

## 综述

## NCOA4介导的铁自噬及其相关疾病的研究进展

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**摘要:** 核受体共激活因子4 (nuclear receptor co-activator 4, NCOA4)作为一种选择性底物受体, 可与胞质铁储存复合物铁蛋白结合, 介导铁自噬(ferritinophagy), 释放大游离铁, 调控体内铁代谢平衡, 从而参与人体生长、发育、代谢等多种生物过程。近年来研究发现, NCOA4介导的铁自噬与肝纤维化、肾细胞癌、神经退行性疾病等多种铁代谢相关疾病的发生及发展密切相关。已经确定一些临床药物可调节NCOA4介导的铁自噬, 显著影响疾病的进展和疗效。本文旨在探讨NCOA4介导的铁自噬在相关疾病中作用的研究进展, 以期临床靶向治疗提供新思路。

**关键词:** NCOA4; 铁自噬; 疾病; 药物

## Research progress on NCOA4-mediated ferritinophagy and related diseases

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**Abstract:** Nuclear receptor co-activator 4 (NCOA4) acts as a selective cargo receptor that binds to ferritin, a cytoplasmic iron storage complex. By mediating ferritinophagy, NCOA4 regulates iron metabolism and releases free iron in the body, thus playing a crucial role in a variety of biological processes, including growth, development, and metabolism. Recent studies have shown that NCOA4-mediated ferritinophagy is closely associated with the occurrence and development of iron metabolism-related diseases, such as liver fibrosis, renal cell carcinoma, and neurodegenerative diseases. In addition, a number of clinical drugs have been identified to modulate NCOA4-mediated ferritinophagy, significantly affecting disease progression and treatment efficacy. This paper aims to review the current research progress on the role of NCOA4-mediated ferritinophagy in related diseases, in order to provide new ideas for targeted clinical therapy.

**Key words:** nuclear receptor co-activator 4 (NCOA4); ferritinophagy; disease; drugs

铁是细胞正常生理功能所需的重要生物金属, 在广泛的细胞代谢过程中发挥作用, 包括红细胞生成、氧结合运输、能量代谢, 以及DNA合成修复等。细胞内铁稳态是一个高度调节的过程, 它依赖

于许多参与铁转运[如转铁蛋白(transferrin, Tf)和转铁蛋白受体(transferrin receptor, TfR)]、储存[铁蛋白, 分为重链(H链, ferritin heavy chain, FTH)和轻链(L链, ferritin light chain, FTL)]和输出[如铁转运

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蛋白(ferroportin, FPN)]的蛋白质<sup>[1]</sup>。铁蛋白可通过两种机制降解:溶酶体和蛋白酶体<sup>[2]</sup>。2014年 Mancias 等<sup>[3]</sup>首次提出铁自噬(ferritinophagy),它是一种特殊类型的经由溶酶体的铁蛋白选择性自噬降解方式,是铁释放的主要过程,蛋白质组学鉴定出核受体共激活因子4 (nuclear receptor co-activator 4, NCOA4)是铁蛋白自噬周转(铁蛋白吞噬)的选择性底物受体<sup>[3]</sup>,其缺乏可引起铁蛋白周转率和生物可利用细胞铁降低,导致贫血和对铁过载敏感性增加;而过表达 NCOA4 可引起游离铁过载,导致氧化应激甚至铁死亡(ferroptosis),从而诱发多种疾病的发生、

发展<sup>[4]</sup>,故 NCOA4 对维持细胞内铁的生物利用度和铁稳态起着至关重要的作用。本文就近年来国内外关于 NCOA4 介导的铁自噬在相关疾病中的最新研究进展进行综述。

## 1 NCOA4介导铁自噬的生物学作用

NCOA4 介导铁自噬的基本生物学作用是通过选择性降解铁蛋白调控铁代谢(图1),在此基础上, NCOA4 参与体内与铁代谢密切相关的生物学过程,如红细胞生成、线粒体呼吸等。以下具体介绍相关生物学过程。

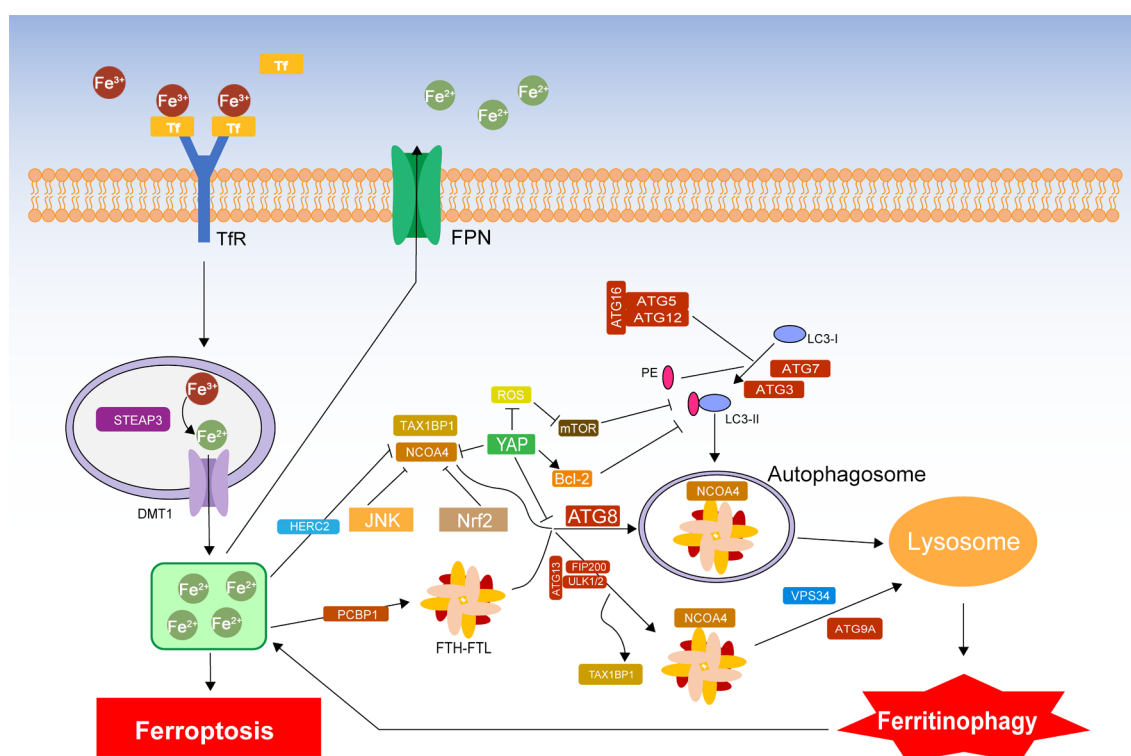


图 1. 核受体共激活因子4 (NCOA4)介导铁自噬的主要分子机制

Fig. 1. The key mechanisms of nuclear receptor co-activator 4 (NCOA4)-mediated ferritinophagy. (1) Classical autophagy pathway: NCOA4 and ferritin, mediated by autophagy related gene 8 (ATG8), are wrapped by membrane-bound LC3-II to form autophagosomes, then the latter are translocated to lysosome for ferritinophagy; (2) ESCRT (endosomal sorting complex required for transport) mechanism: UNC-51-like kinase1/2 (ULK1/2)-focal adhesion kinase family interacting protein of 200 kDa (FIP200) complex regulates the dissociation of NCOA4 from Tax1-binding protein 1 (TAX1BP1) and the combination with ferritin heavy chain (FTH). Both ATG9A and VPS34 (class III phosphatidylinositol 3-kinases) are collectively required for the trafficking of NCOA4 and ferritin to lysosomes; (3) Other regulation mechanisms: Yes associated protein (YAP), nuclear factor E2 related factor 2 (Nrf2), and c-Jun N-terminal kinase (JNK) inhibit NCOA4-mediated ferritinophagy. T-shaped arrows represent inhibition. Tf, transferrin; TfR, transferrin receptor; FPN, ferroportin; STEAP3, six-transmembrane epithelial antigen of prostate 3; DMT1, divalent metal transporter 1; HERC2, HECT and RLD domain containing E3 ubiquitin protein ligase 2; PCBP1, polyC-binding protein 1; FTL, ferritin light chain; ROS, reactive oxygen species; mTOR, mammalian target of rapamycin; Bcl-2, B-cell lymphoma/leukemia-2; PE, phosphatidylethanolamine.

### 1.1 调控铁代谢

NCOA4主要由两种亚型：NCOA4 $\alpha$  (614 aa)和NCOA4 $\beta$  (287 aa)。NCOA4 $\alpha$ 具有NCOA4 $\beta$ 中不具有的239~565片段<sup>[5, 6]</sup>。发生铁自噬时，NCOA4 $\alpha$ 上的保守C末端383~522片段特异性识别、结合FTH上的保守表面精氨酸(R23)，并且残余活性也保留在较小的片段(485~509)中。此过程主要涉及NCOA4疏水残基W497，其次可能还涉及I489、S492、L494和L498<sup>[7]</sup>。远紫外区圆二色光谱(FarUV CD spectra)结果显示，上述383~522片段具有高比例的非结构化二级结构，只有少量预测的螺旋或 $\beta$ 链结构，与预计包含四个 $\alpha$ 螺旋的离散子结构域有所不同<sup>[7, 8]</sup>。NCOA4与FTH结合后通过与自噬相关基因(autophagy related genes, ATG) 8样蛋白如GABARAP (GABA type A receptor-associated protein) 和GABARAPL1 (GABA type A receptor-associated protein-like 1)相互作用<sup>[3, 9]</sup>，促进FTH转运至自噬体，随后至溶酶体进行降解，铁蛋白核心Fe<sup>3+</sup>通过前列腺六段跨膜上皮抗原3 (six-transmembrane epithelial antigen of prostate 3, STEAP3)还原为Fe<sup>2+</sup><sup>[10]</sup>，释放到胞质中成为游离铁，在基础和缺铁条件下维持铁的释放。沉默或敲除NCOA4，细胞内FTH、FTL、TfR1、铁调节蛋白(iron regulatory protein)表达上调，铁蛋白蓄积，铁更新利用受阻，游离铁下降，导致生物可利用的细胞内铁显著减少，出现不依赖于铁调素(hepcidin)的铁过载，从而改变细胞内铁稳态网络<sup>[9, 11]</sup>。

亲和纯化质谱法鉴定结果显示，铁蛋白亚基(FTL、FTH1)和HERC2 (HECT and RLD domain containing E3 ubiquitin protein ligase 2)可与NCOA4相互作用，后者CUL7同源结构域2553~2639片段可与NCOA4的383~522片段结合。在铁充足的细胞条件下，NCOA4与HERC2的结合增加，导致NCOA4的蛋白酶体降解，抑制铁自噬并增加铁蛋白的储存；在缺铁条件下，NCOA4的铁占有率降低，HERC2与NCOA4的结合减少，导致NCOA4稳定并诱导铁蛋白降解和铁释放<sup>[7]</sup>。在NCOA4敲除(knockout, KO)的小鼠胚胎成纤维细胞中的研究显示，NCOA4存在两种状态<sup>[12, 13]</sup>：NCOA4凝聚(NCOA4 condensation)和NCOA4降解(NCOA4 degradation)。在铁充足的细胞早期阶段，铁与NCOA4固有无序区域结合产生多价相互作用，诱导形成不溶性NCOA4凝聚物，并减弱NCOA4与铁

