选择性自噬受体TAX1BP1的研究进展及意义

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摘要 自噬是真核细胞内主要的降解系统之一, 在清除细胞内受损物质方面发挥着重要作用。近年来, 自噬与疾病的关系成为研究的热门话题。自噬功能的异常往往影响着疾病的发生、发展及预后。细胞通过自噬途径选择性地清除某些细胞质成分的过程称为选择性自噬。选择性自噬的发生通常需要自噬受体的参与, 不同的自噬受体发挥的具体功能也不尽相同。其中, Tax1结合蛋白1(Tax1-binding protein 1, TAX1BP1)作为选择性自噬接头蛋白的一员, 主要由一个SKIP羧基同源性域(SKIP carboxyl homology, SKICH)、一个微管相关蛋白I轻链3结合结构域(LC3-interacting region, LIR)、三个卷曲螺旋和一个羧基末端泛素锌指结合(ubiquitin-binding zinc finger, UBZ)结构域构成。这些结构域介导了TAX1BP1与其他蛋白质的相互作用, 并在一定程度上对TAX1BP1在细胞中的功能产生影响。TAX1BP1同时调节NF-κB、JNK等信号通路; 它广泛地参与到线粒体自噬、异体自噬以及溶酶体自噬等自噬进程中去; TAX1BP1的异常表达与炎症反应、恶性肿瘤及循环系统疾病的发生密切相关。该文主要对TAX1BP1的结构功能、调节的信号通路、与自噬的关系, 以及其生理意义进行系统的总结, 为今后TAX1BP1的研究提供新思路。

关键词 自噬受体; TAX1BP1; 炎症; NF-κB; 肿瘤

Research Progress and Significance of Selective Autophagy Receptor TAX1BP1

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Abstract Autophagy is one of the main degradation systems in eukaryotic cells and plays an important role in removing damaged substances in cells. In recent years, the relationship between autophagy and disease has become a hot topic. Abnormal autophagy often affects the occurrence, development and prognosis of diseases. The process of selectively clearing some cytoplasmic components through autophagy is called selective autophagy. The occurrence of selective autophagy usually requires the participation of autophagy receptors, and different autophagy receptors play different functions. Among them, TAX1BP1 (Tax1-binding protein 1), as a member of selective autophagy adaptor protein, is mainly composed of a SKICH (SKIP carboxyl homology domain), a microtubule associated protein I light chain 3 binding region, three coiled coils and a C-terminal ubiquitin binding domain. These domains mediate the interaction between TAX1BP1 and other proteins, and affect the function of TAX1BP1 in cells to

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a certain extent. TAX1BP1 simultaneously regulates NF-κB, JNK and other signal pathways. It is widely involved in autophagy processes such as mitophagy, xenophagy and lysophagy. The abnormal expression of TAX1BP1 is closely related to inflammation, malignant tumors and circulatory diseases. This paper will systematically summarize the structure and function, regulated signal pathway, relationship with autophagy and the physiological significance of TAX1BP1, so as to provide new ideas for the research of TAX1BP1 in the future.

Keywords autophagy receptor; TAX1BP1; inflammation; NF-κB; tumor

自噬是物质降解和代谢的重要机制, 它在去除不规范折叠或聚集的蛋白质、受损的细胞器以及细胞内病原体等方面起着关键的调控作用, 从而维持着真核细胞的代谢平衡[1-3]。根据待降解物质转运至溶酶体方式的不同, 将自噬分为巨自噬、微自噬和分子伴侣介导的自噬(chaperone mediated autophagy, CMA)三种[4]。起初, 人们认为自噬是非选择性的, 而自噬受体的发现则证实了选择性自噬的存在[5]。选择性自噬有很多种, 如线粒体自噬、溶酶体自噬等, 它可以使受损的细胞器、内质网或线粒体氧化应激压力得到清除或缓解, 从而达到维持细胞正常生理功能的效果, 最终影响恶性肿瘤的发生。自噬受体是一种介导自噬选择性的特定接头蛋白[6], 它们的关键作用是将待降解的特异性底物和ATG8家族蛋白连接起来, 随后将其运输至溶酶体进行降解[7-9]。p62/SQSTM1、NRB1、NDP52、TAX1BP1、Nix、Cb1、OPTN等均是目前发现的含有LIR结构域的自噬受体。其中最早进入生物学家视野的自噬接头蛋白是p62[5]。有研究表明, 选择性自噬的发生离不开自噬受体。当选择性自噬发生时, 大量的底物, 包括入侵的病原体、细胞内的微生物成分、受损的细胞器以及I型干扰素和炎症信号通路中的关键分子, 都可以通过自噬受体靶向自噬体而得到清除, 从而维持机体正常的生命活动[10]。Tax1结合蛋白1(Tax1-binding protein 1, TAX1BP1)作为选择性自噬受体的一员, 参与调控多种细胞进程, 且国内尚未发表TAX1BP1相关的综述性文章。因此, 本文对TAX1BP1的蛋白结构、作用功能等进行系统的总结, 以期为后续研究者提供思路。

