内质网应激蛋白XBP1在肿瘤作用中的研究进展

牟艳花 李 斌*

(中南大学湘雅医院, 长沙 410008)

摘要 X-盒结合蛋白1(X-box binding protein 1, XBP1)是内质网应激反应中的主要调控因子。大量研究表明, XBP1高表达于多种恶性肿瘤细胞, 高表达的XBP1能促肿瘤细胞缺氧生存以及诱导肿瘤转移及耐药等。最近发现, XBP1可通过多种机制诱导恶性肿瘤新生血管生成并抑制肿瘤相关免疫, 导致恶性肿瘤细胞的快速增殖、免疫逃逸, 进而加速恶性肿瘤的侵袭转移等。因此, XBP1已成为恶性肿瘤治疗的新靶标, 该文就此作一综述。

关键词 X-盒结合蛋白1; 肿瘤; 血管生成; 肿瘤免疫

New Insights into the Role of Endoplasmic Reticulum Stress Signaling Protein XBP1 in Tumor Progression

Mou Yanhua, Li Bin*

(*XiangYa Hospital Central South University, Changsha 410008, China*)

Abstract X-box binding protein 1 (XBP1) was the main regulatory factor in endoplasmic reticulum stress. XBP1 was highly expressed in different kinds of malignant tumors. Many research findings revealed that XBP1 could promote tumor cells to survive in the condition of hypoxia and induce drug resistance. Recent studies demonstrated that XBP1 could induce angiogenesis in malignant tumors by a varies of mechanisms. And moreover, XBP1 can inhibit the host anti-tumor immunity, and facilitate the immune escape of malignant tumor cells, which thereby leading to rapid proliferation and accelerating the invasion and metastasis of malignant tumors. Therefore, it was postulated that XBP1 inhibition could represent a significant approach to increase the efficacy of cancer treatment, especially in various forms of cancer immunotherapy.

Keywords XBP1; tumor; angiogenesis; tumor immunity

X-盒结合蛋白1(X-box binding protein 1, XBP1)是一种碱性亮氨酸拉链(basic lucien zipper, bZIP)结构蛋白, 作为cAMP应答元件连接蛋白(cAMP response element binding protein, CREB)/激活转录因子(activating transcription factors, ATF)家族中的主要转录因子[1]。XBP1参与人体多种正常生理活动, 如激活的XBP1可通过促进脑源性神经营养因子(brain derived neurotrophic factor, BDNF)表达提升记忆和学习过程[2], 促进浆细胞分化、脂肪合成、肝脏正常发育, 维持胰腺和唾液腺的正常分泌功能等; 通过影响磷脂酰肌醇3-激酶/雷帕霉素靶体蛋白(phosphoinosmde-3-kinase/the mammalian target of rapamycin, PI3K/mTOR)和C/EBP同源性蛋白质(C/EBP homologous protein, CHOP)对细胞的生长和凋亡有重要作用[3]。同时, XBP1是内质网应激时未折叠蛋白质反应(unfolding protein response, UPR)的一个重要转录因子[4], 它可作用于下游多个靶基因, 调控蛋白质的折叠, 减缓内质网压力。因此, XBP1目前已成为恶性肿瘤研究的热点之一, 特别是在诱导血管生成和促肿瘤免疫逃逸等方面的研究。

收稿日期: 2017-07-13 接受日期: 2017-09-06
湖南省自然科学基金(批准号: 14JJ6004)资助的课题
*通讯作者。Tel: 0731-89753034, E-mail: bincsuxy@csu.edu.cn
Received: July 13, 2017 Accepted: September 6, 2017
This work was supported by the Natural Science Foundation of Hunan Province (Grant No.14JJ6004)
*Corresponding author. Tel: +86-731-89753034, E-mail: bincsuxy@csu.edu.cn
网络出版时间: 2017-12-04 12:08:09
URL: http://kns.cnki.net/kcms/detail/31.2035.Q.20171204.1207.018.html

1 XBP1概述

XBP1于1990年最先作为转录因子被发现, 是重要的内质网应激蛋白质, 其基因定位于22q12。内质网应激(endoplasmic reticulum stress, ERS)是指真核细胞内环境在各种内外因素下遭受破坏[5], 引起内质网蛋白质合成和转运障碍, 从而导致大量的未折叠蛋白质聚积在内质网内引起应激反应[6], 启动细胞内的非折叠蛋白质反应下游信号通路, 如活化转录因子6(activating transcription factor 6, ATF6)、肌醇需酶1(inositol requiring enzyme 1, IRE1)[7]和双链RNA依赖的蛋白激酶样ER激酶[double-stranded RNA-dependent protein kinase (PKR)-like ER kinase, PERK]等, 从而调控细胞对应激反应的能力[8]。在非内质网应激情况下, 这些UPR分子通常是与未折叠蛋白质反应的分子伴侣葡萄糖调节蛋白78(glucose regulated protein 78, GRP78)结合[9]而处于失活状态。当发生ERS时, GRP78被活化, 释放IRE1、PERK、ATF6等分子, 从而进一步激活下游的信号分子[10](图1)。其中, IRE1α-XBP1信号通路是ERS最重要的通路之一[11], 涉及人体多种病理状态, 与肿瘤生长、侵袭转移及耐药密切相关[12]。