蛋白之间的相互作用，因此铁蛋白与NCOA4凝聚物隔离而在细胞中积累，从而储存过量的铁；随着补充铁时间的延长和铁含量的增加，不溶性的NCOA4凝聚物与铁蛋白相互作用，通过依赖于Tax1结合蛋白1 (Tax1-binding protein 1, TAX1BP1)但不依赖于ATG7的非经典自噬途径，将铁蛋白递送至溶酶体释放铁，从而防止由于铁储存过多和铁摄取减少导致的相对缺铁。以上结果表明，铁与NCOA4的结合可调节NCOA4的生化特性，形成不溶的固体状凝聚物，NCOA4-铁蛋白轴根据细胞铁的可利用性，经由NCOA4的铁结合活性，通过促进生物分子凝聚物的形成，以及降低与铁蛋白相互作用，来微调细胞内铁稳态，从而在富铁细胞铁蛋白降解中起着关键作用；而在铁耗竭的情况下，不与铁相互作用的NCOA4是可溶的，可以有效地与铁蛋白结合，并通过ATG7依赖性、TAX1BP1非依赖性自噬有效地传递铁蛋白，使细胞能够使用储存铁，从而避免铁缺乏。

目前NCOA4-FTH1递送至溶酶体的确切机制尚不完全清楚，尽管体外结合实验结果表明，NCOA4与多种ATG蛋白相关，经典的自噬通路(含ATG7)可能在铁蛋白递送至溶酶体方面发挥着重要作用<sup>[14, 15]</sup>，但研究显示，自噬基因ATG16L1、ATG14、ATG7和ATG3的缺失并不会严重影响NCOA4的基础水平，用v-ATP酶抑制剂巴弗洛霉素A1(bafilomycin A1)抑制自噬后也不会使NCOA4蓄积，在NCOA4中也没有发现与自噬典型的微管相关蛋白1轻链3 (microtubule-associated protein 1 light chain 3, LC3)相互作用区基序<sup>[16]</sup>，表明没有ATG7的情况下，NCOA4仍然可以进行持续的溶酶体降解，因此可能存在其他非经典的自噬结合基序，NCOA4可与这些替代基序相互作用，通过多种途径降解铁蛋白<sup>[16]</sup>。每种途径的作用可能根据细胞类型甚至铁缺乏类型而不同，例如，Goodwin等人<sup>[16]</sup>报道了一种不依赖于经典ATG8自噬途径的高度调控的铁蛋白降解替代途径——内体分选转运复合体(endosomal sorting complex required for transport, ESCRT)机制，即ESCRT介导的内体分选途径，涉及TAX1BP1、200 kDa黏着斑激酶家族相互作用蛋白(focal adhesion kinase family interacting protein of 200 kDa, FIP200)、ATG9A、III型磷脂酰肌醇3-激酶(class III phosphatidylinositol 3-kinases, PI3K或称为VPS34)；TAX1BP1与NCOA4下调之间存在相关性，

TAX1BP1是NCOA4的重要相互作用物,对于溶酶体降解铁蛋白至关重要;ATG9A的高尔基体定位对于铁蛋白更新非常重要,ATG9A缺失足以完全阻止铁蛋白降解和溶酶体定位,而FIP200缺失则部分阻止铁蛋白更新;抑制VPS34导致高尔基体上铁蛋白与NCOA4共定位增加,表明NCOA4-铁蛋白的转运起源于高尔基体,铁蛋白更新过程需要NCOA4结合伴侣TAX1BP1、VPS34、ATG9A和部分UNC-51样激酶1/2(UNC-51-like kinase1/2,ULK1/2)-FIP200复合物,这是一种不同于ATG8介导选择性自噬的新溶酶体靶向途径。同样,Mejlvang等研究也证明ESCRT III内体通路可介导饥饿诱导自噬受体[如NCOA4、p62、紧邻BRCA1基因1(neighbor of BRCA1 gene 1, NBR1)蛋白、TAX1BP1和核点蛋白52(nuclear dot protein 52, NDP52)]的快速降解<sup>[17]</sup>。

影响铁自噬调控的因素较多,除NCOA4外,还有Hippo信号通路中的核心转录调控因子Yes相关蛋白(Yes associated protein, YAP)。目前已有研究证实,上调YAP可抑制NCOA4的表达及其与FTH相互作用,从而抑制铁自噬,并降低Fe<sup>2+</sup>和脂质过氧化水平,进而抑制铁死亡,此时YAP表现为铁死亡的负调节因子<sup>[11, 18]</sup>;但在部分疾病,如间皮瘤<sup>[19]</sup>中,YAP正向调节铁死亡,故有学者推测YAP在铁死亡过程中的作用可能具有细胞环境特异性<sup>[20-23]</sup>,而其与NCOA4之间的确切关系仍需进一步研究。此外,亦有文献指出上调YAP水平会抑制活性氧簇(reactive oxygen species, ROS)产生,保持哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)活化,从而减少LC 3B-II的表达<sup>[21, 22]</sup>;或上调B细胞淋巴瘤/白血病-2(B-cell lymphoma/leukemia-2, Bcl-2)蛋白水平,以抑制LC 3B-II和自噬<sup>[23]</sup>,从而抑制铁自噬。

## 1.2 调节红细胞生成

红细胞生成包括造血干细胞祖细胞阶段和成熟的去核红细胞之间的几个分化步骤,其特征是细胞内容物逐渐降解,血红蛋白形成<sup>[13, 24]</sup>。血红蛋白化需要大量的铁来合成血红素,人体内3~5 g的铁中约有2 g包含在红细胞血红蛋白中。铁通过循环Tf输送到红细胞,Tf通过TfR介导的内吞作用被内化至细胞内。接下来,进入内体被还原为其Fe<sup>2+</sup>形式并通过二价金属转运蛋白1(divalent metal transporter 1, DMT1)从内体中输出。铁转运到线粒体进行血红素合成有两种不同机制:从内体直接输

送<sup>[25]</sup>或输出到细胞质不稳定铁池,然后在铁蛋白中储存,溶酶体铁蛋白降解,并输送到线粒体<sup>[26]</sup>。NCOA4在多种组织中表达<sup>[27]</sup>,一些证据支持NCOA4的内在红系功能,首先,NCOA4在成熟的正色红细胞中高水平表达<sup>[28]</sup>;其次,体内、外和离体数据表明,NCOA4是红细胞分化和血红蛋白化所必需的,可调节铁掺入血红素<sup>[7, 29, 30]</sup>。

### 1.2.1 红细胞生成的细胞自主作用

在红细胞分化的体外模型K562人红白血病细胞系和小鼠红细胞生成模型G1E-ER4细胞上的研究显示,随着类红素前体的发展,NCOA4蛋白质和RNA水平上调,在铁掺入血红素最高阶段达到最高水平,而耗竭NCOA4可导致血红蛋白化和分化受损<sup>[7, 29]</sup>,提示NCOA4在红细胞生成中具有细胞自主性,将内体输出的铁运送至细胞质铁池,通过铁自噬递送铁至线粒体,并合成血红素。在补充铁的G1E-ER4细胞中,NCOA4的积累被阻断,铁通过将其导向溶酶体来诱导NCOA4降解,此过程需要HERC2。HERC2耗竭的细胞没有表现出铁诱导的NCOA4降解。红细胞末端分化过程中HERC2蛋白和mRNA水平上调,但表达水平不受铁变化调节,NCOA4与胞质铁的直接结合可能介导其与HERC2的相互作用以及随后泛素介导的向溶酶体运输<sup>[13]</sup>。因此,在胞质铁水平低的类红细胞发育时,NCOA4稳定并促进铁蛋白的更新,从而释放铁,将其递送至线粒体以进行血红素合成;在含铁过多的细胞中,NCOA4降解,铁蛋白未降解,保留了储存的铁。基于对血红蛋白化的时间评估,Ryu等<sup>[29]</sup>描述了一个模型系统:在红系早期,铁伴侣多聚rC结合蛋白1(polyrC-binding protein 1, PCBP1)将铁传递给铁蛋白进行储存,而低水平的NCOA4会减少铁自噬,从而进一步促进铁的储存;在血红蛋白合成最多的分化中点(原色成红细胞阶段),PCBP1和NCOA4协调增加铁蛋白和铁自噬流,为血红素合成提供足够的铁;最后在红细胞发育后期(网织红细胞),随着细胞失去细胞器,铁的输入减少,铁蛋白水平降低,任何剩余的内体都可能将铁直接转移到线粒体,进行持续的血红素合成。在大多数情况下,红细胞生成是基于对变化的铁积累做出反应并调节细胞内铁向线粒体流动而进行的。PCBP1负责将铁转移到铁蛋白中,从而有效地利用铁,相反,铁从铁蛋白中的转移取决于NCOA4调节铁蛋白溶酶体降解和铁释放功能,因此,PCBP1和NCOA4

都是铁转移到线粒体的关键介质和调节剂<sup>[13,29]</sup>, 这些发现为理解红细胞生成过程中铁的动态调控提供了重要的理论依据。

Bellelli 等<sup>[9]</sup>研究显示, 敲除小鼠 *NCOA4* 后, 铁自噬受阻, 铁蛋白在多个组织、器官如肝、脾、十二指肠、骨髓和肾脏等蓄积, 进而诱导转铁蛋白饱和度和血清铁蛋白、血清铁水平随之提高, 肝组织铁调素合成增多, 机体出现不依赖于铁调素的系统性铁稳态受损, 同时伴有轻度小红细胞低色素性贫血; 当喂养低铁饲料时, 小鼠表现出严重的小红细胞低色素性贫血, 红细胞计数和血红蛋白水平下降, 及与促红细胞生成素(erythropoietin, EPO)水平升高相关的无效红细胞生成, 而高铁饲料喂养则会导致小鼠死亡及出现肝损伤迹象。Nai 等<sup>[31]</sup>在不依赖输血的 $\beta$ -地中海贫血小鼠模型上的研究显示, 巨噬细胞释放的铁减少是 *NCOA4* KO 动物贫血的主要驱动因素, 在富含铁的情况下缺乏 *NCOA4* 只会导致轻微的小红细胞增多症而不会引发贫血, 保持红细胞正常成熟并且不会损害其克隆形成能力, 因此避免了体内关键的红细胞分化缺陷。