1 TAX1BP1简介

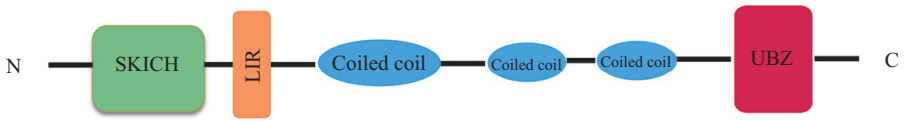
TAX1BP1, 也称T6BP或TXBP151, 分子量为86 kDa[11] , 人*TAX1BP1*基因位于7p15号染色体上[12]。TAX1BP1蛋白在细胞质与细胞核中均有分布, 已被证明在大多数人体组织和已建立的细胞系中大量表达[13]。而在应激环境下, 该蛋白还可以定位于蛋白质聚集体[14]、受损线粒体[15]以及含病原体的自噬体[16]上。

TAX1BP1氨基末端是一个SKIP羧基同源性域(SKIP carboxyl homology, SKICH)[17], 后面紧跟一个LIR基序, 中间是三个卷曲螺旋, 羧基端则包含一个UBZ结构域[11]。其SKICH域能够以某种方式与组蛋白伴侣NAP1[18]直接相互作用, 从而间接与TANK结合激酶1(TANK-binding kinase 1, TBK1)结合, 而TBK1是NF-κB抑制蛋白(NF-κB inhibitory protein, IκB)激酶家族成员, 可以在多个位点直接磷酸化TAX1BP1[19]。TAX1BP1还可通过N末端激活域与糖皮质激素受体形成复合物并激活糖皮质激素反应元件[13]。TAX1BP1的LIR基序与NDP52[20]高度相似, 能够以不同的亲和力与不同的ATG8同源物结合[21-22]。而中央卷曲螺旋域则介导了TAX1BP1[11]的二聚化。TAX1BP1的C-端货物结合区包含两个串联的C_2H_2型锌指(UBZ1和UBZ2), 可作为泛素结合域, 识别RIP1、TRAF6和ITCH等泛素化蛋白[23-24]。与此同时, UBZ结构域也参与了TAX1BP1与肌球蛋白VI的相互作用(图1)[25]。

2 TAX1BP1的功能概况

TAX1BP1最初被鉴定是一种与人T细胞白血病病毒I型(human T cell leukemia virus-I, HTLV-I)调节蛋白Tax相互作用的细胞蛋白[26-28], 后来被证明是一种重要的衔接蛋白, 通过与泛素编辑酶A20、E3泛素连接酶TRAF6和ITCH相结合负调控相关信号通路[11,24,29-31]。最近, TAX1BP1也被证明具有自噬受体的功能, 参与异体自噬和线粒体自噬[21-22,32]等选择性自噬过程。

TAX1BP1还涉及一些其他的功能。例如, TAX1BP1是人乳头瘤病毒18型(human papilloma-virus type 18, HPV18) E2蛋白的新型结合伴侣, 与转录共激活因子P300一起促进E2依赖性转录[33]。异补骨



N: 氨基末端; SKICH: SKIP羧基同源性域; LIR: 微管相关蛋白I轻链3结合结构域; coiled coil: 卷曲螺旋结构域; UBZ: 泛素结合结构域; C: 羧基末端。

N: N-terminal; SKICH: SKIP carboxyl homology domain; LIR: microtubule associated protein I light chain 3 binding region; coiled coil: coiled coil domain; UBZ: ubiquitin binding domain; C: C-terminal.

图1 TAX1BP1蛋白结构域示意图(根据BLAST网站预测得出)

Fig.1 The schematic representation of the domains of TAX1BP1 protein (according to the prediction of BLAST website)

脂查尔酮(isobavachalcone, IBC)可以通过上调TAX1BP1从而抑制小胶质细胞的活化, 进而使得TAX1BP1成为IBC抑制小胶质细胞活化的新靶点[34]。TAX1BP1还起细胞生长和凋亡调节剂的作用。如TAX1BP1的过表达可以抑制小鼠胚胎成纤维细胞(NIH3T3)中肿瘤坏死因子(tumor necrosis factor, TNF)诱导的细胞凋亡[35]。此外, TAX1BP1在膜运输[25]、神经传递[36]和抗病毒[37]过程中也发挥着重要的作用。下面重点对TAX1BP1调节的信号通路以及TAX1BP1对于自噬的调控作用进行总结。

2.1 TAX1BP1调节的信号通路

2.1.1 NF-κB信号通路 NF-κB, 一种重要的细胞转录因子, 广泛分布于细胞质中。正常情况下, NF-κB由于与IκB的结合而呈现出非活性状态。而当机体受到细胞因子、病毒、氧化剂以及紫外线等的影响时, NF-κB被激活。被激活的NF-κB会与IκB发生解离, 移位至细胞核并与相应靶基因的κB基序结合从而调控相关靶基因的表达。NF-κB在许多细胞进程中均发挥着重要的功能, 其在炎症及免疫反应中的作用尤为突出。

