic, NOD)性胃轻瘫模型中发现, 氯化血红素可通过减少ROS和提高酪氨酸激酶活性, 达到保护ICC的作用。

4 HO-1与下消化道的疾病

4.1 HO-1在术后肠梗阻和脓毒血症中的作用

在肠组织中, HO-1主要在肠黏膜上皮细胞中表达[28]。HO-1可以通过减少炎症细胞浸润减少肠黏膜损伤[29]。Yoda等[30]在吲哚美辛介导的小肠损伤模型中研究发现, 通过兰索拉唑和萝卜硫素诱导*HO-1*基因表达, 能够减轻小肠损伤。CO介导许多HO-1的生物学作用。CO的释放分子(CO releasing molecules, CO-RM$_S$)在术后肠梗阻中能减轻肠道损伤和脓毒血症症状。Yeh等[17]在患脓毒血症的小鼠体内使用CO-RMs 6 h之后, 发现细菌计数减少, 全身中毒症状减轻。De Backer等[17]发现, CO-RMs能够通过MAPK信号通路(p38和ERK1/2)诱导*HO-1*基因表达, 发挥抗炎作用, 从而改善术后肠梗阻。相反, 使用HO-1抑制剂卟铬(chromium mesoporphyrin, CrMP)可使原本的保护作用消失, 加重肠道损伤。这些研究表明, HO-1可能在术后肠梗阻和脓毒血症相关小肠疾病中发挥重要作用。

4.2 HO-1在肠道缺血/再灌注损伤(ischemia/reperfusion, I/R)中的作用

由于血液供应的中断和恢复引起的I/R常会发生肠道损伤。HO-1转录因子Nrf2是细胞调节抗氧化应激反应的重要转录因子, 可上调多种抗氧化酶及解毒酶, 提高谷胱甘肽及超氧化物歧化酶等抗氧化物质的水平, 清除自由基等氧化物质, 维持细胞内的氧化还原平衡状态, 发挥细胞保护作用。在I/R引起小肠的损伤中, HO-1具有抗炎和细胞保护作用[31]。因此, 在肠道I/R时服用CoPP和谷氨酰胺等诱导HO-1表达, 能够抑制炎性细胞因子, 达到减轻I/R损伤的目的[32]。Yano等[33]在*HO-1*和*Bach1*基因缺失的小鼠模型研究发现, *HO-1*缺失的小鼠体内*HO-1*表达水平降低, 加剧了I/R损伤, 而*Bach1*缺失的小鼠体内*HO-1*高表达, 能够减轻I/R损伤。Scott等[34]研究发现, 低浓度的CO可减轻I/R引起的肠道炎性反应, 还可预防肠组织移植中I/R损伤。同时, 胆绿素和胆红素也能够保护细胞免受I/R损伤[34]。但是, *HO-1*的高表达会引起血管狭窄或阻塞, 导致大肠血流量不足进而引起缺血性结肠炎, 因此, *HO-1*的高表达也被认为是缺血性结肠炎的病因之一[35]。

4.3 HO-1在炎性肠病中的作用

炎性肠病(inflammatory bowel disease, IBD)包括溃疡性结肠炎和克罗恩病, 溃疡性结肠炎只累及

结肠和直肠, 而克罗恩病能够影响胃肠道的任何部位[36]。Takagi等[29]在结肠炎的患者和结肠炎小鼠模型中发现, HO-1表达量均出现了升高的现象。氯化血红素、血红素和CoPP均可促进大肠组织的HO-1高表达, 改善结肠炎预后[37]。其中, 氯化血红素还能够通过抑制iNOS表达改善结肠癌预后。Wang等[38]在三硝基苯磺酸(2,4,6-trinitrobenzene sulfonic acid, TNBS)诱导的急性结肠炎模型中研究发现, 受损结肠组织中HO-1的表达和活性均增加, HO-1通过抑制iNOS表达及NO生成, 对结肠组织提供了保护作用。Paul等[29]在聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的结肠炎小鼠模型中研究发现, 使用HO-1诱导剂CoPP能够减轻结肠的炎症。相反, Naito等[39]使用HO-1抑制剂SnMP和锌原卟啉(zinc protoporphyrin, ZnPP)降低了HO-1的活性, 加重结肠的炎症损伤。Khor等[40]在*Nrf2*缺陷型小鼠中研究发现, HO-1的表达活性下降, 结肠炎发病率升高。而*Bach1*基因缺陷型小鼠中, 发现结肠黏膜中HO-1表达增加, 能够减轻TNBS诱导的结肠组织炎症[41]。