### 1.2.2 红细胞生成的细胞非自主作用

*NCOA4* 在支持基础红细胞生成中除具有细胞自主作用外, 还具有细胞非自主作用, 比如红细胞特定靶向性缺失的 *NCOA4<sup>fl/fl</sup>;EpoR-Cre* 小鼠中两个年龄段(刚出生和成年期)的贫血程度均低于全身性敲除 *NCOA4* 小鼠; 此外, *NCOA4* 功能在红细胞生成或从铁蛋白动员铁的过程中存在不同的时间依赖性, 与刚出生小鼠观察到的中度至重度贫血相比, *NCOA4<sup>fl/fl</sup>;EpoR-Cre* 成年小鼠中观察到的贫血没有那么严重, 仅出现轻度低色素性小细胞性贫血, 但对溶血更敏感, 由于贫血相对较轻且明显发生血红蛋白合成, 类红细胞必须具有绕过 *NCOA4* 介导的铁蛋白更新并将铁传递至线粒体的机制, 可能激活了一种不依赖 *NCOA4* 的通路或通过低氧诱导因子(hypoxia inducible factor, HIF)-2 $\alpha$ -EPO 轴激活补偿机制, 逆转了成年期急性贫血的进展, 使急性贫血和红细胞生成缺陷表现正常化<sup>[32]</sup>。

### 1.3 线粒体呼吸

铁在线粒体中用作生成铁硫簇蛋白和含血红素蛋白, 主要存在于线粒体呼吸链复合物中, 特别是复合物 I、II 和 IV。剥夺铁可诱导呼吸链复合物 I、II 和 III 含量减少, 且与耗氧率和线粒体膜电位降低有关, *NCOA4* 介导的铁蛋白降解是维持线粒体铁

储存、线粒体呼吸活动、呼吸链复合物组装和膜电位所必需的, 有助于维持线粒体呼吸。基础条件下, 敲低 *NCOA4* 细胞分离的线粒体复合物 I 和 II 组装、耗氧率水平和膜电位明显降低; 此外, 缺乏 FTL 可减少 *NCOA4* 和 FTH1 之间的相互作用并延迟铁蛋白复合物的降解<sup>[33]</sup>。

### 1.4 其他

软骨细胞可通过激活核因子 E2 相关因子 2 (nuclear factor E2 related factor 2, Nrf2) 抑制 *NCOA4* 介导的铁自噬, 调节铁稳态, 避免软骨终板变性和钙化<sup>[34]</sup>; 在缺氧时候, 巨噬细胞通过激活 c-Jun 氨基末端激酶 (c-Jun N-terminal kinase, JNK) 上调 microRNA 6862-5p, 下调 *NCOA4* mRNA 水平, 从而上调 FTH 和线粒体铁蛋白表达, 避免细胞发生铁死亡<sup>[35]</sup>; 自然杀伤细胞中 FTH 含量下降可减少主要组织相容性复合体(major histocompatibility complex, MHC) 含量, 铁水平下降也能通过抑制干扰素  $\gamma$  (interferon  $\gamma$ , IFN- $\gamma$ ) 受体信号转导阻碍信号转导及转录激活蛋白 1 (signal transducer and activator of transcription 1, STAT1) 磷酸化、核易位和基因转录激活, 下调 MHCI, 提高自然杀伤细胞靶点识别原代癌细胞和巨噬细胞的敏感性<sup>[36]</sup>。

此外, *NCOA4* 最初是在酵母双杂交筛选中发现的, 作为雄激素受体的共激活剂<sup>[37]</sup>。随后, 它也被报道为 DNA 复制的阻遏物<sup>[38]</sup>, 可通过 N 端结构域与微小染色体维持蛋白(minichromosome maintenance proteins, MCM) 2-7 解旋酶复合物结合来抑制 DNA 复制起点的激活, 其在体外丢失使细胞易受到复制应激和衰老的影响<sup>[39]</sup>。此外, *NCOA4* 作为其他核受体的调节剂, 可以调节一些额外的核受体, 例如类固醇激素受体、甲状腺激素受体、维生素 A 和 D 受体等<sup>[38]</sup>; 介导的铁自噬可以为分裂细胞提供铁, 满足骨髓干细胞增殖过程中对铁的高需求, 从而促进其在缺氧条件下增殖<sup>[40]</sup>。

## 2 *NCOA4* 介导的铁自噬与相关疾病

铁自噬作为一种选择性自噬, 主要负责降解铁蛋白, 释放细胞内的铁, 参与某些与铁代谢相关疾病的发生和发展, 例如神经退行性疾病<sup>[41]</sup>、心肌细胞肥大<sup>[42]</sup>、尿路感染<sup>[43]</sup>、结核病<sup>[44]</sup>等。近年靶向铁自噬治疗各系统疾病的研究也日益增多, 某些中药可与 *NCOA4* 或 FTH1 结合, 或下调 *NCOA4*, 抑制 *NCOA4* 介导的铁自噬, 从而发挥机体保护作用,

如雨生红球藻等的提取物虾青素(astaxanthin)可上调铁蛋白和下调NCOA4,抑制铁自噬,减少肺上皮细胞死亡,缓解急性肺损伤<sup>[45]</sup>;广泛存在于被子植物中的槲皮素(quercetin)可与NCOA4特异性反应,阻断FTH降解,下调细胞内铁水平和铁死亡,缓解丙烯酰胺诱导的肝损伤<sup>[46]</sup>;传统药用植物主要活性成分柯里拉京(corilagin)在mRNA和蛋白质水平上抑制缺血/再灌注诱导的NCOA4上调,低铁条件触发核NCOA4稳定并与DNA复制起点结合,抑制DNA复制起源激活;还可通过与FTH1的竞争性结合破坏FTH1和NCOA4的直接相互作用,最终减轻肠缺血/再灌注损伤<sup>[47]</sup>;免疫抑制剂环孢菌素A(cyclosporin A)可通过人抗原R蛋白(human antigen R, HuR)促进NCOA4介导的铁自噬,减轻神经炎症和神经元凋亡,改善甲氨蝶呤(methotrexate)诱导的认知障碍<sup>[48]</sup>等。以上研究均是使用药物靶向NCOA4介导的铁自噬,从而治疗相关疾病,为临床进一步优化治疗方案提供了重要依据。

## 2.1 铁自噬与消化系统疾病

Jiang等<sup>[49]</sup>研究显示,高脂饮食可降低肝脏NCOA4、FTH和溶酶体相关膜蛋白-2(lysosome-associated membrane protein-2,在溶酶体的生物发生、自噬体和吞噬体的成熟中起着关键作用)的共定位以及溶酶体活性,抑制肝脏铁自噬流,干扰铁代谢(如NCOA4和FTH表达),并通过内质网应激导致肝脏胰岛素抵抗,损害葡萄糖摄取;而通过腺病毒介导的基因转移上调HepG2细胞NCOA4表达可改善内质网应激和葡萄糖摄取,用小干扰RNA(small interfering RNA, siRNA)敲低NCOA4则消除这种改善作用。

Bellelli等<sup>[9]</sup>研究显示,高铁饮食1个月后,NCOA4 KO动物谷丙转氨酶和谷草转氨酶(肝脏功能损伤的标志物)水平均显著高于野生型小鼠,表明NCOA4 KO动物肝脏过早损伤;在高铁饮食2个月后,脂肪变性(肝硬变的征兆)在NCOA4 KO小鼠相对野生型小鼠更为明显,表明前者组织损伤更为严重。

NCOA4介导的铁自噬是酒精性肝病损伤的致病机制之一。槲皮素<sup>[50]</sup>和水飞蓟提取物水飞蓟宾(silibinin)<sup>[51]</sup>皆可通过调节NCOA4介导的铁自噬,从而减轻肝脏线粒体功能障碍,缓解肝脏损伤。而在非酒精性脂肪性肝病研究中,莪术醇(curcuminol)

可通过上调YAP蛋白水平降低NCOA4,抑制肝细胞衰老<sup>[11]</sup>。

众所周知,活化的肝星状细胞会逐渐转化为成纤维细胞,是肝细胞外基质过度沉积导致肝纤维化的重要细胞来源<sup>[52]</sup>。越来越多证据表明,可以通过上调NCOA4介导的铁自噬来诱导肝星状细胞铁死亡,促进细胞衰老,以对抗肝纤维化<sup>[53,54]</sup>。Sun等研究显示,从黄芩提取的千层纸素A(oroxylin A)可通过cGAS-干扰素基因刺激因子(stimulator of interferon genes, STING)信号通路促进干扰素- $\beta$ (interferon- $\beta$ , IFN- $\beta$ )等细胞因子的分泌,激活NCOA4,从而缓解肝纤维化<sup>[55]</sup>;双氢青蒿素(dihydroartemisinin)通过上调BECN1(Beclin 1)mRNA的N<sup>6</sup>-甲基腺苷(N<sup>6</sup>-methyladenosine)修饰,促进NCOA4介导的铁自噬<sup>[56,57]</sup>。

NCOA4介导的铁自噬是治疗肝癌的潜在新靶点。研究显示,多靶点激酶抑制剂索拉非尼(sorafenib)可诱导肝星状细胞死亡,从而缓解肝细胞癌纤维化进程,其作用机制是通过促进HuR与BECN1 mRNA相互作用,上调BECN1蛋白表达水平,引起NCOA4介导的铁自噬<sup>[58]</sup>;同时索拉非尼可导致肝细胞癌纤维化患者肝星状细胞锌指蛋白36(zinc finger protein 36)下调,上调NCOA4表达,诱导铁自噬<sup>[59]</sup>;取自柠檬叶等多种植物的秦皮乙素(esculetin)<sup>[60]</sup>和存在于多种植物精油中的氧化石竹烯(caryophyllene oxide)<sup>[61]</sup>通过触发NCOA4介导的铁自噬,发挥对肝癌细胞增殖的抑制作用;来自华泽兰的新型倍半萜内酯组分(EchLESs)通过激活HIF- $\alpha$ ,在转录水平上提高NCOA4 mRNA表达,在转录后水平减少NCOA4的降解,促进NCOA4介导的铁自噬,导致肝癌细胞死亡<sup>[62]</sup>;抗生素茴香霉素(anisomycin)激活的p38丝裂原活化蛋白激酶(p38 mitogen-activated protein kinase, p38MAPK)通过共定位促进组蛋白H3S10磷酸化,上调NCOA4表达水平,促进肝癌细胞死亡<sup>[63]</sup>。

此外,研究显示,桑叶提取物隐绿原酸(cryptochlorogenic acid)可通过浓度依赖性方式下调NCOA4蛋白表达水平,在糖尿病中发挥抗胰岛功能损伤的作用<sup>[64]</sup>。Zhao等研制出胰腺癌特异性抗体神经纤毛蛋白2(neuropilin-2, NRP2)修饰的新型药物递送系统,命名为GEM-DVDMS@MOFs@COF-NRP2(简称GDMCN2),用于吉西他滨耐药性胰腺