TAX1BP1最初被认为是NF-κB信号通路激活因子TRAF6和抑制因子A20的结合伙伴[11,35], 这些发现表明, TAX1BP1能够调节NF-κB通路的激活。随后, TAX1BP1又被证明是一种泛素结合蛋白, 通过招募去泛素化酶A20激活受体复合物, 充当TNF-α和IL-1β诱导的NF-κB通路的负调节因子[23]。而且动物模型实验也进一步验证了其在NF-κB通路中的负调控作用。*TAX1BP1*基因敲除的小鼠肝脏中的巨噬细胞数量增加, 从而导致包括肝脏在内的不同器官的炎症增加、NF-κB信号上调[23,38]。而将野生型骨髓移植到*TAX1BP1*敲除小鼠则可以逆转其炎症表型, 表明该炎症表型取决于髓系细胞[23]。此外, TAX1BP1还可通过与OPTN协同作用来增加Tax1的泛素化以及Tax1介导的NF-κB信号转导[39]。而且EB病毒(Epstein-Barr virus, EBV) BART miRNA miR-BART15-3p可以通过结合*TAX1BP1* mRNA的3′-UTR来调节NF-κB的活性[40]。因此, 这些研究综合表明, TAX1BP1可以广泛地参与到NF-κB信号通路中去, 并发挥其负调控功能。

2.1.2 Ras-Raf-MEK-JNK信号通路 C-Jun氨基末端激酶(C-Jun N-terminal kinase, JNK)是一种广泛表达于各种组织中的有丝分裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)。炎症因子、内质网应激、氧化应激等各种细胞因子和应激刺激的出现会使MAPK通路处于激活状态, 进而特异性识别JNK上特殊位点的磷酸化, 从而激活JNK, 使其作用于不同的底物并引起不同的细胞生理反应, 最终对细胞凋亡、胚胎发育、免疫应答反应等各种生理病理现象产生影响[41]。

研究者用TNF-α、IL-1和LPS分别刺激野生型和*TAX1BP1*基因敲除小鼠, 发现随着处理时间的增加, *TAX1BP1*基因敲除小鼠表现出增强而又持久的JNK激酶活性。免疫共沉淀实验也得到了同样的结果: 在缺乏*TAX1BP1*的小鼠成纤维细胞中, TNF-α、IL-1和LPS介导的JNK活化升高且持续存在[42]。这就说明, TAX1BP1介导了JNK活化的下调。但也有人对*TAX1BP1*敲除小鼠的腹腔巨噬细胞中JNK活性进行检测, 发现其并没有出现增强且持续的JNK磷酸化。此外, 作者还采用AP-1依赖性荧光素酶分析进一步检查, 发现TAX1BP1的过表达也未能影响AP-1依赖性报告基因*IL-1β*活化[23], 这与前人的研究相悖。因此, 综合来看, TAX1BP1在JNK信号通路中的作用机理尚未确定, 需要后续科研者的深入研究证实。

2.2 TAX1BP1对自噬的调控作用

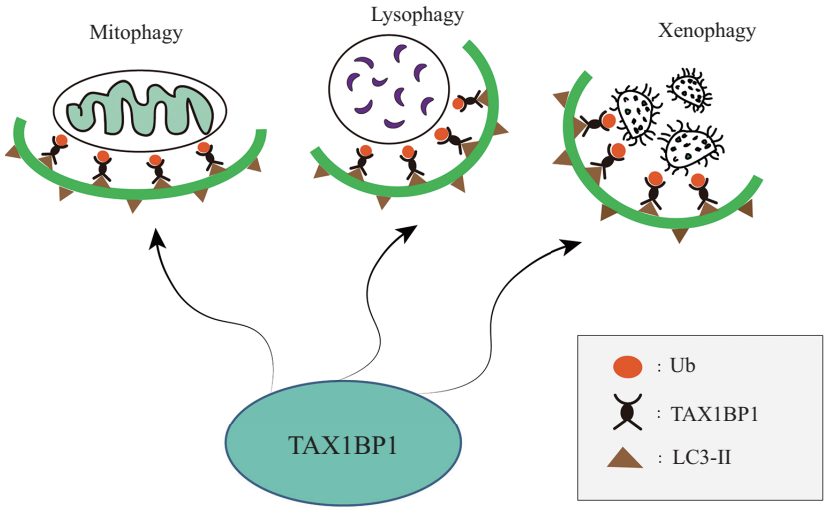
近十年来, TAX1BP1在自噬中的重要性引起了

科研工作者的极大关注[31,43-44]。在没有LC3脂化的情况下, TAX1BP1的N-端可以将FIP200聚集在NBR1周围从而促进自噬体的持续形成[45]。TAX1BP1的LIR结构域充当自噬受体区, 募集蛋白质进行降解。TAX1BP1的C-端包含两个锌指, 它们作为新的泛素结合结构域起作用[46]。

*TAX1BP1*过表达或敲除均会影响细胞内的基础自噬流。例如给小鼠注射链脲佐菌素(streptozocin, STZ)诱导糖尿病小鼠12周时, 小鼠心脏中自噬水平显著下降, 此时TAX1BP1表达量也同步下降。当在糖尿病小鼠中过表达TAX1BP1时, 则发现*Atg7*、*Atg12*等自噬相关基因表达量显著回升, LC3II/I值增加, p62累积量减少。同时, 用mRFP-GFP-LC3检测自噬通量, 发现TAX1BP1的过表达导致红色斑点数明显增加[47]。这就表明TAX1BP1的过表达增加了自噬水平, 而这种自噬增强是通过NF-κB信号通路的激活引起的。同样, 研究还发现*TAX1BP1*的缺失会抑制LC3、GABARAP与TAX1BP1的结合, 从而引起自噬诱导的缺陷, 进而导致mTOR复合物形成和激活受阻[44]。下面将近年来TAX1BP1介导的选择性自噬进行汇总(图2)。