XBP1是一种锌指结构的转录因子。通常情况下, XBP1分别以非活性XBP1(XBP1 unspliced, XBP1u)和活性XBP1(XBP1 spliced, XBP1s)的形式存在[13]。在内质网应激状态下, IRE1α活化XBP1u为XBP1s[14], 并作为有效的转录因子作用于细胞核内的多个靶基因。其调节基因涉及蛋白质折叠、内质网相关蛋白降解(ER-associated protein degradation, ERAD), 以促进蛋白质折叠和ERS平衡修复等相关基因转录表达[15], 如XBP1激活*EDEM*(ER degradation enhancer, mannosidase alpha-like)基因而降解被结合的未折叠蛋白质。XBP1诱导*P58IPK*(protein kinase inhibitor P58)基因表达[16], 抑制内质网分子PERK磷酸化, 从而抑制PERK磷酸化真核起始因子2(eukaryotic initiation factor 2, eIF2)所致的蛋白质翻译等。

2 XBP1在肿瘤中的作用

研究证实, 大部分恶性肿瘤细胞高表达XBP1; 恶性肿瘤细胞的快速增殖和微环境的变化均可以上调XBP1表达, 如缺氧、营养缺乏和致瘤压力等均可诱导ERS[5]。同时, 治疗恶性肿瘤的各种方法如放疗、化疗及靶向治疗等亦可导致显著的ERS[17-18]。XBP1可通过上调下游多个靶基因减轻ERS, 尽可能使恶性肿瘤细胞恢复内质网平衡稳态。然而, 过度的ERS反应可诱导肿瘤细胞严重的应激反应, 导致细胞不可逆恢复甚至死亡。

因此, 肿瘤细胞的适应性XBP1高表达是其能在各种恶劣的微环境中存活、增殖、侵袭和转移的重要因素。研究发现, 高表达的XBP1可通过抑制蛋白质合成、诱使细胞休眠和阻抑细胞凋亡等一系列的途径应对细胞损害, 提高肿瘤细胞生存和耐药性; XBP1也可显著促肿瘤血管生成, 诱使免疫细胞变性从而使肿瘤细胞免疫逃逸等促肿瘤细胞转移浸润(图2)。同时, 临床研究也证实, 乳腺癌[19]和肝癌细胞中的XBP1表达增加; *XBP1* mRNA水平与多发性骨髓瘤的临床分期、恶性程度等密切相关, 且XBP1s是多发性骨髓瘤总存活率独立的预后指标[20]。XBP1s升高与膀胱癌预后差具有显著相关性。因此, 近年来, XBP1已成为恶性肿瘤治疗的新靶点。

2.1 XBP1在缺氧环境下对肿瘤细胞存活及新陈代谢的影响

因恶性肿瘤细胞的失控性增殖, 往往导致其缺氧及营养供给不足[21]; 同时, 新生血管的不完整、局部化学物质、神经支配的刺激造成血管的收缩和舒张节律紊乱等加重了其供血障碍。因此, 在低氧环境中恶性肿瘤细胞需诱导一系列的信号通路以适

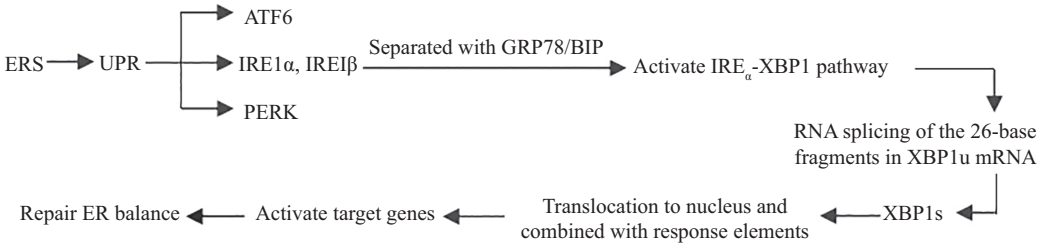

图1 内质网应激主要信号通路(根据参考文献[5,10-11,14]修改)

Fig.1 Major signaling pathways of endoplasmic reticulum stress (modified from references [5,10-11,14])

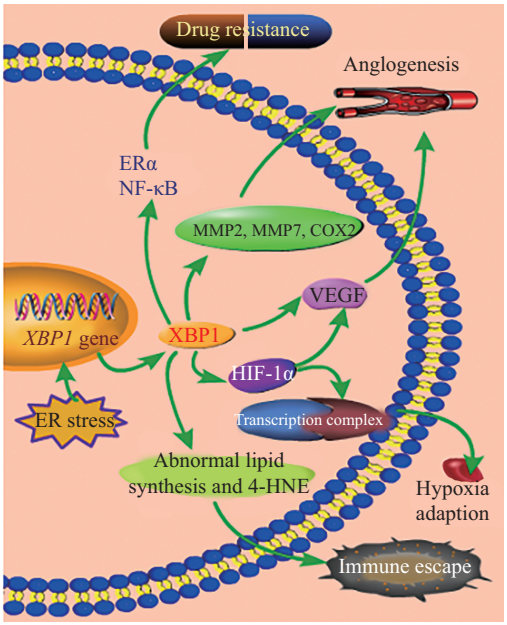

图2 XBP1在肿瘤细胞中主要作用(根据参考文献[25,37,41,44,50,55]修改)

Fig.2 The role of XBP1 in tumor progression (modified from references [25,37,41,44,50,55])