癌的治疗, GDMCN2靶向进入肿瘤细胞, 在超声照射下逐渐释放声敏剂华卟啉钠(sinoporphyrin sodium)和抗癌药吉西他滨(gemcitabine), 华卟啉钠产生的ROS损伤线粒体, 诱导内质网应激, 最终通过上调NCOA4介导的铁自噬和下调谷胱甘肽过氧化酶4(glutathione peroxidase 4, GPX4)发挥杀死肿瘤细胞的作用; 同时, ROS导致DNA损伤增加, 抑制肿瘤细胞增殖, 一定程度上克服了吉西他滨耐药性<sup>[65]</sup>。

总之, NCOA4介导的铁自噬在消化系统疾病中起着关键作用, 通过调节NCOA4及其上游分子触发铁自噬, 可引起肝星状细胞与癌细胞铁死亡, 因此NCOA4有潜力成为相关疾病的治疗靶点。

## 2.2 铁自噬与生殖系统疾病

研究表明, NCOA4与生殖系统肿瘤发生有关。NCOA4 mRNA和NCOA4 $\alpha$ 蛋白水平与卵巢癌转化呈正相关。Rockfield等在正常子宫内膜细胞中过表达癌基因*HRAS*<sup>V12A</sup>和*c-MYC*<sup>T58A</sup>、失活抑癌基因*p53*, 成功制备出转化的子宫内膜异位细胞, 实现诱导癌细胞转化, 引起NCOA4 mRNA(NCOA4 $\alpha$ 和NCOA4 $\beta$ )和蛋白质(NCOA4 $\alpha$ )表达上调, 故NCOA4 $\alpha$ 蛋白在多种恶性细胞系以及一系列卵巢癌亚型(相对于正常邻近组织)中增加, 提示NCOA4在卵巢癌症生物学中可能参与从前体到卵巢癌的转变<sup>[66]</sup>。

另一方面, 在前列腺癌中, NCOA4 $\alpha$ 充当肿瘤抑制因子, 通过上调凋亡基因*Bax*和裂解半胱天冬酶3以及下调抗凋亡基因*Bcl-XL*, 以雄激素和雄激素受体依赖性方式发挥其肿瘤抑制功能; 而NCOA4 $\beta$ 与前列腺癌细胞增殖和侵袭相关, 通过上调细胞周期蛋白A和B1的表达、降低细胞周期素依赖性激酶抑制蛋白的表达, 以促进细胞周期的进程; 同时通过下调E-钙黏蛋白、紧密连接蛋白3和7的表达, 以降低细胞间的黏附力, 成为肿瘤细胞生长和转移的调节因子<sup>[67, 68]</sup>。在前列腺癌细胞系PC-J上的研究显示, NCOA4在晚期前列腺癌中的高表达增加二氢睾酮诱导的前列腺特异性抗原启动子对雄激素的敏感性和刺激作用, 这可能是激素难治性前列腺癌前列腺特异性抗原高表达原因之一<sup>[69]</sup>。而且前列腺特异性抗原的增加也可以通过调节*p53*途径来上调NCOA4诱导的雄激素受体表达水平, 从而减少前列腺癌细胞凋亡和增加细胞增殖<sup>[70]</sup>。

综上, NCOA4在生殖系统肿瘤中具有重要作用, 可能参与卵巢癌的转变过程; 而在前列腺癌

中, NCOA4 $\alpha$ 作为肿瘤抑制因子, 通过调节凋亡相关基因发挥其功能, 而NCOA4 $\beta$ 则与细胞增殖和侵袭相关, 促进细胞周期进程和肿瘤细胞生长转移。

## 2.3 铁自噬与泌尿系统疾病

铁是宿主和病原体的关键营养素, 调节铁的可用性是宿主抵御病原体的关键。尿路上皮细胞中的铁过载以NCOA4依赖方式诱导铁自噬, 导致尿路致病性大肠杆菌的铁可用性增加, 引发细菌过度增殖和宿主细胞死亡, 继而发生尿路感染, 因此通过NCOA4调节膀胱中的铁水平, 可以为控制尿路致病性大肠杆菌生存性、尿路上皮细胞死亡和复发性尿路感染提供治疗途径<sup>[43]</sup>。

此外, *NCOA4*基因已被证明与泌尿系统癌症发生和发展密切相关。STING可通过促进NCOA4介导的铁自噬促进细胞死亡, 这是缺血性急性肾损伤期间肾小管损伤机制之一<sup>[71]</sup>。*NCOA4*基因已被证明与膀胱癌、肾细胞癌(如肾透明细胞癌)发生和发展密切相关<sup>[72, 73]</sup>, 可能作为潜在预后生物标志物和治疗靶点<sup>[74]</sup>。在肾透明细胞癌上的进一步研究显示, *NCOA4*基因的低表达与IFN- $\gamma$ 受体信号转导受损有关<sup>[75]</sup>, NCOA4表达水平与巨噬细胞、肥大细胞和调节性T细胞等免疫细胞浸润相关<sup>[75, 76]</sup>, 但其中具体机制仍需进一步研究。

甘草提取物异甘草素(isoliquiritigenin)可下调NCOA4表达, 减轻脂多糖(lipopolysaccharide, LPS)诱导脓毒性急性肾损伤中肾小管内线粒体损伤<sup>[77]</sup>。黄芪提取物毛蕊异黄酮(calycosin)可部分逆转糖尿病肾脏病变中NCOA4上调, 减轻肾损伤<sup>[78]</sup>。

综上, 在泌尿系统疾病中, NCOA4作为一个关键调节因子, 可通过抑制铁自噬过程以影响铁含量, 从而在泌尿系统感染和膀胱癌、肾细胞癌等泌尿系统肿瘤发生、发展中发挥重要作用, 深入了解其在铁代谢和免疫调节中的作用机制可为未来的研究和治疗提供新的方向。

## 2.4 铁自噬与神经系统疾病

研究表明, *NCOA4*可作为有利基因被纳入胶质母细胞瘤风险评分预后模型<sup>[79]</sup>。Zhang等<sup>[80]</sup>研究显示, 衣被蛋白复合物 $\zeta$ 1亚基(coatome protein complex subunit zeta 1, COPZ1)-NCOA4-FTH1轴可通过调节铁代谢和自噬过程, 诱导铁死亡, 从而抑制肿瘤细胞的增殖, 延长动物生存期, 其可能成为胶质母细胞瘤治疗靶点; Li等<sup>[81]</sup>研究显示, 三结构域蛋白(tripartite motif-containing protein, TRIM) 7可用K48

连接链直接结合并泛素化 NCOA4, 抑制其活性, 以减少胶质母细胞瘤细胞死亡, 此外 TRIM7 缺失会使人胶质母细胞瘤细胞对抗肿瘤药物替莫唑胺 (temozolomide) 治疗敏感。Zuo 等研究显示, NCOA4 介导铁自噬的增强参与多巴胺能神经元损伤, 这是百草枯诱导帕金森病的新潜在机制<sup>[82]</sup>。在缺血性脑卒中上的研究显示, 抑制 NCOA4 介导的铁自噬可显著减轻脑缺血/再灌注损伤, 直接阻断 NCOA4-FTH1 相互作用<sup>[83]</sup>和通过抑制泛素特异性蛋白酶 14 (ubiquitin-specific protease 14, USP14) 对 NCOA4 泛素化调节<sup>[84]</sup>是以 NCOA4 为靶点干预缺血性脑卒中的可能途径。此外 *NCOA4* 基因还与肌萎缩侧索硬化症、多发性硬化症等神经系统疾病有关: 在肌萎缩侧索硬化症中, *NCOA4* 是肌萎缩侧索硬化症风险基因共表达模块 SC.M2 中的一个关键枢纽基因, 该模块与细胞内运输、自噬有关, 且与少突胶质细胞功能相关, 且模块富集程度与肌萎缩侧索硬化症的遗传风险显著相关<sup>[85]</sup>; 而在多发性硬化症中, *NCOA4* 是多发性硬化症患者外周血中差异表达基因之一, 其低表达与患者的高风险评分和短无复发生存期 (relapse-free survival) 相关<sup>[86]</sup>。

用于镇静的右美托咪定 (dexmedetomidine) 可通过促进 NCOA4 介导的铁自噬, 削弱抗癌药甲氨蝶呤诱导的神经毒性和神经炎症损伤, 减轻甲氨蝶呤诱导的认知障碍<sup>[87]</sup>。用何首乌主要成分二苯乙烯苷 (tetrahydroxy stilbene glycoside) 治疗阿尔茨海默病小鼠模型时, 大脑皮层和海马体的神经细胞出现 NCOA4 表达下调<sup>[88]</sup>。

铁自噬在神经系统损伤中的具体作用还需进一步研究, 通过促进或抑制 NCOA4 介导的铁自噬减轻神经损伤有望应用于临床相关神经系统疾病治疗。

## 2.5 铁自噬与呼吸系统疾病

已有证据表明, *NCOA4* 基因对于预测肺腺癌患者的预后至关重要, 其表达水平与肺腺癌患者的预后呈负相关, 且静息肥大细胞与静息树突状细胞浸润程度可对基因的风险评分产生影响, 表明其可在预测预后中发挥重要作用<sup>[89, 90]</sup>。YAP 过表达可破坏 NCOA4-FTH1 相互作用, 阻止铁蛋白降解 (可产生大量  $\text{Fe}^{2+}$ ), 从而阻止细胞质  $\text{Fe}^{2+}$  通过 Sideroflexin 1 转运到线粒体中, 进一步减少线粒体 ROS 产生和铁死亡, 以缓解脓毒症诱导的急性肺损伤<sup>[18]</sup>。在慢性阻塞性肺病肺气肿上的研究显示, 香烟烟雾可导致

NCOA4 介导的人支气管上皮细胞铁死亡, 促进 M2 巨噬细胞极化, 从而提高基质金属蛋白酶 9 和 12 的水平, 破坏肺泡细胞外基质并导致肺气肿发生<sup>[91]</sup>。

Li 等<sup>[92]</sup>研究显示, 从樟科植物提取的右旋龙脑 (D-borneol) 可通过促进 NCOA4 介导的铁自噬增强顺铂敏感性, 以增强顺铂抑制非小细胞肺癌的作用。Yuan 等<sup>[93]</sup>研究显示, 高寒带落叶松根部提取的二氢槲皮素 (dihydroquercetin) 可抑制支气管上皮细胞中 NCOA4 介导的铁自噬, 从而改善  $\text{SiO}_2$  诱导的肺纤维化。

上述研究表明, 相关药物可通过抑制 NCOA4 介导的铁自噬避免肺部损伤, 或通过诱导癌细胞铁自噬以增强对抗癌药的敏感性, 这些发现为不同呼吸系统疾病患者治疗方案的制定提供有力依据。