2.2.1 TAX1BP1与线粒体自噬 线粒体自噬是细胞进化出的用来清除功能紊乱或多余线粒体, 从而维持胞内线粒体数量和质量稳态的关键机制。在这个过程中, 待降解的线粒体被双膜囊泡包被, 随后通过自噬受体与LC3结合形成自噬体, 自噬体最终与溶酶体融合以降解内容物[48]。TAX1BP1在线粒体自噬中同样扮演着重要的角色。在线粒体自噬过程中, 泛素化的线粒体通过泛素分子结合受体蛋白TAX1BP1[15]实现对LC3的招募。而将*NDP52*、*OPTN*、*TAX1BP1*这三个自噬受体同时敲除则可以抑制线粒体自噬的发生。这就表明, 线粒体自噬的发生需要TAX1BP1的参与。

2.2.2 TAX1BP1与异体自噬 自噬机制被用作抵抗微生物感染的防御系统, 这一过程称为异体自噬[49-50]。鼠伤寒沙门氏菌是深入研究自噬降解有关病原菌的实例之一。在入侵过程中, 鼠伤寒沙门氏菌在细胞内含沙门氏菌的液泡(salmonella-containing vacuole, SCV)中驻留并复制, 但它也可能逃逸到细胞质中被泛素分子所识别。被泛素化标记的鼠伤寒沙门氏菌随后被选择性自噬受体识别从而诱导细胞自噬的发生[7]。先前的研究表明, p62[51]、NDP52[52]和OPTN[53]等自噬受体均通过自噬体参与泛素鼠伤寒沙门氏菌的清除。TAX1BP1则可以在鼠伤寒沙门氏菌感染后靶向β干扰素TIR结构域衔接蛋白(TIR-domain containing adaptor inducing interferon-β, TRIF), 从而导致其自噬降解并减弱NF-κB信号转导作用[54]。此外, 半乳糖凝集素-8(galectin-8, GAL8)还可以通过与TAX1BP1结合, 从而使得带有泛素分子标记的结核分歧杆菌通过选



绿色弧形: 自噬隔离膜; 箭头: TAX1BP1参与调控的自噬类型; Ub: 泛素分子。

Green arc: autophagy isolation membrane; arrow: the types of autophagy regulated by TAX1BP1; Ub: ubiquitin molecule.

图2 TAX1BP1调控自噬示意图

Fig.2 The schematic diagram of TAX1BP1 regulating autophagy

择性自噬途径被清除掉[55]。

2.2.3 TAX1BP1与溶酶体自噬 溶酶体膜具有一定的通透性, 当受到溶酶体药物等的刺激时, 溶酶体膜通透性随即发生改变并进一步导致溶酶体损伤, 严重时可引起细胞死亡[56]。因此细胞就进化出了复杂的防御机制, 这个机制通过两个途径来完成。一是受损溶酶体的修复。这一途径需要热休克蛋白HSP70与脂质结合稳定溶酶体膜以及内吞体分选转运复合体(endosomal sorting complex required for transport, ESCRT)修复溶酶体膜上的小孔来完成。另一个途径就是激活信号级联, 促进新溶酶体的再生。一般过程为mTORC1复合物从溶酶体解离, 然后导致转录因子TFEB的去磷酸化并进入细胞核, 最终导致缺陷型溶酶体被选择性巨自噬途径清除, 而促进新溶酶体再生这个过程就是溶酶体自噬[57-58]。值得注意的是, 近两年的研究表明, TAX1BP1也参与到了溶酶体自噬中去。*L*-亮氨酰-*L*-亮氨酸甲酯(*L*-leucyl-*L*-leucine methyl ester, LLOMe)是一种诱导溶酶体自噬发生的药物。当使用LLOMe处理诱导溶酶体自噬发生后, TAX1BP1与溶酶体相关膜蛋白1(lysosome associated membrane protein 1, LAMP1)存在明显的共定位, 也就是说, 当溶酶体自噬发生时, TAX1BP1能够被募集到受损的溶酶体附近[59], 这就揭示了其在溶酶体自噬中的作用, 后续可对其参与溶酶体自噬的具体分子机制详加探究。

3 TAX1BP1的生理意义

3.1 TAX1BP1与炎症反应

炎症反应好发于全身各个组织与器官, 是一种比较常见的生理病理现象。细胞炎性的发生通常是由于细菌感染导致NF-κB移位至细胞核并发挥转录因子的作用, 从而调节促炎细胞因子的产生[60]。研究者构建*TAX1BP1*敲除小鼠, 发现在TNF-α或IL-1β的诱导下, 相比于野生型小鼠, *TAX1BP1*敲除小鼠激活NF-κB的效果更显著[23]。而且*TAX1BP1*敲除小鼠出生时发育正常, 但随着年龄的增长, 出现了炎症性心脏瓣膜炎和皮肤皮炎以及过早死亡的现象[23,38]。