应缺血缺氧环境, 其中IRE1α-XBP1为重要的信号通路之一。IRE1α活化后, 使XBP1s在细胞核内与低氧诱导的缺氧诱导因子-1α(hypoxia inducible factor-1 alpha, HIF-1α)结合, 形成转录复合体, 协同调节HIF-1α靶基因(如*EGFA*、*PDK1*、*GLUT1*和*DDIT4*)转录, 从而增强肿瘤细胞在缺氧环境中的生存能力[19,22]。将细胞置于条件性低氧(氧气浓度低于0.1%)中, 其XBP1s表达显著增高; 而沉默*XBP1*后, 肿瘤细胞生存和增殖能力显著下降[23], 甚至出现细胞死亡。研究证实, XBP1激活可能是胶质瘤细胞耐受缺氧和营养物质匮乏等内环境应激的重要标志[24]。

低氧环境下, 肿瘤细胞新陈代谢发生明显改变, 包括蛋白质合成、脂肪合成和糖酵解等[25]。IRE1α-XBP1信号通路可调控上述多种代谢过程相关的靶基因, 包括ERS相关蛋白降解及蛋白质折叠相关靶基因、氧化还原酶和转葡糖基酶等而提高蛋白质折叠能力, 并控制mRNA翻译的速度[26], 从而减低ERS而恢复肿瘤细胞稳态。

XBP1s在脂肪合成中也起着重要作用, 是必需的脂肪合成转录因子[27]。敲除*XBP1s*则抑制脂肪合成[28]。上调XBP1的表达, 可提高胆碱胞苷酰基转移酶(choline cytidylyltransferase, CCT)和转磷酸胆碱酶(choline phosphotransferase, CPT)的活性, 增加磷脂酰胆碱的合成[29], 也可上调短链脂肪酸受体(G protein-coupled receptor 43, GPR43)的表达[30]。XBP1可通过直接调节脂肪合成相关的基因, 如*SCD1*、*CYP51*、*PMVK*、*SC4MOL*、*HSD17B7*、*IDIL*等[31-32], 也可能是通过抑制Wnt10b/β-联蛋白通路调节脂代谢[33]。另一重要分子成纤维细胞生长因子-21(fibroblast growth factor-21, FGF-21)被证明可被IRE1α-XBP1和eIF2α-ATF4通路双重调节, 在调节糖和脂质代谢中具有重要作用[34]。

在低氧环境下, 糖酵解途径是肿瘤细胞又一条重要的能量代谢途径; 相对于正常细胞, 糖酵解途径关键酶之一己糖激酶(hexokinase, HK)的表达在肿瘤细胞中显著升高[35]。XBP1可协同HIF-1α促进糖酵解途径的多种酶相关基因如葡萄糖转运子-1和糖酵解酶基因等的转录和翻译[19], 从而保证肿瘤细胞的营养等。低氧环境下沉默*XBP1*, 胶质瘤细胞糖酵解明显抑制, 乳酸生成量和ATP生成量明显下降, 细胞存活显著受抑制[24]。

以上研究表明, XBP1可同时调控糖、蛋白质及脂肪等物质代谢来维持恶性肿瘤细胞在缺氧环境下的存活和增殖能力。

2.2 XBP1诱导恶性肿瘤的血管生成而促其侵袭转移

血管内皮生长因子(vascular endothelial growth factor, VEGF)与肿瘤的侵袭和血管密度密切相关, 在诱导内皮细胞迁移及促新生血管形成起着关键作用。VEGF包括VEGFA、VEGFB、VEGFC等不同的配体, 通过与VEGF受体FLT、FLT1、FLT4等结合而发挥促肿瘤血管生成作用。UPR三条信号通路IRE1α-XBP1、PERK-ATF4、ATF6均可以调节VEGFA的转录, 而IRE1α-XBP1在肿瘤中诱导新生血管生成中起主要作用[36]。研究结果表明, VEGF的表达水平与XBP1升高显著相关。XBP1s可与*VEGFA*基因启动子ACGT序列结合, 上调*VEGFA*基因的转录, 从而提高*VEGFA* mRNA水平[37]。此外, *XBP1* mRNA还可通过PI3K/Akt/GSK3β/β-catenin/E2F2通路激活VEGF, 而促进内皮细胞生长和新生血管生成[14]; 而上调的VEGF可通过KDR/XBP1u/IRE1α相互作用上调XBP1的表达[36], 后者进一步调控VEGFA的表达, 形成了XBP1-VEGF-XBP1的正反馈循环, 使两者在恶性肿瘤细胞中水平持续增高, 从而不断促进恶性肿瘤的新生血管生成。

XBP1除调控*VEGF*表达外, 低氧状态下, XBP1的靶基因还包括与血管生成相关的*MMP2*、*MMP7*和*COX2*等。Romero-Ramirez等[38]研究表明, IRE1α对血管生成起到重要作用。抑制神经胶质瘤细胞中的IRE1α表达, VEGF-A、IL-1β、IL-6和IL-8等表达明显下降, 肿瘤生长显著受抑[39]。同时发现, 活化的XBP1与胰腺癌[38]和乳腺癌血管生成有关[40]。胰腺癌中XBP1的表达与血管内皮细胞CD31关系密切, 进一步说明XBP1与血管生成密切相关[41]。而MicroRNA-214可结合*XBP1* mRNA 3′UTR,下调XBP1的表达水平, 抑制肿瘤血管生成[42]。