同样, 胆绿素和CO在结肠炎中也发挥重要作用。在DSS诱导的急性结肠炎模型中, 分别给予胆绿素和CoPP, 结果发现, 给予胆绿素的实验组能产生更强的保护效应。在Th1介导的慢性结肠炎小鼠模型中, CO能够通过抑制iNOS的活性和NO的生成, 发挥抗炎作用[42]。在Th2介导的T细胞受体α(T cell receptor α, *TCRα*)基因缺陷小鼠结肠炎模型中, CO能够促进抗炎因子IL-10和IL-22的释放而发挥作用[43]。Schulz等[44]在TNBS诱导的急性结肠炎模型研究时发现, 5-氨基水杨酸(5-amino salicylic acid, 5-ASA)可以促进HO-1表达, 减轻结肠损伤。

4.4 HO-1在坏死性小肠结肠炎中的作用

坏死性小肠结肠炎(necrotizing enterocolitis, NEC)是在部分早产儿或低体重儿中出现的病变, 主要累及远端回肠和结肠。HO-1的活性影响NEC的发生发展, *HO-1*基因敲除小鼠体内IL-1β、P-选凝素和基质金属蛋白酶2(matrix metalloprotein 2, MMP2)的表达升高, 肠道炎症加剧, 且更容易发生肠损伤和NEC, 小鼠死亡率升高[45]。

4.5 HO-1在放射性肠炎中的作用

放射性肠炎是腹部的放射治疗出现的一种肠内壁黏膜损伤伴有炎细胞浸润的疾病。在大鼠实验中, 谷氨酰胺能够诱导细胞内HO-1高表达, HO-1通过抑制核转录因子-kappa B(nuclear transcription factor-kappa B, NF-κB)通路, 降低过氧化物酶(myeloperoxidase, MPO)和胱冬肽酶-3(cysteine protease protein-3, caspase-3)活性以及丙二醛(malondialdehyde, MDA)水平, 从而抑制细胞凋亡, 发挥改善放射性肠炎预后的作用。同样, 生长抑素类似物奥曲肽也能通过诱导细胞HO-1高表达来减轻放射性肠炎损伤[46]。相反地, 使用ZnPP抑制HO-1表达后再用X线照射大鼠, 会加重大鼠肠道放射损伤[47]。

4.6 HO-1在胰腺疾病中的作用

胰腺炎是一种常见的炎性疾病, 按病程分为急性胰腺炎(acute pancreatitis, AP)和慢性胰腺炎(chronic pancreatitis, CP)。临床上, AP可以从短暂轻微的自限性炎症发展到高死亡率的多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS)[48]。AP常见的诱因是结石和过量饮酒, 此外还有遗传、肥胖和吸烟等。AP反复发作可以引起CP。CP的特点是炎症反应、纤维化以及慢性腹痛, 它也是胰腺导管癌(pancreatic ductal adenocarcinoma, PDAC)发生的高危因素[49]。CP的发生率较AP低, 但是患者的生活质量显著降低。目前, 急慢性胰腺炎的治疗局限于改善疾病症状及预后, 疾病的病因亟待研究。