B淋巴细胞属于炎症细胞的一种, 在免疫反应中起关键作用。有研究者建立了*TAX1BP1*敲除型鸡淋巴瘤(DT40) B细胞, 该细胞对CD40诱导的细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)激活信号过度反应, ERK磷酸化显著增强, B淋巴细胞诱导成熟蛋白1(B lymphocyte induced maturation protein-1, Blimp-1)表达水平增加。此外, *TAX1BP1*敲除细胞表面IgM的表达水平显著降低。而且, *TAX1BP1*敲除小鼠的生发中心形成和抗原特异性抗体产生量减少[61]。这些发现表明, TAX1BP1限制ERK激活和Blimp-1表达, 并调节生发中心的形成。

同样, T细胞也在免疫过程中发挥着极其重要的作用。T细胞在免疫反应过程中能够被激活并迅速增殖, 它们不仅可以直接杀死靶细胞, 还能够调控B细胞产生抗体, 并参与构成淋巴细胞。研究发现*TAX1BP1*敲除后, T细胞出现了生长缓慢的现象, 细胞周期也有所延长, 并且由于生物合成缺陷, 细胞均停滞在S期[44]。

芝麻素是芝麻种子木脂素的主要成分, 可以上调肺组织中A20和TAX1BP1的表达水平, 并促进两者之间的结合能力。有人发现芝麻素可以减轻角叉菜胶诱导的大鼠肺部炎症, 其机制可能与A20和TAX1BP1的表达上调从而负调控NF-κB通路有关[62]。

3.2 TAX1BP1与恶性肿瘤

目前的研究表明, TAX1BP1参与到多种肿瘤疾病进程中, 其中TAX1BP1在肝癌中的作用呈现双重性。NF-κB信号通路在肝稳态和癌症发展中起重要作用, 而TAX1BP1作为NF-κB的负调控因子, 它在小鼠中的缺失会导致NF-κB上调, 从而导致包括肝脏在内的不同器官的炎症增加[23]。丙型肝炎病毒(hepatitis C virus, HCV)核心蛋白与肝细胞癌(hepatocellular carcinoma, HCC)的发生有关。在HepG2细胞中诱导HCV核心蛋白的表达可以上调TAX1BP1和A20的表达, 导致肝细胞增殖减少, 促炎信号被抑制[63]。也有人通过在野生型和*TAX1BP1*敲除小鼠中用二乙基亚硝胺(diethylnitrosamine, DEN)诱发肝癌, 发现*TAX1BP1*敲除小鼠肝脏中炎症细胞数量增加。随后, 他们将野生型和*TAX1BP1*敲除小鼠中分离出的肝巨噬细胞进行分析则发现*TAX1BP1*敲除小鼠中NF-κB信号通路的激活情况以及促炎性细胞因子的转录水平均要高于对照组, 并且*TAX1BP1*敲除小鼠中肝癌细胞数量也要明显高于对照组[64]。这些均表明TAX1BP1起到了抑制促炎信号以及防止肝癌发生的作用。但后者研究结果与此相悖, 有研究表明, TAX1BP1拷贝数在几种肝癌细胞系以及患者中是增加的, 而肝癌患者中基因拷贝数增加通常与HCV

抗体阳性和肿瘤体积大有关, 这就暗示了TAX1BP1对肝癌的促进作用[65]。

头颈癌是指发生在头部和颈部器官、皮肤、软组织、肌肉、神经等的癌症。研究者评估了191名头颈癌患者和200名无肿瘤病史的患者的性别、年龄、吸烟和饮酒习惯。采用PCR-RFLP方法提取基因组DNA后进行分子分析, 发现*TAX1BP1*基因多态性与口腔癌之间存在关联[66]。

同时也有人对TAX1BP1在胃癌中的参与机制进行了研究。miRNA(microRNA)是一类非编码RNA分子。EBV-miR-BART15-3p对*TAX1BP1*的下调增强了胃癌细胞对5-氟尿嘧啶(5-FU)的化学敏感性[40]。

3.3 TAX1BP1与循环系统疾病

糖尿病性心肌病是一种在糖尿病人群中发生的心室功能障碍, 而这种障碍通常不是由冠状动脉粥样硬化和高血压引起的[67]。该病是一种循环系统疾病, 其突出特点是心脏肥大和纤维化, 并伴随着心脏收缩和舒张功能受损[68-70]。之前的研究表明, 糖尿病性心肌病与自噬抑制和心脏炎症增加有关。而TAX1BP1对自噬和炎症的影响提示它可能参与糖尿病心肌病的进展。结果证实, 在STZ诱导的糖尿病小鼠心脏中, *TAX1BP1*表达水平显著降低, 而进一步过表达TAX1BP1后, 糖尿病小鼠的心肌肥大和纤维化均得到改善, 同时也降低了其炎症水平, 并使其氧化应激和细胞凋亡水平得到进一步抑制[47]。这就揭示了TAX1BP1在循环系统疾病中的重要作用。

4 展望

近年来, 随着对自噬受体TAX1BP1的深入研究, 它的重要性逐渐显现, TAX1BP1具有功能多样性的特点, 其在膜转运、转录调节和凋亡等方面均有涉及。TAX1BP1可以下调NF-κB信号转导, 但在JNK信号通路中的作用仍存在争议。随着研究的深入推进, 我们有望探寻其在NF-κB、JNK以外的其他信号通路中的具体分子机制。TAX1BP1广泛地参与到异体自噬、线粒体自噬以及溶酶体自噬等自噬进程中去, 但其参与溶酶体自噬的具体分子机制尚不清楚, 且目前对于TAX1BP1在自噬中的作用机制研究相对较少。此外, TAX1BP1在NF-κB信号通路中的重要作用揭示了其对于炎症相关疾病发展的独特意义, 这一发现在动物模型中也得到了验证。最后, TAX1BP1在胃癌以及口腔癌中的作用已经得到了证实, 但其对于肝癌的影响尚有分歧。因此, 后续可对TAX1BP1进行更加深入的研究, 不断揭示其在更多信号通路以及相关疾病中的关键作用。

参考文献 (References)

[1] BIOCHEM A R. The ubiquitin system [J]. Annual Rev Biochem, 1998, 67(1): 425-79.