XBP1还可协同低氧诱导下的HIF-1α表达, 调控其多个靶基因, 包括*MMP2*、*MMP9*、*COX2*、*iNOS*、*VEGF*、*PDK1*、*GLUT1*和*DDIT4*的表达[43-44]。研究发现, 使用shRNA沉默*XBP1*, HIF-1α在肿瘤组织的表达下降, 诱导$CD44^{high}CD24^{low}$的XBP1的数量减少, 新生血管生成受抑, 肿瘤血管数量减少[45]。

研究证实, 血管生成与侵袭转移关系密切, 新生的血管内皮和基底膜存在缺陷, 细胞易通过基底膜屏障进入血液循环, 向远端扩散和转移。XBP1可通过诱导新生血管生成和上调侵袭转移相关基因表达, 而促进肿瘤转移。同时发现, XBP1可上调GRP78的水平[46], 而GRP78高表达, 与肿瘤细胞(如前列腺癌、乳腺癌、食管癌等)浸润深度和淋巴结转移密切相关。此外, Rajapaksna等[47]还发现, XBP1可促进Snail表达诱导乳腺癌侵袭转移。Mhaidat等[48]发现, XBP1高表达的结肠癌细胞远处转移常见。Chen等[44]的研究显示, 沉默*XBP1*可以阻断三阴性乳腺癌的肺转移发生。上述结果表明, XBP1通过多途径促进恶性肿瘤新生血管生成及其侵袭转移等。

2.3 XBP1诱导肿瘤细胞产生耐药

肿瘤细胞耐药是患者治疗失败的主要原因, XBP1在肿瘤耐药中起到非常重要的作用[46]。IRE1-XBP1-NCOA轴的过度活化可导致ER阳性乳腺癌对内分泌治疗的抵抗[49]。Rong等[50]的研究结果也显示, XBP1高表达可增加乳腺癌细胞的内分泌治疗的抵抗性; 进一步的研究表明, XBP1可通过上调ERα表达及核转录因子-κB(nuclear factor-kappa B, NF-κB)水平而导致内分泌治疗的失败, 抑制XBP1上调的NF-κB可逆转XBP1过表达引起的抗雌激素药物抵抗, 从而增强药物对肿瘤细胞的敏感性。McCloy等[51]的研究也证实了XBP1参与ERS受体阳性乳腺癌细胞对雌激素受体拮抗剂的抵抗, 使用STF-083010(一种特异性IRE-1α核酸内切酶抑制剂)下调XBP1的表达, 可恢复乳腺癌细胞对他莫昔芬的敏感性。Mimura等[52]的研究显示, 使用IRE1特异性抑制剂MKC-3946阻断XBP1剪接活化, 可逆转多发性骨髓瘤细胞的耐药性。

2.4 XBP1通过多种途径调控肿瘤免疫反应

肿瘤细胞通过对免疫细胞及免疫系统进行修饰或抑制, 从而使其逃逸机体免疫系统的监控、打击及吞噬是恶性肿瘤持续增殖和侵袭转移的重要原因。树突状细胞(dendritic cells, DC)是刺激细胞毒性T淋巴细胞和启动、维持T细胞依赖的抗肿瘤免疫所必需的抗原提呈细胞[53]。近期研究发现, XBP1是肿瘤微环境中抑制DC功能的关键因子[54], 其诱导肿瘤微环境中的DC细胞中甘油三酯的合成模式发生改变, 导致脂质的异常积累; XBP1促进活性氧族(reactive oxygen species, ROS)的多功能反应副产物4-HNE(4-hydroxy-trans-2-nonenal)的合成, 从而显著抑制了树突状细胞(thymic deutrtic cells, tDC)的功能, 丧失了其对肿瘤的抗原提呈作用和促抗肿瘤T细胞的活化功能[55]。同时, XBP1可通过调控下游多个靶基因的表达, 阻断树突状细胞刺激活化其他免疫细胞(如Th细胞)的能力。Juan等[54]的研究发现, 激活DC中*XBP1*表达能抑制DC功能, 诱导肿瘤细胞的免疫逃逸。通过纳米颗粒介导的基因沉默方法特异性沉默tDC的*XBP1*表达, 可恢复tDC的免疫刺激活性, 触发对肿瘤的强大免疫反应。Cubillos-Ruiz等[56]报道, 敲除*XBP1*基因可使DC表面的MHC-I/肽络合物的表达上调, 从而增强抗肿瘤$CD4^+$及$CD8^+$T细胞的活性。基于以上研究, XBP1是DC-CIK细胞免疫治疗的重要靶分子, 成为肿瘤免疫治疗中又一热点[57]。

XBP1还可与B细胞中主要组织相容性复合体II(major histocompatibility complex II, MHCII)类分子基因启动子的X-BOX元件结合, 调节MHCII类分子的表达而调控肿瘤免疫反应[58]。同时, XBP1是目前能选择性和特异性参与浆细胞分化的唯一转录因子[59], 是B淋巴细胞最终分化成浆细胞所必需的[60], 而且IRE1α-XBP1是刺激浆细胞分泌抗体的重要信号通路[61]。敲除淋巴系统*XBP1*表达, 不但影响抗体的分泌, 也阻滞浆细胞的分化成熟[58]。研究发现, 多个因子如tRNA剪接连接酶的催化亚单元RTCB及mTOR均依赖于XBP1s表达促进B细胞分泌抗体[62], 从而进一步表明, XBP1在B细胞介导的抗体分泌及免疫调