## 2.6 铁自噬与循环系统疾病

研究显示, 激活 NCOA4 介导的铁自噬可诱导心肌细胞死亡, 促进心力衰竭的发生、发展<sup>[94]</sup>。LPS 对 NCOA4 介导的铁自噬的诱导作用也是脓毒症诱发心脏损伤的关键机制之一<sup>[95]</sup>。NCOA4 介导的铁自噬也参与氧化锌纳米颗粒诱导的血管内皮细胞铁死亡的过程<sup>[96]</sup>。

他汀类药物阿托伐他汀 (atorvastatin) 可通过抑制 NCOA4 介导的铁自噬逆转异丙肾上腺素诱导的心功能障碍与心脏重塑<sup>[97]</sup>。来自柑橘皮的川陈皮素 (nobiletin) 可下调 NCOA4 等蛋白表达, 从而减轻 2 型糖尿病心肌缺血/再灌注损伤<sup>[98]</sup>。抗氧化剂褪黑素 (melatonin) 和铁螯合剂去铁胺 (deferoxamine) 皆可显著下调 NCOA4 mRNA 水平, 缓解抗癌药阿霉素 (doxorubicin) 诱导的急性心脏细胞损伤, 从而保护心脏功能, 而联合用药改善作用更强<sup>[99]</sup>。

## 2.7 NCOA4介导的铁自噬与免疫系统疾病

NCOA4 介导的铁自噬是类风湿性关节炎纤维样滑膜细胞铁死亡的关键驱动因素, 在低氧条件下, HIF-1 $\alpha$  表达上调, 使 LPS 诱导的此种滑膜细胞铁自噬和铁死亡下调, 低剂量金诺芬 (auranofin) 可下调 HIF-1 $\alpha$  表达, 诱导滑膜细胞铁自噬和铁死亡的再增敏, 减少滑膜增生, 这可能是治疗类风湿性关节炎患者滑膜增生的有效且有价值的策略<sup>[100]</sup>。抗氧化剂亚精胺 (spermidine) 抑制白介素 1 $\beta$  (interleukin-1 $\beta$ , IL-1 $\beta$ ) 诱导的铁自噬 (由 NCOA4 介导), 保护软骨细胞, 从而减轻类风湿性关节炎软骨损伤<sup>[101]</sup>。以上这些研究表明, 针对 NCOA4 的治疗对类风湿性关节炎等免疫系统疾病具有潜在的应用价值。

2.8 铁自噬与其他疾病

在传染性疾病中，结核分枝杆菌可通过对 p38-蛋白激酶 B1 信号通路的激活，上调 TRIM21 蛋白表达水平以增加 HERC2 降解，促进 NCOA4 介导的铁自噬以释放游离铁，促进巨噬细胞内结核分枝杆菌生长<sup>[44]</sup>；而血红素加氧酶 1 (heme oxygenase 1, HMOX1)对巨噬细胞具有一定保护作用，siRNA 敲低 *HMOX1* 基因可显著提高细胞内 ROS、Fe<sup>2+</sup> 和 NCOA4<sup>[102]</sup>。引发人单核细胞埃立克体病的查菲埃立克体可通过埃立克体 IV 型分泌系统分泌效应子 Etf-3 (*Ehrlichia* translocated factor-3)高亲和力直接结合 FTL，诱导 NCOA4 介导的铁自噬，促进其在细胞内增殖<sup>[103]</sup>。布鲁氏菌可分泌 Dps 蛋白 (DNA starvation/stationary phase protection protein) 以激活 NCOA4 介导的铁自噬，来增强细菌生长并引发巨噬细胞坏死<sup>[104]</sup>。

在其他疾病研究中，Guggisberg 等<sup>[105]</sup>在小鼠巨噬细胞系 J774 细胞上的研究显示，LPS 可抑制

NCOA4 转录和蛋白水平表达，阻碍巨噬细胞吞噬红细胞回收铁，进一步导致铁代谢紊乱和炎症反应的加剧，提示 NCOA4 介导的铁自噬可作为全身性铁失调疾病(如炎症性贫血和遗传性血色素沉着症等)的潜在治疗靶点。在脓毒症上的研究显示，单核细胞内 STING CDN 结合的结构域 (CDN-binding domain, CBD)中 Q237、E316、S322 与 NCOA4 卷曲螺旋结构域之间的相互作用增强 NCOA4 介导的铁自噬；此外，这种相互作用可增强 STING 二聚体稳定性，加剧炎症反应，并抑制 NCOA4 作为过氧化物酶体增殖物激活受体  $\alpha$  (peroxisome proliferator-activating receptor  $\alpha$ , PPAR $\alpha$ )共调节因子的功能，这是脓毒症的致死机制之一<sup>[106]</sup>。

3 总结和展望

综上所述，NCOA4 介导的铁自噬在多种疾病的发病机制和治疗中扮演关键角色(总结于表 1)，例如顺铂、吉西他滨等<sup>[65, 92]</sup>通过铁自噬诱导铁死亡，

表 1. NCOA4 介导的铁自噬在相关疾病中的作用机制及其治疗  
Table 1. The mechanisms and treatment of NCOA4-mediated ferritinophagy in related diseases

| Systems          | Related diseases                  | Drugs                  | Effects                                                                                                                                                                                    | References |
|------------------|-----------------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Digestive system | Intestinal injuries               | Corilagin              | Inhibits ischemia-reperfusion-induced ferroptosis                                                                                                                                          | [47]       |
|                  |                                   | Quercetin              | Down-regulates intracellular iron levels and inhibits ferroptosis                                                                                                                          | [46]       |
|                  | Alcoholic liver disease           | Quercetin              | Ameliorates alcohol-induced liver mitochondrial damage and protects hepatocytes                                                                                                            | [50]       |
|                  |                                   | Silibinin              | Modulates mitochondrial autophagy and iron metabolism against ethanol and acetaldehyde-induced hepatocyte injury                                                                           | [51]       |
|                  | Non-alcoholic fatty liver disease | Curcumol               | Inhibits hepatocyte senescence by inhibiting iron overload                                                                                                                                 | [11]       |
|                  | Liver fibrosis                    | Oroxylin A             | Promotes hepatic stellate cell ferroptosis and cellular senescence, and inhibits activation of hepatic stellate cells into fibroblasts, thereby preventing extracellular matrix deposition | [55]       |
|                  |                                   | Schisandrin B          |                                                                                                                                                                                            | [54]       |
|                  |                                   | Artesunate             |                                                                                                                                                                                            | [53]       |
|                  |                                   | Dihydroartemisinin     |                                                                                                                                                                                            | [56, 57]   |
|                  |                                   | Sorafenib              |                                                                                                                                                                                            | [58, 59]   |
|                  | Liver (cell) cancer               | Esculetin              | Promotes NCOA4-mediated ferritinophagy and induces ferroptosis in liver cancer cells                                                                                                       | [60]       |
|                  |                                   | Caryophyllene oxide    |                                                                                                                                                                                            | [61]       |
|                  |                                   | EChLEs                 | Promotes ferroptosis by enhancing mitochondrial dysfunction and apoptosis                                                                                                                  | [62]       |
|                  | Diabetes                          | Anisomycin             | Promotes ferroptosis in hepatocellular carcinoma cells                                                                                                                                     | [63]       |
|                  |                                   | Cryptochlorogenic acid | Inhibits ferroptosis to counteract islet injury                                                                                                                                            | [64]       |
|                  | Pancreatic cancer                 | Sinoporphyrin sodium   | Induces ferroptosis and enhances the sensitivity of chemotherapeutic agents in pancreatic cancer cells                                                                                     | [65]       |

续表 1

| Systems            | Related diseases                          | Drugs                            | Effects                                                                                                                                   | References   |
|--------------------|-------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Urinary system     | Acute kidney injury                       | Isoliquiritigenin                | Attenuates mitochondrial damage and inhibits ferroptosis in renal tubules                                                                 | [77]         |
|                    | Diabetic nephropathy                      | Calycosin                        | Inhibits ferroptosis to attenuate diabetes-induced renal tubular injury                                                                   | [78]         |
| Nervous system     | Cognitive impairment                      | Cyclosporin A<br>Dexmedetomidine | Inhibits ferroptosis to attenuate neuronal inflammatory injury and methotrexate-induced cognitive impairment                              | [48]<br>[87] |
|                    | Alzheimer's disease                       | Tetrahydroxy stilbene glycoside  | Inhibits neuronal ferroptosis to alleviate Alzheimer's disease                                                                            | [88]         |
| Respiratory system | Acute lung injury                         | Astaxanthin                      | Attenuates lipid peroxidation and ferroptosis, and reduces unstable iron overload in lung epithelial cells                                | [45]         |
|                    | Non-small cell lung cancer                | D-borneol and cisplatin          | Induces ferroptosis in non-small cell lung cancer cells                                                                                   | [92]         |
|                    | Pulmonary fibrosis                        | Dihydroquercetin                 | Inhibits ferroptosis and ameliorates SiO <sub>2</sub> induced lung fibrosis in human bronchial epithelial cells                           | [93]         |
| Circulatory system | Heart failure                             | Atorvastatin                     | Inhibits ferroptosis, cardiac remodelling, oxidative stress, and iron overload, and ameliorates isoproterenol-induced cardiac dysfunction | [97]         |
|                    | Myocardial ischemia-reperfusion injury    | Nobiletin                        | Inhibits ferroptosis and attenuates myocardial ischemia-reperfusion injury in type 2 diabetes mellitus                                    | [98]         |
|                    | Acute cardiac injury                      | Melatonin and deferoxamine       | Protects cardiac function by alleviating adriamycin-induced cardiac cell ferroptosis                                                      | [99]         |
| Immune system      | Rheumatoid arthritis synovial hyperplasia | Low dose of auranofin            | Promotes fibroblast-like synovial cell ferroptosis, accelerates inflammation, and reduces synovial proliferation                          | [100]        |
|                    | Rheumatoid arthritis cartilage damage     | Spermidine                       | Inhibits ferroptosis and protects cartilage                                                                                               | [101]        |

克服传统药物耐药性；电离辐射通过NCOA4介导的铁自噬加速动脉粥样硬化斑块进展<sup>[107]</sup>，诱导肠上皮细胞死亡<sup>[108]</sup>，0.2~0.4 T中等强度静磁场则刺激骨肉瘤干细胞自我更新且易出现肺转移倾向<sup>[109]</sup>。以上这些研究提示以NCOA4为靶点的干预药物或手段可作为相关疾病预防、治疗的新思路和新方向。

NCOA4介导的铁自噬在疾病中发挥何种作用尚有争议，例如，Liu等<sup>[50]</sup>发现乙醇促进NCOA4介导的铁自噬，导致肝脏损伤；而Song等<sup>[51]</sup>研究显示，乙醇抑制NCOA4介导的铁自噬，诱导肝脏线粒体功能障碍，继而引发肝脏损伤。在以上两项研究中，NCOA4对酒精性肝病的作用是相反的。基于NCOA4在全身铁稳态中的重要性，转录因子与信号通路对NCOA4的调控机制、NCOA4介导铁自噬的分子机制、NCOA4与FTH1递送至溶酶体的确切机制及与其他自噬途径的相互作用关系等尚待进一步研究。