[2] ZHOU C F, LIANG Y Y, ZHOU L, et al. TSPAN1 promotes autophagy flux and mediates cooperation between WNT-CTNNB1 signaling and autophagy via the MIR454-FAM83A-TSPAN1 axis in pancreatic cancer [J]. Autophagy, 2021, 17(10): 3175-95.

[3] ZHOU C F, QIAN X H, HU M, et al. STYK1 promotes autophagy through enhancing the assembly of autophagy-specific class III phosphatidylinositol 3-kinase complex I [J]. Autophagy, 2020, 16(10): 1786-806.

[4] MIZUSHIMA N, KOMATSU M. Autophagy: renovation of cells and tissues [J]. Cell, 2011, 147(4): 728-41.

[5] ANDING A L, BAEHRECKE E H. Cleaning house: selective autophagy of organelles [J]. Dev Cell, 2017, 41(1): 10-22.

[6] KIRKIN V. History of the selective autophagy research: How did it begin and where does it stand today [J]? J Mol Biol, 2020, 432(1): 3-27.

[7] JOHANSEN T, LAMARK T. Selective autophagy mediated by autophagic adapter proteins [J]. Autophagy, 2011, 7(3): 279-96.

[8] ROGOV V, DOTSCH V, JOHANSEN T, et al. Interactions between autophagy receptors and ubiquitin-like proteins form the molecular basis for selective autophagy [J]. Mol Cell, 2014, 53(2): 167-78.

[9] STOLZ A, ERNST A, DIKIC I. Cargo recognition and trafficking in selective autophagy [J]. Nat Cell Biol, 2014, 16(6): 495-501.

[10] SHARMA V, VERMA S, SERANOVA E, et al. Selective autophagy and xenophagy in infection and disease [J]. Front Cell Dev Biol, 2018, 6: 147.

[11] LING L, GOEDDEL D V. T6BP, a TRAF6-interacting protein involved in IL-1 signaling [J]. Proc Natl Acad Sci USA, 2000, 97(17): 9567-72.

[12] NAGARAJA G M, KANDPAL R P. Chromosome 13q12 encoded Rho GTPase activating protein suppresses growth of breast carcinoma cells, and yeast two-hybrid screen shows its interaction with several proteins [J]. Biochem Biophys Res Commun, 2004, 313(3): 654-65.

[13] CHIN K T, CHUN A C, CHING Y P, et al. Human T-cell leukemia virus oncoprotein tax represses nuclear receptor-dependent transcription by targeting coactivator TAX1BP1 [J]. Cancer Res, 2007, 67(3): 1072-81.

[14] SARRAF S A, SHAH H V, KANFER G, et al. Loss of TAX1BP1-directed autophagy results in protein aggregate accumulation in the brain [J]. Mol Cell, 2020, 80(5): 779-95,e10.

[15] LAZAROU M, SLITER D A, KANE L A, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy [J]. Nature, 2015, 524(7565): 309-14.

[16] LIN C Y, NOZAWA T, MINOWA-NOZAWA A, et al. LAMTOR2/LAMTOR1 complex is required for TAX1BP1-mediated xenophagy [J]. Cell Microbiol, 2019, 21(4): e12981.

[17] GURUNG R, TAN A, OOMS L M, et al. Identification of a novel

domain in two mammalian inositol-polyphosphate 5-phosphatases that mediates membrane ruffle localization. The inositol 5-phosphatase skip localizes to the endoplasmic reticulum and translocates to membrane ruffles following epidermal growth factor stimulation [J]. J Biol Chem, 2003, 278(13): 11376-85.

[18] THURSTON T L M, RYZHAKOV G, BLOOR S, et al. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria [J]. Nat Immunol, 2009, 10(11): 1215-21.

[19] BENJAMIN, RICHTER, DANIELLE, et al. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria [J]. Proc Natl Acad Sci USA, 2016 , 113(15): 4039-44.

[20] VON MUHLINEN N, AKUTSU M, RAVENHILL B J, et al. LC3C, Bound selectively by a noncanonical LIR motif in NDP52, is required for antibacterial autophagy [J]. Mol Cell, 2012, 48(3): 329-42.

[21] NEWMAN A C, SCHOLEFIELD C L, KEMP A J, et al. TBK1 kinase addiction in lung cancer cells is mediated via autophagy of Tax1bp1/Ndp52 and non-Canonical NF-κB signalling [J]. PLoS One, 2012, 7(11): e50672.

[22] TUMBARELLO D A, MANNA P T, ALLEN M, et al. The autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy [J]. PLoS Pathog, 2015, 11(10): e1005174.