控中的重要作用。

IRE1α-XBP1活化与外周血单核细胞来源的巨噬细胞活化产生炎症因子密切相关, 其中, Toll蛋白(Toll-like receptor, TLR)激活的XBP1是巨噬细胞持续产生炎性细胞因子的必需条件[63]。用LPS刺激小鼠巨噬细胞后, XBP1被TLR信号通路激活, 活化的XBP1s能协同上调IL-6、TNF-α和IFN-β等关键炎症因子表达。IRE1α-XBP1通路还可通过激活糖原合成酶激酶-3β(glycogen synthase kinase-3β, GSK3β)促进IL-1β的产生。敲除或抑制巨噬细胞中的*XBP1*表达使特异性炎性细胞因子(如IL-6和IFN-β)生成受抑。此外, IRE1α-XBP1还可以增加肺泡巨噬细胞数量, 因此, XBP1表达及活化对巨噬细胞的生成活化的重要作用, 进一步提示XBP1在恶性肿瘤中的免疫监控的关键作用。

XBP1对效应$CD8^+$T细胞的最终分化有重要作用。IRE1α在$CD4^+CD8^+$胸腺T细胞和$CD8^+$脾T细胞中显著活化。在李氏菌感染时, 效应$CD8^+$T细胞中IRE1α-XBP1通路被活化。多种类型粒细胞的正常分化均依赖于XBP1, XBP1是维持嗜酸性粒细胞系祖细胞生存和定向分化所必需的, 敲除*XBP1*后, 嗜酸性粒细胞颗粒形成受阻, 嗜酸性粒细胞生成缺陷[64]。而IRE1α-XBP1通路的激活影响粒细胞的活性, 并调控其相关的免疫调节作用, 而且XBP1对小肠潘氏细胞活动也有重要的调控作用[65]。

2.5 XBP1靶向治疗

基于XBP1促恶性肿瘤代谢、诱导肿瘤耐药以及促肿瘤新生血管形成, 尤其在介导肿瘤细胞免疫逃逸中的重要作用, 靶向XBP1已成为恶性肿瘤治疗的新方向。然而, 直接针对XBP1转录分子的药理抑制剂在设计及临床应用存在一定的困难; 因此, 目前主要通过抑制其上游分子IRE1对XBP1的活化作用。抑制XBP1表达活化, 目前已取得了一定的临床治疗效果。Mimura等[66]发现, MKC-3946(IRE1α抑制剂)可抑制XBP1的剪接活化, 与蛋白酶体抑制剂bortezomib(BTZ)联合应用显著提高了MM治疗疗效。Toyocamycin可抑制IRE1a诱导的ATP依赖的*XBP1* mRNA切割, 其联合BTZ可更有效治疗MM[67]。4μ8C是IREα核酸酶的直接抑制剂, 与IREα结合抑制XBP1的表达, 目前在治疗宫颈癌的实验研究中取得了一定的疗效。Trierxin可抑制子宫颈癌HeLa细胞的XBP1生成, 从而抑制子宫颈癌HeLa细胞增殖[68]。同时, 通过抑制XBP1的表达, 可协同其他UPR途径抑制剂, 更有效地杀灭肿瘤细胞。

用siRNA载体选择性抑制XBP1表达, 可诱导Th细胞的抗肿瘤免疫调节作用[17], 增强肿瘤细胞内浸润T细胞的抗原识别能力[69]; 同时, 抑制XBP1表达或活性可恢复肿瘤微环境中的DC功能, 显著增强了DC等免疫细胞强大的抗肿瘤效应, 明显改善了卵巢癌患者的治疗效果, 并极大地延长了患者的无病生存期和总生存期。

3 结语

综上所述, XBP1是一种新近发现的与肿瘤相关的蛋白质, XBP1通过作用于多个靶基因及分子等, 增强肿瘤细胞在缺氧环境中的生存能力及放化疗抵抗, 诱导新生血管生成以促进肿瘤侵袭转移, 并通过作用于多个免疫细胞等显著抑制机体的抗肿瘤免疫作用。因此, 以XBP1为靶点的抗肿瘤治疗有着广阔的发展前景, 特别是在调控肿瘤相关免疫治疗中, 有望成为又一新的靶标。

参考文献 (References)

1 Iwakoshi NN, Lee AH, Vallabhajosyula P, Otipoby KL, Rajewsky K, Glimcher LH. Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1. Nat Immunol 2003; 4(4): 321-9.

2 Martínez G, Vidal RL, Mardones P, SerranoFG, Ardiles AO, Wirth C, *et al*. Regulation of memory formation by the transcription factor XBP1. Cell Rep 2016; 14(6): 1382-94.

3 Yoshida H, Oku M, Suzuki M, Mori K. pXBP1(U) encoded in XBP1 pre-mRNA negatively regulates unfolded protein response activator pXBP1(S) in mammalian ER stress response. J Cell Biol 2006; 172(4): 565-75.

4 Glimcher LH. XBP1: the last two decades. Ann Rheum Dis 2010; 69(Suppl 1): 67-71.

5 Hetz C, Chevet E, Harding HP. Targeting the unfolded protein response in disease. Nat Rev Drug Discov 2013; 12(9): 703-19.