动物AP模型研究表明, 用蛙皮素或缺乏胆碱的饮食(choline-deficient diet, CDD)处理能产生不同程度的AP, 并且动物体内HO-1表达增加; 在腹腔或静脉注射氯化血红素2 h后动物体内HO-1表达量升高, 提示氯化血红素可能对胰腺炎有治疗作用[50]。临床AP研究表明, AP进展期患者外周血单核–巨噬细胞HO-1的表达量升高, 随着AP病情好转而下降[51]; 研究表明, 胰腺炎中HO-1及其效应分子主要是通过巨噬细胞发挥作用, HO-1能够促进巨噬细胞由M1巨噬细胞向创伤愈合诱导型M2巨噬细胞转型, 诱导抗炎因子IL-10释放, 抑制促炎因子(TNF-α、IL-6和IL-1β)释放, 从而缓解重症AP的症状[50]; 此外, CO能够阻断NF-κB信号通路, 减轻实验性AP[52]。而胆绿素通过激活AhR/IL-22信号通路也能减轻实验性AP症状[7]。在胰腺纤维化中, 起主要作用的是胰腺星状细胞(pancreatic stellate cells, PSCs)。研究发现, 姜黄素可以促进HO-1表达, 抑制PSCs增殖, 从而减缓纤维化进程[53]。而CO能通过激活p38/MAPK途径来抑制PSCs增殖, 减缓纤维化进程[53]。同样, 体外研究表明, HO-1在CP中有潜在的保护作用, 但仍需要进一步验证。

5　HO-1在肝脏疾病中的作用

在休克或外科手术如肝切除和肝移植中常会出现肝I/R损伤。在肝脏慢性I/R损伤大鼠模型中, 手术前使用CoPP或过表达*HO-1*可减轻肝脏I/R损伤, 其机制可能是通过NF-κB通路减少肝细胞凋亡[54]。类似地, 在急性肝脏I/R损伤小鼠模型中也发现HO-1高表达能够起到保护肝脏的作用[55], 其机制是血红素促进HO-1表达, HO-1通过p38/MAPK信号通路增强细胞自噬作用, 清除损伤的细胞。实验还发现, 肝脏脓毒症或LPS也能促进巨噬细胞表达HO-1, 减少肝细胞死亡并通过自噬作用保护肝脏[56]。相反, 使用HO-1抑制剂ZnPP会增加肝细胞损伤和凋亡。

终末期肝病的治疗方法是原位肝移植(orthotopic liver transplantation, OLT)。然而, 移植造成的I/R损伤会通过FasL(Fas ligand)凋亡途径引起排斥反应[57]。在OLT动物模型中研究发现, HO-1能阻断FasL介导的细胞凋亡, 提高肝移植存活率。CO能减少Th-1型细胞因子水平缓解肝移植的排斥反应[58]。在人体肝移植临床研究中发现, 相对于移植前诱导*HO-1*高表达, 移植时诱导*HO-1*的表达能更好地发挥保护作用, 增强肝胆功能[59]。临床研究还发现, A(-413)T基因型(*HO-1*高表达)的供体肝脏相比于TT基因型(*HO-1*低表达)的供体肝脏, 移植1年后存活率更高, A(-413)T基因型的患者比TT基因型患者接受肝移植后体内HO-1表达量更高, 血清转氨酶上升幅度更小[60]。

肝脏纤维化是炎症和氧化刺激激活肝星状细胞(hepatic stellate cells, HSCs), 导致连续的创伤愈合反应而引起的疾病。HO-1能够影响肝纤维化的发展。实验中, 用腺病毒转染处理使造血干细胞高表达*HO-1*可以抑制HSC增殖, 抑制I型胶原和转化生长因子-β_1(transforming growth factor-β_1, TGF-β_1)转录, 减轻四氯化碳(carbon tetrachloride, CCl_4)诱导的肝脏结节性纤维化[61]。HO-1也能影响酒精性和免疫性肝损伤的进程[57,62]。在免疫性肝损伤模型中, 应用CoPP或腺病毒转染使*HO-1*高表达, 可以保护小鼠肝脏免遭抗CD95抗体(ab)、抗CD3抗体(ab)、D-氨基半乳糖、LPS和TNF-α的损害。其机制包括: HO-1通过抑制胱冬肽酶-3的激活保护肝细胞[62]; CO与胆绿素通过抑制Th-1型炎性细胞因子TNF-α和干扰素-γ(interferon-γ, IFN-γ)减轻免疫性肝损伤[57]。在酒精性肝损伤中, 血红素和槲皮素能促进肝细胞表达HO-1, 并通过MAPK/Nrf2通路减轻乙醇引起的肝细胞氧化损伤[63]; 一定浓度的血红素和CO可以抑制乙醇的直接细胞毒性和乙醇诱导的细胞色素P450 2E1(CYP2E1)的活性, 对肝细胞产生保护作用[64]。相反, 使用MAPK信号转导剂、ZnPP或原卟啉(protoporphyrin, SnPP)会显著降低槲皮素的保护作用并增加乙醇的细胞毒性, 加重肝损伤[63]。