[23] PELOPONESE J M, VERSTREPEN L, ZAPART G, et al. Inflammatory cardiac valvulitis in TAX1BP1-deficient mice through selective NF-κB activation [J]. EMBO J, 2008, 27(4): 629-41.

[24] SHEMBADE N, HARHAJ N S, PARVATIYAR K, et al. The E3 ligase Itch negatively regulates inflammatory signaling pathways by controlling the function of the ubiquitin-editing enzyme A20 [J]. Nat Immunol, 2008, 9(3): 254-62.

[25] MORRISWOOD B, RYZHAKOV G, PURI C, et al. T6BP and NDP52 are myosin VI binding partners with potential roles in cytokine signalling and cell adhesion [J]. J Cell Sci, 2007, 120(Pt 15): 2574-85.

[26] GACHON F, PELERAUX A, THEBAULT S, et al. CREB-2, a cellular CRE-dependent transcription repressor, functions in association with Tax as an activator of the human T-cell leukemia virus type 1 promoter [J]. J Virol, 1998, 72(10): 8332-7.

[27] CHUN A, ZHOU Y, WONG C, et al. Coiled-coil motif as a structural basis for the interaction of HTLV type 1 Tax with cellular cofactors [J]. AIDS Res Hum Retroviruses, 2000, 16(16): 1689-94.

[28] IHA H, KASAI T, KIBLER K V, et al. Pleiotropic effects of HTLV type 1 Tax protein on cellular metabolism: mitotic checkpoint abrogation and NF-κB activation [J]. AIDS Res Hum Retroviruses, 2000, 16(16): 1633-8.

[29] DE VALCK D, JIN D Y, HEYNINCK K, et al. The zinc finger protein A20 interacts with a novel anti-apoptotic protein which is cleaved by specific caspases [J]. Oncogene, 1999, 18(29): 4182-90.

[30] SHEMBADE N, HARHAJ N S, LIEBL D J, et al. Essential role for TAX1BP1 in the termination of TNF-α, IL-1- and LPS-mediated NF-κB and JNK signaling [J]. EMBO J, 2007, 26(17): 3910-22.

[31] VERSTREPEN L, VERHELST K, CARPENTIER I, et al. TAX1BP1, a ubiquitin-binding adaptor protein in innate immunity and beyond [J]. Trends Biochem Sci, 2011, 36(7): 347-54.

[32] LAZAROU M, SLITER D A, KANE L A, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy [J]. Nature, 2015, 524(7565): 309.

[33] WANG X, NAIDU S R, SVERDRUP F, et al. Tax1BP1 interacts with papillomavirus E2 and regulates E2-dependent transcription and stability [J]. J Virol, 2009, 83(5): 2274-84.

[34] LI Z, WANG Q, LUAN H, et al. A novel target TAX1BP1 and P38/Nrf2 pathway independently involved in the anti-neuroinflammatory effect of isobavachalcone [J]. Free Radic Biol Med, 2020, 153: 132-9.

[35] DE VALCK D, JIN D Y, HEYNINCK K, et al. The zinc finger protein A20 interacts with a novel anti-apoptotic protein which is cleaved by specific caspases [J]. Oncogene, 1999, 18(29): 4182-90.

[36] ULRICH M, SEEBER S, BECKER C M, et al. Tax1-binding protein 1 is expressed in the retina and interacts with the GABA(C) receptor rho1 subunit [J]. Biochem J, 2007, 401(2): 429-36.

[37] PARVATIYAR K, BARBER G N, HARHAJ E W. TAX1BP1 and A20 inhibit antiviral signaling by targeting TBK1-IKKi kinases [J]. J Biol Chem, 2010, 285(20): 14999-5009.

[38] NAKANO S, IKEBE E, TSUKAMOTO Y, et al. Commensal microbiota contributes to chronic endocarditis in TAX1BP1 deficient mice [J]. PLoS One, 2013, 8(9): e73205.

[39] JOURNO C, FILIPE J, ABOUT F, et al. NRP/optineurin cooperates with TAX1BP1 to potentiate the activation of NF-κB by human T-lymphotropic virus type 1 tax protein [J]. PLoS Pathog, 2009, 5(7): e1000521.

[40] CHOI H, LEE S K. TAX1BP1 downregulation by EBV-miR-BART15-3p enhances chemosensitivity of gastric cancer cells to 5-FU [J]. Arch Virol, 2017, 162(2): 369-77.

[41] HAYDEN H S, GHOSH S K. Signaling to NF-κB [J]. Genes Dev, 2004, 18(18): 2195.

[42] SHEMBADE N, HARHAJ N S, LIEBL D J, et al. Essential role for TAX1BP1 in the termination of TNF-α-, IL-1- and LPS-mediated NF-κB and JNK signaling [J]. EMBO J, 2007, 26(17): 3910-22.

[43] TUMBARELLO D A, MANNA P T, ALLEN M, et al. The autophagy receptor TAX1BP1 and the molecular motor myosin VI are required for clearance of salmonella typhimurium by autophagy [J]. PLoS Pathog, 2015, 11(10): e1005174.

[44] WHANG M I, TAVARES R M, BENJAMIN D I, et al. The ubiquitin binding protein TAX1BP1 mediates autophagasome induction and the metabolic transition of activated T cells [J]. Immunity, 2017, 46(3): 405-20.