6 Li J, Chen Z, Gao LY, Colorni A, Ucko M, Fang S, *et al*. A transgenic zebrafish model for monitoring xbp1 splicing and endoplasmic reticulum stress *in vivo*. Mech Dev 2015; 137: 33-44.

7 Li H, Korennykh AV, Behrman SL. Mammalian endoplasmic reticulum stress sensor IRE1 signals by dynamic clustering. Proc Natl Acad Sci USA 2010; 107(37): 16113-8.

8 Hassan H, Tian X, Inoue K, Chai N, Liu C, Soda K, *et al*. Essential role of X-box binding protein-1 during endoplasmic reticulum stress in podocytes. J Am Soc Nephrol 2016; 27(4): 1055-65.

9 Bright MD, Itzhak DN, Wardell CP, Morgan GJ, Davies FE. Cleavage of BLOC1S1 mRNA by IRE1 is sequence specific, temporally separate from XBP1 splicing, and dispensable for cell viability under acute endoplasmic reticulum stress. Mol Cell Biol 2015; 35(12): 2186-202.

10 Chen C, Zhang X. IRE1α-XBP1 pathway promotes melanoma progression by regulating IL-6/STAT3 signaling. J Transl Med 2017; 15(1): 42.
11 Wang Y, Xing P, Cui W, Wang W, Cui Y, Ying G, *et al*. Acute endoplasmic reticulum stress-independent unconventional splicing of xbp1 mrna in the nucleus of mammalian cells. Int J Mol Sci 2015; 6(6): 13302-21.
12 Jiang D, Niwa M, Koong AC. Targeting the IRE1α-XBP1 branch of the unfolded protein response in human diseases. Semin Cancer Biol 2015; 33: 48-56.
13 Lew QJ, Chu KL, Chia YL, Soo B, Jia PH, Ng CH, *et al*. GCN5 inhibits XBP-1S-mediated transcription by antagonizing PCAF action. Oncotarget 2015; 6(1): 271-87.
14 Drori A, Messerle M, Brune W, Tirosh B. Lack of XBP-1 impedes murine cytomegalovirus gene expression. PLoS One 2014; 9(10): e110942.
15 Brodsky JL, Merz A, Serio T. Organelle and proteome quality control mechanisms: how cells are able to keep calm and carry on. Mol Biol Cell 2014; 25(6): 733-4.
16 Fedeles SV, So JS, Shrikhande A, LeeSH, GallagherAR, Barkauskas CE, *et al*. Sec63 and Xbp1 regulate IRE1α activity and polycystic disease severity. J Clin Invest 2015; 125(5): 1955-67.
17 Cubillos-Ruiz JR, Mohamed E, Rodriguez PC. Unfolding anti-tumor immunity: ER stress responses sculpt tolerogenic myeloid cells in cancer. J Immunother Cancer 2017; 5: 5.
18 Salaroglio IC, Panada E, Moiso E, Buondonno I, Provero P, Rubinstein M, *et al*. PERK induces resistance to cell death elicited by endoplasmic reticulum stress and chemotherapy. Mol Cancer 2017; 16(1): 91.
19 Chen X, Iliopoulos D, Zhang Q, Tang Q, Greenblatt MB, Hatziapostolou M, *et al*. XBP1 promotes triple-negative breast cancer by controlling the HIF1α pathway. Nature 2014; 508(7494): 103-7.
20 Bagratuni T, Wu P, Gonzalez de Castro D, Davenport EL, DickensNJ, WalkerBA, *et al*. XBP1s levels are implicated in the biology and outcome of myeloma mediating different clinical outcomes to thalidomide-based treatments. Blood 2010; 116(2): 250-3.
21 Kathagen A, Schulte A, Balcke G, Martens T, Matschke J, Soriano R, *et al*. Hypoxia and oxygenation induce a metabolic Switch between pentose phosphate pathway and glycolysis in glioma stem-likecells. Acta Neuropathol 2013; 126(5): 763-80.
22 BethO A, Artlett CM, Connie S, Sihem SG, Weis RD, Thacker JD. Targeting the unfolded protein response, XBP1, and the NLRP3 inflammasome in fibrosis and cancer. Cancer Biol Ther 2014;15(4): 452-62.
23 Romero-Ramirez L, Cao H, Regalado MP. X box-binding protein 1 regulates angiogenesis in human pancreatic adenocarcinomas. Transl Oncol 2009; 2(1): 31-8.
24 柴 双, 卞齐龙, 于 涛, 欧阳仲瑞, 赵海杞, 刘珈杞, 等. XBP1对低氧环境下胶质瘤细胞活力及糖酵解的影响. 中国肿瘤临床(Chai Shuang, Bian Qilong, Yu Tao, OuYang Zhongrui, Zhao Haiqi, Liu Jiaqi, *et al*. Effects of XBP1 on glioma cell viability and glycolysis under hypoxia. Chinese Journal of Clinical Oncology) 2016; 43(20): 892-7.
25 麦 青, 张 雁. 肿瘤代谢异质性的研究进展. 中国细胞生物学学报(Mai Qing, Zhang Yan. Heterogenesis in cancer metabolism. Chinese Journal of Cell Biology) 2017; 39(6): 786-95.
26 Bettigole SE, Lis R, Adoro S, LeeAH, Spencer LA, Weller PF, *et al*. The transcription factor XBP1 is selectively required for eosinophil differentiation. Nat Immunol 2015; 16(8): 829-37.
27 Kang YJ, Lu MK, Guan KL. The TSC1 and TSC2 tumor suppressors are required for proper ER stress response and protect cells from ER stress-induced apoptosis. Cell Death Differ 2011; 18(1): 133-44.
28 Gregor MF, Misch ES, Yang L, Hummasti S, Inouye KE, Lee AH, *et al*. The role of adipocyte XBP1 in metabolic regulation during lactation. Cell Rep 2013; 3(5): 1430-9.
29 Kim SK, OhE, Yun M, Lee SB, Chae GT. Palmitate induces cisternal ER expansion via the activation of XBP-1/CCTα-mediated phospholipid accumulation in RAW 264.7 cells. Lipids Health Dis 2015; 14(1): 1-12.
30 Ang Z, Er JZ, Dinga JL. The short-chain fatty acid receptor GPR43 is transcriptionally regulated by XBP1 in human monocytes. Sci Rep 2015; 5: 8134.
31 Ning J, Hong T, Ward A, Pi J, Liu Z, Liu HY, *et al*. Constitutive role forIRE1α-XBP1 signaling pathway in the insulin-mediated hepatic lipogenic program. Endocrinology 2011; 152(6): 2247-55.
32 So JS, Hur KY, Tarrio M, Ruda V, Frank-kamenetsky M, Fitzgerald K, *et al*. Silencing of lipid metabolism genes through IRE1α-mediated mRNA decay lowers plasma lipids inmice. Cell Metab 2012; 16(4): 487-99.
33 Cho YM, Kim DH, Kwak SN, Jeong SW, Kwon OJ. X-box binding protein 1 enhances adipogenic differentiation of 3T3-L1 cells through the downregulation of Wnt10b expression. FEBS Lett 2013; 587(11): 1644-9.
34 Jiang S, Yan C, Fang QC, Shao ML, Zhang YL, LiuY, *et al*. Fibroblast growth factor 21 is regulated by the IRE1α-XBP1 branch of the unfolded protein response and counteracts endoplasmic reticulum stress-induced hepatic steatosis. J Biol Chem 2014; 289(43): 29751-65.
35 Wolf A, Agnihotri S, Micallef J, Mukherjee J, Sabha N, Cairns R, *et al*. Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. J Exp Med 2011; 208(2): 313-26.
36 Zeng L, Xiao Q, Chen M, Margariti A, Martin D, Ivetic A, *et al*. Vascular endothelial cell growth-activated XBP1 splicing in endothelial cells is crucial for angiogenesis. Circulation 2013; 127(16): 1712-22.
37 Miyagi H, Kanemoto S, Saito A, Asada R, Iwamoto H, Izumi S, *et al*. Transcriptional regulation of VEGFA by the endoplasmic reticulum stress transducer OASIS in ARPE-19 cells. PLoS One 2013; 8(1): e55155.
38 Romero-Ramirez L, Cao H, Regalado MZ. X-Box-binding protein 1 regulates angiogenesisin human pancreatic adenocarcinomas. Transl Oncol 2009; 2(1): 31-8.
39 Yang J, Cheng D, Zhou S, Zhu B, Hu T, Yang Q. Over-expression of X-Box binding protein 1 (XBP1) correlates to poor prognosis and up-regulation of PI3K/mTOR in human osteosarcoma. Int J Mol Sci 2015; 16(12): 28635-46.
40 Ruan Q, Xi L, Boye SL, Han S, Chen ZJ, Hauswirth WW, *et al*. Development of an anti-angiogenic therapeutic model combining scAAV2-delivered siRNAs and Noninvasive photoacoustic