参考文献

- 1 Pantopoulos K, Porwal SK, Tartakoff A, Devireddy L. Mechanisms of mammalian iron homeostasis. *Biochemistry* 2012; 51(29): 5705-5724.
- 2 Latunde-Dada GO. Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy. *Biochim Biophys Acta Gen Subj* 2017; 1861(8): 1893-1900.
- 3 Mancias JD, Wang X, Gygi SP, Harper JW, Kimmelman AC. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature* 2014; 509 (7498): 105-109.
- 4 Sun Y, Li C, Feng J, Li Y, Zhai X, Zhang L, Li C. Ferritinophagic flux activation in CT26 cells contributed to EMT inhibition induced by a novel iron chelator, DpdpA. *Oxid Med Cell Longev* 2019; 2019: 8753413.
- 5 Yeh S, Chang C. Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. *Proc Natl Acad Sci U S A* 1996; 93(11): 5517-5521.
- 6 Alen P, Claessens F, Schoenmakers E, Swinnen JV, Verho-

- even G, Rombauts W, Peeters B. Interaction of the putative androgen receptor-specific coactivator ARA70/ELE1alpha with multiple steroid receptors and identification of an internally deleted ELE1beta isoform. *Mol Endocrinol* 1999; 13 (1): 117-128.
- 7 Mancias JD, Pontano Vaiteas L, Nissim S, Biancur DE, Kim AJ, Wang X, Liu Y, Goessling W, Kimmelman AC, Harper JW. Ferritinophagy via NCOA4 is required for erythropoiesis and is regulated by iron dependent HERC2-mediated proteolysis. *ELife* 2015; 4: e10308.
  - 8 Gryzik M, Srivastava A, Longhi G, Bertuzzi M, Gianoncelli A, Carmona F, Poli M, Arosio P. Expression and characterization of the ferritin binding domain of Nuclear Receptor Coactivator-4 (NCOA4). *Biochim Biophys Acta Gen Subj* 2017; 1861(11 Pt A): 2710-2716.
  - 9 Bellelli R, Federico G, Matte A, Colecchia D, Iolascon A, Chiariello M, Santoro M, De Franceschi L, Carlomagno F. NCOA4 deficiency impairs systemic iron homeostasis. *Cell Rep* 2016; 14(3): 411-421.
  - 10 Vogt AS, Arsiwala T, Mohsen M, Vogel M, Manolova V, Bachmann MF. On iron metabolism and its regulation. *Int J Mol Sci* 2021; 22(9): 4591.
  - 11 Qi X, Song A, Ma M, Wang P, Zhang X, Lu C, Zhang J, Zheng S, Jin H. Curcumin inhibits ferritinophagy to restrain hepatocyte senescence through YAP/NCOA4 in non-alcoholic fatty liver disease. *Cell Prolif* 2021; 54(9): e13107.
  - 12 Kuno S, Fujita H, Tanaka YK, Ogra Y, Iwai K. Iron-induced NCOA4 condensation regulates ferritin fate and iron homeostasis. *EMBO Rep* 2022; 23(5): e54278.
  - 13 Philpott CC. The flux of iron through ferritin in erythrocyte development. *Curr Opin Hematol* 2018; 25(3): 183-188.
  - 14 Dowdle WE, Nyfeler B, Nagel J, Elling RA, Liu S, Triantafellow E, Menon S, Wang Z, Honda A, Pardee G, Cantwell J, Luu C, Cornella-Taracido I, Harrington E, Fekkes P, Lei H, Fang Q, Digan ME, Burdick D, Powers AF, Helliwell SB, D'Aquino S, Bastien J, Wang H, Wiederschain D, Kuerth J, Bergman P, Schwalb D, Thomas J, Ugwonalu S, Harbinski F, Tallarico J, Wilson CJ, Myer VE, Porter JA, Bussiere DE, Finan PM, Labow MA, Mao X, Hamann LG, Manning BD, Valdez RA, Nicholson T, Schirle M, Knapp MS, Keane EP, Murphy LO. Selective VPS34 inhibitor blocks autophagy and uncovers a role for NCOA4 in ferritin degradation and iron homeostasis *in vivo*. *Nat Cell Biol* 2014; 16 (11): 1069-1079.
  - 15 Hou W, Xie Y, Song X, Sun X, Lotze MT, Zeh HJ, Kang R, Tang D. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy* 2016; 12(8): 1425-1428.
  - 16 Goodwin JM, Dowdle WE, DeJesus R, Wang Z, Bergman P, Kobylarz M, Lindeman A, Xavier RJ, McAllister G, Nyfeler B, Hoffman G, Murphy LO. Autophagy-independent lysosomal targeting regulated by ULK1/2-FIP200 and ATG9. *Cell Rep* 2017; 20(10): 2341-2356.
  - 17 Mejlvang J, Olsvik H, Svenning S, Bruun J-A, Abudu YP, Larsen KB, Brech A, Hansen TE, Brenne H, Hansen T, Stenmark H, Johansen T. Starvation induces rapid degradation of selective autophagy receptors by endosomal microautophagy. *J Cell Biol* 2018; 217(10): 3640-3655.
  - 18 Zhang J, Zheng Y, Wang Y, Wang J, Sang A, Song X, Li X. YAP1 alleviates sepsis-induced acute lung injury via inhibiting ferritinophagy-mediated ferroptosis. *Front Immunol* 2022; 13: 884362.
  - 19 Wu J, Minikes AM, Gao M, Bian H, Li Y, Stockwell B, Chen Z, Jiang X. Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling. *Nature* 2019; 572 (7769): 402-406.
  - 20 Magesh S, Cai D. Roles of YAP/TAZ in ferroptosis. *Trends Cell Biol* 2022; 32(9): 729-732.
  - 21 Zhou Y, Wang Y, Zhou W, Chen T, Wu Q, Chutturghoon VK, Lin B, Geng L, Yang Z, Zhou L, Zheng S. YAP promotes multi-drug resistance and inhibits autophagy-related cell death in hepatocellular carcinoma via the RAC1-ROS-mTOR pathway. *Cancer Cell Int* 2019; 19: 179.
  - 22 Wu X, Sheng H, Zhao L, Jiang M, Lou H, Miao Y, Cheng N, Zhang W, Ding D, Li W. Co-loaded lapatinib/PAB by ferritin nanoparticles eliminated ECM-detached cluster cells via modulating EGFR in triple-negative breast cancer. *Cell Death Dis* 2022; 13(6): 557.
  - 23 Jin L, Chen Y, Cheng D, He Z, Shi X, Du B, Xi X, Gao Y, Guo Y. YAP inhibits autophagy and promotes progression of colorectal cancer via upregulating Bcl-2 expression. *Cell Death Dis* 2021; 12(5): 457.
  - 24 Nguyen AT, Prado MA, Schmidt PJ, Sendamarai AK, Wilson-Grady JT, Min M, Campagna DR, Tian G, Shi Y, Dederer V, Kawan M, Kuehnle N, Paulo JA, Yao Y, Weiss MJ, Justice MJ, Gygi SP, Fleming MD, Finley D. UBE2O remodels the proteome during terminal erythroid differentiation. *Science* 2017; 357(6350): eaan0218.
  - 25 Sheftel AD, Zhang AS, Brown C, Shiriha OS, Ponka P. Direct interorganellar transfer of iron from endosome to mitochondrion. *Blood* 2007; 110(1): 125-132.
  - 26 Vaisman B, Fibach E, Konijn AM. Utilization of intracellular ferritin iron for hemoglobin synthesis in developing human erythroid precursors. *Blood* 1997; 90(2): 831-838.
  - 27 Kollara A, Brown TJ. Variable expression of nuclear receptor coactivator 4 (NcoA4) during mouse embryonic development. *J Histochem Cytochem* 2010; 58(7): 595-609.
  - 28 An X, Schulz VP, Li J, Wu K, Liu J, Xue F, Hu J, Mohandas N, Gallagher PG. Global transcriptome analyses of human and murine terminal erythroid differentiation. *Blood* 2014; 123(22): 3466-3477.
  - 29 Ryu MS, Zhang D, Protchenko O, Shakoury-Elizeh M, Phil-