6　结语

综上所述, HO-1是血红素分解代谢过程中的限速酶, 主要受Nrf2和Bach1因子调控(图1)。随着研究深入, 谷氨酰胺、生长抑素及其类似物、姜黄素、氯化血红素、蛙皮素、CoPP等HO-1诱导剂以及SnPP、SnMP、ZnPP等抑制剂已经在基础研究和临床治疗中得到广泛应用。HO-1及其降解产物(CO、胆绿素及Fe^{2+})能够通过各种途径调节机体免疫功能、抑制炎症反应和细胞凋亡, 在消化系统疾病中发挥重要的保护作用。但是, 高浓度的HO-1、胆绿素及CO具有组织毒性和神经毒性, 会导致部分患者出现头痛、呕吐等症状。虽然大量的动物实验证实, HO-1具有良好的临床应用前景, 但其临床的推广仍有待进一步验证。

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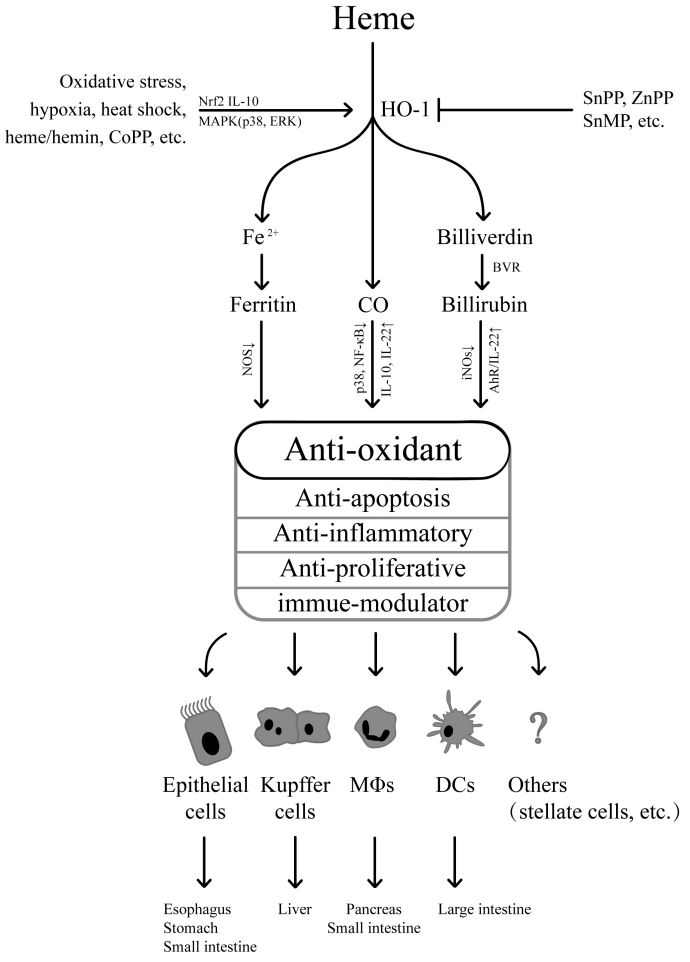

图1 HO-1在消化系统疾病中的作用(根据参考文献[1]修改)

Fig.1 Roles of HO-1 in diseases of digestive system (modified from reference [1])

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