imaging of tumor vasculature development. Cancer Lett 2013; 332(1): 120-9.

41 王 宇, 刘耀华, 赵世光. XBP1在肿瘤中作用的研究进展. 中华肿瘤防治志(Wang Yu, Liu Yaohua, Zhao Shiguang. Research advances of XBP1's role in tumor. Chinese Journal of Cancer Prevention and Treatment) 2012; 19(10): 787-90.

42 Duan Q, Yang L, Gong W, Chaugai S, Wang F, Chen C, *et al*. MicroRNA-214 is upregulated in heart failure patients and suppresses XBP1-mediated endothelial cells angiogenesis. J Cell Physiol 2015; 230(8): 1964-73.

43 Xia T, Tong S, Fan K, Zhai W, Fang B, Wang SH, *et al*. XBP1 inducesMMP-9 expression to promote proliferation and invasion in human esophageal squamous cell carcinoma. Am J Cancer Res 2016; 6(9): 2031-40.

44 Chen X, Iliopoulos D, Zhang Q, Tang Q, Greenblatt MB, Hatziapostolou M, *et al*. XBP1 promotes triple negative breast cancer by controlling the HIF1α pathway. Nature 2014; 508(7494): 103-7.

45 Jie M, Ruan S, Wang M, Dan Y, Fan N, Meng Q, *et al*. A novel chemical, STF-083010, reverses tamoxifen-related drug resistance in breast cancer by inhibiting IRE1/XBP1. Oncotarget 2015; 6(38): 40692-703.

46 Shou J, Massarweh S, Osborne CK, Wakeling AE, Ali S, Weiss H, *et al*. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Ins 2004; 96(12): 926-35.

47 Rajapaksa G, Nikolos F, Bado I, Clarke R, Gustafsson JÅ, Thomas C. ERβ decreases breast cancer survival by regulating the IRE1/XBP-1 pathway. Oncogene 2015; 34(31): 4130-41.