- pott CC. PCBP1 and NCOA4 regulate erythroid iron storage and heme biosynthesis. *J Clin Invest* 2017; 127(5): 1786-1797.
- 30 Gao X, Lee H-Y, Li W, Platt RJ, Barrasa MI, Ma Q, Elmes RR, Rosenfeld MG, Lodish HF. Thyroid hormone receptor beta and NCOA4 regulate terminal erythrocyte differentiation. *Proc Natl Acad Sci U S A* 2017; 114(38): 10107-10112.
- 31 Nai A, Lidonnici MR, Federico G, Pettinato M, Olivari V, Carrillo F, Geninatti C, Ferrari G, Camaschella C, Silvestri L, Carlomagno F. NCOA4-mediated ferritinophagy in macrophages is crucial to sustain erythropoiesis in mice. *Haematologica* 2021; 106(3): 795-805.
- 32 Santana-Codina N, Gableske S, Quiles del Rey M, Małachowska B, Jedrychowski MP, Biancur DE, Schmidt PJ, Fleming MD, Fendler W, Harper JW, Kimmelman AC, Mancias JD. NCOA4 maintains murine erythropoiesis via cell autonomous and non-autonomous mechanisms. *Haematologica* 2019; 104(7): 1342-1354.
- 33 Fujimaki M, Furuya N, Saiki S, Amo T, Imamichi Y, Hattori N. Iron supply via NCOA4-mediated ferritin degradation maintains mitochondrial functions. *Mol Cell Biol* 2019; 39(14): e00010-00019.
- 34 Ma Z, Lu H, Feng X, Du T, Li J, Zhang Q, Gu X, Shao Y, Jing X, Su C. Nrf2 protects against cartilage endplate degeneration through inhibiting NCOA4-mediated ferritinophagy. *Int J Mol Med* 2024; 53(2): 15.
- 35 Fuhrmann DC, Mondorf A, Beifuß J, Jung M, Brüne B. Hypoxia inhibits ferritinophagy, increases mitochondrial ferritin, and protects from ferroptosis. *Redox Biol* 2020; 36: 101670.
- 36 Sottile R, Federico G, Garofalo C, Talerico R, Faniello MC, Quaresima B, Cristiani CM, Di Sanzo M, Cuda G, Ventura V, Wagner AK, Contrò G, Perrotti N, Gulletta E, Ferrone S, Kärre K, Costanzo FS, Carlomagno F, Carbone E. Iron and ferritin modulate MHC class I expression and NK cell recognition. *Front Immunol* 2019; 10: 224.
- 37 Ting HJ, Bao BY, Hsu CL, Lee YF. Androgen-receptor co-regulators mediate the suppressive effect of androgen signals on vitamin D receptor activity. *Endocrine* 2005; 26(1): 1-9.
- 38 Kollara A, Brown TJ. Expression and function of nuclear receptor co-activator 4: evidence of a potential role independent of co-activator activity. *Cell Mol Life Sci* 2012; 69(23): 3895-3909.
- 39 Bellelli R, Castellone MD, Guida T, Limongello R, Dathan NA, Merolla F, Cirafici AM, Affuso A, Masai H, Costanzo V, Grieco D, Fusco A, Santoro M, Carlomagno F. NCOA4 transcriptional coactivator inhibits activation of DNA replication origins. *Mol Cell* 2014; 55(1): 123-137.
- 40 Yang A, Wang L, Jiang K, Lei L, Li H. Nuclear receptor co-activator 4-mediated ferritinophagy drives proliferation of dental pulp stem cells in hypoxia. *Biochem Biophys Res Commun* 2021; 554: 123-130.
- 41 Baksi S, Singh N.  $\alpha$ -Synuclein impairs ferritinophagy in the retinal pigment epithelium: Implications for retinal iron dys-homeostasis in Parkinson's disease. *Sci Rep* 2017; 7(1): 12843.
- 42 Tang M, Huang Z, Luo X, Liu M, Wang L, Qi Z, Huang S, Zhong J, Chen J-X, Li L, Wu D, Chen L. Ferritinophagy activation and sideroflexin1-dependent mitochondria iron overload is involved in apelin-13-induced cardiomyocytes hypertrophy. *Free Radic Biol Med* 2019; 134: 445-457.
- 43 Bauckman KA, Mysorekar IU. Ferritinophagy drives uropathogenic *Escherichia coli* persistence in bladder epithelial cells. *Autophagy* 2016; 12(5): 850-863.
- 44 Dai Y, Zhu C, Xiao W, Huang K, Wang X, Shi C, Lin D, Zhang H, Liu X, Peng B, Gao Y, Liu CH, Ge B, Kaufmann SH, Feng CG, Chen X, Cai Y. Mycobacterium tuberculosis hijacks host TRIM21- and NCOA4-dependent ferritinophagy to enhance intracellular growth. *J Clin Invest* 2023; 133(8): e159941.
- 45 Dong X, Li D, Fang Z, Zhang C, Wang J, Wan X. Astaxanthin alleviates lipopolysaccharide-induced acute lung injury by suppressing ferroptosis. *Food Funct* 2023; 14(13): 6115-6127.
- 46 Huang T, Zhang K, Wang J, He K, Zhou X, Nie S. Quercetin alleviates acrylamide-induced liver injury by inhibiting autophagy-dependent ferroptosis. *J Agric Food Chem* 2023; 71(19): 7427-7439.
- 47 Wang Y, Li B, Liu G, Han Q, Diao Y, Liu J. Corilagin attenuates intestinal ischemia/reperfusion injury in mice by inhibiting ferritinophagy-mediated ferroptosis through disrupting NCOA4-ferritin interaction. *Life Sci* 2023; 334: 122176.
- 48 Ding H, Xiang R, Jia Y, Ye J, Xia Z. Cyclosporin A-mediated translocation of HuR improves MTX-induced cognitive impairment in a mouse model via NCOA4-mediated ferritinophagy. *Aging (Albany NY)* 2023; 15(21): 12537-12550.
- 49 Jiang C, Zhang S, Li D, Chen L, Zhao Y, Mei G, Liu J, Tang Y, Gao C, Yao P. Impaired ferritinophagy flux induced by high fat diet mediates hepatic insulin resistance via endoplasmic reticulum stress. *Food Chem Toxicol* 2020; 140: 111329.
- 50 Liu J, Chen H, Lin H, Peng S, Chen L, Cheng X, Yao P, Tang Y. Iron-frataxin involved in the protective effect of quercetin against alcohol-induced liver mitochondrial dysfunction. *J Nutr Biochem* 2023; 114: 109258.
- 51 Song XY, Liu PC, Liu WW, Zhou J, Hayashi T, Mizuno K, Hattori S, Fujisaki H, Ikejima T. Silibinin inhibits ethanol- or acetaldehyde-induced ferroptosis in liver cell lines. *Toxi-*

- col In Vitro 2022; 82: 105388.
- 52 Pellicoro A, Ramachandran P, Iredale JP, Fallowfield JA. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. *Nat Rev Immunol* 2014; 14(3): 181-194.
  - 53 Kong Z, Liu R, Cheng Y. Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. *Biomed Pharmacother* 2019; 109: 2043-2053.
  - 54 Ma M, Wei N, Yang J, Ding T, Song A, Chen L, Zheng S, Jin H. Schisandrin B promotes senescence of activated hepatic stellate cell via NCOA4-mediated ferritinophagy. *Pharm Biol* 2023; 61(1): 621-629.
  - 55 Sun Y, Weng J, Chen X, Ma S, Zhang Y, Zhang F, Zhang Z, Wang F, Shao J, Zheng S. Oroxylin A activates ferritinophagy to induce hepatic stellate cell senescence against hepatic fibrosis by regulating cGAS-STING pathway. *Biomed Pharmacother* 2023; 162: 114653.
  - 56 Zhang Z, Wang X, Wang Z, Zhang Z, Cao Y, Wei Z, Shao J, Chen A, Zhang F, Zheng S. Dihydroartemisinin alleviates hepatic fibrosis through inducing ferroptosis in hepatic stellate cells. *Biofactors* 2021; 47(5): 801-818.
  - 57 Shen M, Guo M, Li Y, Wang Y, Qiu Y, Shao J, Zhang F, Xu X, Yin G, Wang S, Chen A, Zhang Z, Zheng S. m6A methylation is required for dihydroartemisinin to alleviate liver fibrosis by inducing ferroptosis in hepatic stellate cells. *Free Radic Biol Med* 2022; 182: 246-259.
  - 58 Zhang Z, Yao Z, Wang L, Ding H, Shao J, Chen A, Zhang F, Zheng S. Activation of ferritinophagy is required for the RNA-binding protein ELAVL1/HuR to regulate ferroptosis in hepatic stellate cells. *Autophagy* 2018; 14(12): 2083-2103.
  - 59 Zhang Z, Guo M, Li Y, Shen M, Kong D, Shao J, Ding H, Tan S, Chen A, Zhang F, Zheng S. RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells. *Autophagy* 2020; 16(8): 1482-1505.
  - 60 Xiu Z, Li Y, Fang J, Han J, Li S, Li Y, Yang X, Song G, Li Y, Jin N, Zhu Y, Zhu G, Sun L, Li X. Inhibitory effects of esculetin on liver cancer through triggering NCOA4 pathway-mediation ferritinophagy *in vivo* and *in vitro*. *J Hepatocell Carcinoma* 2023; 10: 611-629.
  - 61 Xiu Z, Zhu Y, Han J, Li Y, Yang X, Yang G, Song G, Li S, Li Y, Cheng C, Li Y, Fang J, Li X, Jin N. Caryophyllene oxide induces ferritinophagy by regulating the NCOA4/FTH1/LC3 pathway in hepatocellular carcinoma. *Front Pharmacol* 2022; 13: 930958.
  - 62 Zhu ZH, Xu XT, Shen CJ, Yuan JT, Lou SY, Ma XL, Chen X, Yang B, Zhao HJ. A novel sesquiterpene lactone fraction from *Eupatorium chinense* L. suppresses hepatocellular carcinoma growth by triggering ferritinophagy and mitochondrial damage. *Phytomedicine* 2023; 112: 154671.
  - 63 Chen W, Yang W, Zhang C, Liu T, Zhu J, Wang H, Li T, Jin A, Ding L, Xian J, Tian T, Pan B, Guo W, Wang B. Modulation of the p38 MAPK pathway by anisomycin promotes ferroptosis of hepatocellular carcinoma through phosphorylation of H3S10. *Oxid Med Cell Longev* 2022; 2022: 6986445.
  - 64 Zhou Y. The protective effects of cryptochlorogenic acid on  $\beta$ -cells function in diabetes *in vivo* and *in vitro* via inhibition of ferroptosis. *Diabetes Metab Syndr Obes* 2020; 13: 1921-1931.
  - 65 Zhao Z, Wu Y, Liang X, Liu J, Luo Y, Zhang Y, Li T, Liu C, Luo X, Chen J, Wang Y, Wang S, Wu T, Zhang S, Yang D, Li W, Yan J, Ke Z, Luo F. Sonodynamic therapy of NRP2 monoclonal antibody-guided MOFs@COF targeted disruption of mitochondrial and endoplasmic reticulum homeostasis to induce autophagy-dependent ferroptosis. *Adv Sci (Weinh)* 2023; 10(30): e2303872.
  - 66 Rockfield S, Flores I, Nanjundan M. Expression and function of nuclear receptor coactivator 4 isoforms in transformed endometriotic and malignant ovarian cells. *Oncotarget* 2017; 9(4): 5344-5367.
  - 67 Peng Y, Li CX, Chen F, Wang Z, Ligr M, Melamed J, Wei J, Gerald W, Pagano M, Garabedian MJ, Lee P. Stimulation of prostate cancer cellular proliferation and invasion by the androgen receptor co-activator ARA70. *Am J Pathol* 2008; 172(1): 225-235.
  - 68 Ligr M, Li Y, Zou X, Daniels G, Melamed J, Peng Y, Wang W, Wang J, Ostrer H, Pagano M, Wang Z, Garabedian MJ, Lee P. Tumor suppressor function of androgen receptor co-activator ARA70 $\alpha$  in prostate cancer. *Am J Pathol* 2010; 176(4): 1891-1900.
  - 69 Tsui KH, Feng TH, Chung LC, Chao CH, Chang PL, Juang HH. Prostate specific antigen gene expression in androgen insensitive prostate carcinoma subculture cell line. *Anticancer Res* 2008; 28(4A): 1969-1976.
  - 70 Niu Y, Yeh S, Miyamoto H, Li G, Altuwaijri S, Yuan J, Han R, Ma T, Kuo HC, Chang C. Tissue prostate-specific antigen facilitates refractory prostate tumor progression via enhancing ARA70-regulated androgen receptor transactivation. *Cancer Res* 2008; 68(17): 7110-7119.
  - 71 Jin L, Yu B, Wang H, Shi L, Yang J, Wu L, Gao C, Pan H, Han F, Lin W, Lai EY, Wang YF, Yang Y. STING promotes ferroptosis through NCOA4-dependent ferritinophagy in acute kidney injury. *Free Radic Biol Med* 2023; 208: 348-360.
  - 72 Yang Y, Hu H, Chen L, Zhang H, Yang J. A new survival model based on ferroptosis-related genes (FRGS) for prognostic prediction in bladder cancer. *Actas Urol Esp (Engl Ed)* 2022; 46(8): 494-503.
  - 73 Li L, Xu Y, Yang W, Zhang K, Zhang Z, Zhou J, Gong Y, Gong K. Construction of a two-gene prognostic model related to ferroptosis in renal cell carcinoma. *Transl Androl*