[45] OHNSTAD A E, DELGADO J M, NORTH B J, et al. Receptor-mediated clustering of FIP200 bypasses the role of LC3 lipidation in autophagy [J]. EMBO J, 2020, 39(24): e104948.

[46] VERSTREPEN L, VERHELST K, CARPENTIER I, et al. TAX1BP1, a ubiquitin-binding adaptor protein in innate immunity and beyond [J]. Trends Biochem Sci, 2011, 36(7): 347-54.

[47] XIAO Y, WU Q Q, DUAN M X, et al. TAX1BP1 overexpression attenuates cardiac dysfunction and remodeling in STZ-induced diabetic cardiomyopathy in mice by regulating autophagy [J]. Biochim Biophys Acta Mol Basis Dis, 2018, 1864(5 Pt A): 1728-

43.
[48] ASHRAFI G, SCHWARZ T L. The pathways of mitophagy for quality control and clearance of mitochondria [J]. Cell Death Differ, 2013, 20(1): 31-42.
[49] DERETIC V. Autophagy in infection [J]. Curr Opin Cell Biol, 2010, 22(2): 252-62.
[50] LEVINE B. Eating oneself and uninvited guests: autophagy-related pathways in cellular defense [J]. Cell, 2005, 120(2): 159-62.
[51] ZHENG Y T, SHAHNAZARI S, BRECH A, et al. The adaptor protein p62/SQSTM1 targets invading bacteria to the autophagy pathway [J]. J Immunol, 2009, 183(9): 5909-16.
[52] THURSTON T L, RYZHAKOV G, BLOOR S, et al. The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria [J]. Nat Immunol, 2009, 10(11): 1215-21.
[53] WILD P, FARHAN H, MCEWAN D G, et al. Phosphorylation of the autophagy receptor optineurin restricts *Salmonella* growth [J]. Science, 2011, 333(6039): 228-33.
[54] YANG Q, LIU T T, LIN H, et al. TRIM32-TAX1BP1-dependent selective autophagic degradation of TRIF negatively regulates TLR3/4-mediated innate immune responses [J]. PLoS Pathog, 2017, 13(9): e1006600.
[55] BELL S L, LOPEZ K L, COX J S, et al. Galectin-8 senses phagosomal damage and recruits selective autophagy adapter TAX1BP1 to control mycobacterium tuberculosis infection in macrophages [J]. mBio, 2021, 12(4): e0187120.
[56] PAPADOPOULOS C, MEYER H. Detection and clearance of damaged lysosomes by the endo-lysosomal damage response and lysophagy [J]. Curr Biol, 2017, 27(24): R1330-41.
[57] RADULOVIC M, SCHINK K O, WENZEL E M, et al. ESCRT-mediated lysosome repair precedes lysophagy and promotes cell survival [J]. EMBO J, 2018, 37(21): e99753.
[58] HUNG Y H, CHEN M W, YANG J Y, et al. Spatiotemporally controlled induction of autophagy-mediated lysosome turnover [J]. Nat Commun, 2013, 4: 2111.
[59] KOERVER L, PAPADOPOULOS C, LIU B, et al. The ubiquitin-conjugating enzyme UBE2QL1 coordinates lysophagy in response to endolysosomal damage [J]. EMBO Rep, 2019, 20(10): e48014.
[60] HAYDEN M S, GHOSH S. Shared principles in NF-κB signaling [J]. Cell, 2008, 132(3): 344-62.
[61] MATSUSHITA N, SUZUKI M, IKEBE E, et al. Regulation of B cell differentiation by the ubiquitin-binding protein TAX1BP1 [J]. Sci Rep, 2016, 6: 31266.
[62] YE H, SUN L Y, LI J, et al. Sesamin attenuates carrageenan-induced lung inflammation through upregulation of A20 and TAX1BP1 in rats [J]. Int Immunopharmacol, 2020, 88: 107009.
[63] NGUYEN H, SANKARAN S, DANDEKAR S. Hepatitis C virus core protein induces expression of genes regulating immune evasion and anti-apoptosis in hepatocytes [J]. Virology, 2006, 354(1): 58-68.
[64] WAIDMANN O, PLELI T, WEIGERT A, et al. Tax1BP1 limits hepatic inflammation and reduces experimental hepatocarcinogenesis [J]. Sci Rep, 2020, 10(1): 16264.
[65] YASUO, TANAKA, AND, et al. Gain of GRHL2 is associated with early recurrence of hepatocellular carcinoma [J]. J Hepatol, 2008, 49(5): 746-57.
[66] RUIZ M T, BALACHI J F, FERNANDES R A, et al. Analysis of the TAX1BP1 gene in head and neck cancer patients [J]. Braz J Otorhinolaryngol, 2010, 76(2): 193-8.
[67] GRANT P J, COSENTINO F. The 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD [J]. Eur Heart J, 2019, 40(39): 3215-7.
[68] KANNEL W B, MCGEE D L. Diabetes and cardiovascular disease. The framingham study [J]. JAMA, 1979, 241(19): 2035-8.
[69] DEVEREUX R B, ROMAN M J, PARANICAS M, et al. Impact of diabetes on cardiac structure and function: the strong heart study [J]. Circulation, 2000, 101(19): 2271-6.
[70] BUGGER H, ABEL E D. Molecular mechanisms of diabetic cardiomyopathy [J]. Diabetologia, 2014, 57(4): 660-71.