48 Mhaidat NM, Alzoubi KH, Abushbak A. X-box-binging protein 1(XBP1) enhances colorectal cancer cell invasion. J Chemother 2015; 27(3): 167-73.

49 Gupta A, Hossain MM, Miller N, Kerin M, Callagy G, Gupta S. NCOA3 coactivator is a transcriptional target of XBP1 and regulates PERK-eIF2α-ATF signalling in breast cancer. Oncogene 2016; 35(45): 5860-71.

50 Hu R, Warri A, Jin L, Zwart A, Riggins RB, Fang HB, *et al*. NF-κB signaling is required for XBP1 (unspliced and spliced)-mediated effects on antiestrogen responsiveness and cell fate decisions in breast cancer. Mol Cell Biol 2015; 35(2): 379-90.

51 Ming J, Ruan S, Wang M, Ye D, Fan N, Meng Q, *et al*. A novel chemical,STF-083010, reverses tamoxifen-related drug resistance in breast cancer by inhibiting IRE1/XBP1. Oncotarget 2015; 6(38): 40692-703.

52 Mimura N, Fulciniti M, Gorgun G. Blockade of XBP1-1 splicing by inhibition of IRE1α is a promising therapeutic option in multiple myeloma. Blood 2012; 119(24): 5772-81.

53 Garris CS, Pittet MJ. ER stress in dendritic cells promotes cancer. Cell 2015; 161(7): 1492-3.

54 Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, *et al*. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell 2015; 161(7): 1527-38.

55 Herber DL, Cao W, Nefedova Y, Novitskiy SV, Nagaraj S, Tyurin VA, *et al*. Lipid accumulation and dendritic cell dysfunction in cancer. Nat Med 2010; 16(8): 880-6.

56 董召刚, 张 岩, 曲 迅. 低氧微环境下内质网应激及其相关疾病. 基础医学与临床(Dong Zhaogang, Zhang Yan, Qu Xun. Endoplasmic reticulum stress within hypoxia microenvironment and its related dieases. Basic & Clinical Medicine) 2009; 29(6): 649-53.

57 王 玲, 邱志敏, 傅颖媛. DC-CIK细胞免疫治疗恶性肿瘤的研究进展. 实用癌症杂志(Wang Ling, Qiu Zhiming, Fu Yingyuan. Research progress of DC-CIK cell immunotherapy for malignant tumor. The Practical Journal of Cancer) 2017; 32(2): 345-8.

58 Mohamed E, Cao Y, Rodriguez PC. Endoplasmic reticulum stress regulates tumor growth and anti-tumor immunity: a promising opportunity for cancer immunotherapy. Cancer Immunol Immunother 2017; 66(8): 1069-78.

59 Martinon F, Chen X, Lee AH, Glimcher LH. TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. Nat Immunol 2010; 11(5): 411-8.

60 Taubenheim N, Tarlinton DM, Crawford S, Corcoran LM, Hodgkin PD, Nutt SL. High rate of antibody secretion is not integral to plasma cell differentiation as revealed by XBP-1 deficiency. J Immunol 2012; 189(7): 3328-38.

61 IAragon IV, Barrington RA, Jackowski S, Mori K, Brewer JW. The specialized unfolded protein response of B lymphocytes: ATF6α-independent development of antibody-secreting B cells. Mol Immunol 2012; 51(3/4): 347-55.

62 Benhamron S, Pattanayak SP, Berger M, Tirosh B. mTOR activation promotes plasma cell differentiation and bypasses XBP-1 for immunoglobulin secretion. Mol Cell Biol 2015; 35(1): 153-66.

63 Martinon F, Chen X, Lee AH, Glimcher LH. Toll-like receptor activation of XBP1 regulates innate immune responses in macrophages. Nat Immunol 2010; 11(5): 411-8.

64 Grootjans J, Kaser A, Kaufman RJ, Blumberg RS. The unfolded protein response in immunity and inflammation. Nat Rev Immunol 2016; 16(8): 469-84.

65 Janssens S, Pulendran B, Lambrecht BN. Emerging functions of the unfolded protein response in immunity. Nat Immunol 2014; 15(10): 910-9.

66 Lee AH, Iwakoshi NN, Anderson KC, Glimcher LH. Proteasome inhibitors disrupt theunfolded protein response in myeloma cells. Proc Natl Acad Sci USA 2003; 100(17): 9946-51.

67 Ri M, Tashiro E, Oikawa D, Shinjo S, Tokuda M, Yokouchi Y, *et al*. Identification of Toyocamycin, an agent cytotoxic for multiple myeloma cells, as a potent inhibitor of ER stress-induced XBP1 mRNA splicing. Blood Cancer J 2012; 2(7): e79.

68 Tashiro E, Hironiwa N, Kitagawa M, Futamura Y, Suzuki S, Nishio M, *et al*. Trierixin, a novel inhibitor of ER stress-induced XBP1 activation from streptomyces sp1. J Antibiot (Tokyo) 2007; 60(9): 547-53.

69 Cubillos-Ruiz JR, Bettigole SE, Glimcher LH. Molecular pathways: immunosuppressive roles of IRE1α-XBP1 signaling in dendritic cells of the tumor microenvironment. Clin Cancer Res 2016; 22(9): 2121-6.