- Urol 2023; 12(7): 1167-1183.
- 74 Zheng B, Niu Z, Si S, Zhao G, Wang J, Yao Z, Cheng F, He W. Comprehensive analysis of new prognostic signature based on ferroptosis-related genes in clear cell renal cell carcinoma. *Aging (Albany NY)* 2021; 13(15): 19789-19804.
- 75 Mou Y, Wu J, Zhang Y, Abdihamid O, Duan C, Li B. Low expression of ferritinophagy-related NCOA4 gene in relation to unfavorable outcome and defective immune cells infiltration in clear cell renal carcinoma. *BMC Cancer* 2021; 21(1): 18.
- 76 Hong Y, Lin M, Ou D, Huang Z, Shen P. A novel ferroptosis-related 12-gene signature predicts clinical prognosis and reveals immune relevancy in clear cell renal cell carcinoma. *BMC Cancer* 2021; 21(1): 831.
- 77 Tang Y, Luo H, Xiao Q, Li L, Zhong X, Zhang J, Wang F, Li G, Wang L, Li Y. Isoliquiritigenin attenuates septic acute kidney injury by regulating ferritinophagy-mediated ferroptosis. *Ren Fail* 2021; 43(1): 1551-1560.
- 78 Huang D, Shen P, Wang C, Gao J, Ye C, Wu F. Calycosin plays a protective role in diabetic kidney disease through the regulation of ferroptosis. *Pharm Biol* 2022; 60(1): 990-996.
- 79 Chen W, Lei C, Wang Y, Guo D, Zhang S, Wang X, Zhang Z, Wang Y, Ma W. Prognostic prediction model for glioblastoma: A ferroptosis-related gene prediction model and independent external validation. *J Clin Med* 2023; 12(4): 1341.
- 80 Zhang Y, Kong Y, Ma Y, Ni S, Wikerholmen T, Xi K, Zhao F, Zhao Z, Wang J, Huang B, Chen A, Yao Z, Han M, Feng Z, Hu Y, Thorsen F, Wang J, Li X. Loss of COPZ1 induces NCOA4 mediated autophagy and ferroptosis in glioblastoma cell lines. *Oncogene* 2021; 40(8): 1425-1439.
- 81 Li K, Chen B, Xu A, Shen J, Li K, Hao K, Hao R, Yang W, Jiang W, Zheng Y, Ge F, Wang Z. TRIM7 modulates NCOA4-mediated ferritinophagy and ferroptosis in glioblastoma cells. *Redox Biol* 2022; 56: 102451.
- 82 Zuo Y, Xie J, Li X, Li Y, Thirupathi A, Zhang J, Yu P, Gao G, Chang Y, Shi Z. Ferritinophagy-mediated ferroptosis involved in paraquat-induced neurotoxicity of dopaminergic neurons: Implication for neurotoxicity in PD. *Oxid Med Cell Longev* 2021; 2021: 9961628.
- 83 Fang Y, Chen X, Tan Q, Zhou H, Xu J, Gu Q. Inhibiting ferroptosis through disrupting the NCOA4-FTH1 interaction: A new mechanism of action. *ACS Cent Sci* 2021; 7(6): 980-989.
- 84 Li C, Sun G, Chen B, Xu L, Ye Y, He J, Bao Z, Zhao P, Miao Z, Zhao L, Hu J, You Y, Liu N, Chao H, Ji J. Nuclear receptor coactivator 4-mediated ferritinophagy contributes to cerebral ischemia-induced ferroptosis in ischemic stroke. *Pharmacol Res* 2021; 174: 105933.
- 85 Wang JC, Ramaswami G, Geschwind DH. Gene co-expression network analysis in human spinal cord highlights mechanisms underlying amyotrophic lateral sclerosis susceptibility. *Sci Rep* 2021; 11(1): 5748.
- 86 Ye F, Liang J, Li J, Li H, Sheng W. Development and validation of a five-gene signature to predict relapse-free survival in multiple sclerosis. *Front Neurol* 2020; 11: 579683.
- 87 Chen J, Wang J, Li C, Ding H, Ye J, Xia Z. Dexmedetomidine reverses MTX-induced neurotoxicity and inflammation in hippocampal HT22 cell lines via NCOA4-mediated ferritinophagy. *Aging (Albany NY)* 2021; 13(4): 6182-6193.
- 88 Gao Y, Li J, Wu Q, Wang S, Yang S, Li X, Chen N, Li L, Zhang L. Tetrahydroxy stilbene glycoside ameliorates Alzheimer's disease in APP/PS1 mice via glutathione peroxidase related ferroptosis. *Int Immunopharmacol* 2021; 99: 108002.
- 89 Zhang A, Yang J, Ma C, Li F, Luo H. Development and validation of a robust ferroptosis-related prognostic signature in lung adenocarcinoma. *Front Cell Dev Biol* 2021; 9: 616271.
- 90 Ma C, Li F, Luo H. Prognostic and immune implications of a novel ferroptosis-related ten-gene signature in lung adenocarcinoma. *Ann Transl Med* 2021; 9(13): 1058.
- 91 Liu J, Zhang Z, Yang Y, Di T, Wu Y, Bian T. NCOA4-mediated ferroptosis in bronchial epithelial cells promotes macrophage M2 polarization in COPD emphysema. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 667-681.
- 92 Li J, Yuan J, Li Y, Wang J, Xie Q, Ma R, Wang J, Ren M, Lu D, Xu Z. d-Borneol enhances cisplatin sensitivity via autophagy dependent EMT signaling and NCOA4-mediated ferritinophagy. *Phytomedicine* 2022; 106: 154411.
- 93 Yuan L, Sun Y, Zhou N, Wu W, Zheng W, Wang Y. Dihydroquercetin attenuates silica-induced pulmonary fibrosis by inhibiting ferroptosis signaling pathway. *Front Pharmacol* 2022; 13: 845600.
- 94 Ito J, Omiya S, Rusu M-C, Ueda H, Murakawa T, Tanada Y, Abe H, Nakahara K, Asahi M, Taneike M, Nishida K, Shah AM, Otsu K. Iron derived from autophagy-mediated ferritin degradation induces cardiomyocyte death and heart failure in mice. *Elife* 2021; 10: e62174.
- 95 Li N, Wang W, Zhou H, Wu Q, Duan M, Liu C, Wu H, Deng W, Shen D, Tang Q. Ferritinophagy-mediated ferroptosis is involved in sepsis-induced cardiac injury. *Free Radic Biol Med* 2020; 160: 303-318.
- 96 Qin X, Zhang J, Wang B, Xu G, Yang X, Zou Z, Yu C. Ferritinophagy is involved in the zinc oxide nanoparticles-induced ferroptosis of vascular endothelial cells. *Autophagy* 2021; 17(12): 4266-4285.
- 97 Ning D, Yang X, Wang T, Jiang Q, Yu J, Wang D. Atorvastatin treatment ameliorates cardiac function and remodeling induced by isoproterenol attack through mitigation of ferroptosis. *Biochem Biophys Res Commun* 2021; 574: 39-47.
- 98 Huang Q, Tian L, Zhang Y, Qiu Z, Lei S, Xia ZY. Nobiletin alleviates myocardial ischemia-reperfusion injury via fer-

- roptosis in rats with type-2 diabetes mellitus. *Biomed Pharmacother* 2023; 163: 114795.
- 99 Hanna M, Seddiek H, Aboulhoda BE, Morcos GNB, Akabawy AMA, Elbaset MA, Ibrahim AA, Khalifa MM, Khalifah IM, Fadel MS, Shoukry T. Synergistic cardioprotective effects of melatonin and deferoxamine through the improvement of ferritinophagy in doxorubicin-induced acute cardiotoxicity. *Front Physiol* 2022; 13: 1050598.
  - 100 Wang Y, Ding H, Zheng Y, Wei X, Yang X, Wei H, Tian Y, Sun X, Wei W, Ma J, Tian D, Zheng F. Alleviated NCOA4-mediated ferritinophagy protected RA FLSs from ferroptosis in lipopolysaccharide-induced inflammation under hypoxia. *Inflamm Res* 2024; 73(3): 363-379.
  - 101 Cheng Q, Ni L, Liu A, Huang X, Xiang P, Zhang Q, Yang H. Spermidine protects cartilage from IL-1 $\beta$ -mediated ferroptosis. *Mol Cell Biochem* 2024; 479(10): 2785-2794.
  - 102 Ma C, Wu X, Zhang X, Liu X, Deng G. Heme oxygenase-1 modulates ferroptosis by fine-tuning levels of intracellular iron and reactive oxygen species of macrophages in response to *Bacillus Calmette-Guerin* infection. *Front Cell Infect Microbiol* 2022; 12: 1004148.
  - 103 Yan Q, Zhang W, Lin M, Teymournejad O, Budachetri K, Lakritz J, Rikihisa Y. Iron robbery by intracellular pathogen via bacterial effector-induced ferritinophagy. *Proc Natl Acad Sci U S A* 2021; 118(23): e2026598118.
  - 104 Hop HT, Huy TXN, Lee HJ, Kim S. Intracellular growth of *Brucella* is mediated by Dps-dependent activation of ferritinophagy. *EMBO Rep* 2023; 24(9): e55376.
  - 105 Guggisberg CA, Kim J, Lee J, Chen X, Ryu MS. NCOA4 regulates iron recycling and responds to hepcidin activity and lipopolysaccharide in macrophages. *Antioxidants (Basel)* 2022; 11(10): 1926.
  - 106 Wu J, Liu Q, Zhang X, Tan M, Li X, Liu P, Wu L, Jiao F, Lin Z, Wu X, Wang X, Zhao Y, Ren J. The interaction between STING and NCOA4 exacerbates lethal sepsis by orchestrating ferroptosis and inflammatory responses in macrophages. *Cell Death Dis* 2022; 13(7): 653.
  - 107 Wu Z, Chen T, Qian Y, Luo G, Liao F, He X, Xu W, Pu J, Ding S. High-dose ionizing radiation accelerates atherosclerotic plaque progression by regulating P38/NCOA4-mediated ferritinophagy/ferroptosis of endothelial cells. *Int J Radiat Oncol Biol Phys* 2023; 117(1): 223-236.
  - 108 Zhou H, Zhou YL, Mao JA, Tang LF, Xu J, Wang ZX, He Y, Li M. NCOA4-mediated ferritinophagy is involved in ionizing radiation-induced ferroptosis of intestinal epithelial cells. *Redox Biol* 2022; 55: 102413.
  - 109 Zhao B, Yu T, Wang S, Che J, Zhou L, Shang P. Static magnetic field (0.2-0.4 T) stimulates the self-renewal ability of osteosarcoma stem cells through autophagic degradation of ferritin. *Bioelectromagnetics* 2021; 42(5): 371-383.