

内质网应激与肿瘤转移

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【摘要】 肿瘤转移是一个多步骤、低效率的生物学过程,在这个复杂过程中,肿瘤细胞发生遗传学及表观遗传学改变,使肿瘤细胞适应转移过程中所面临的不利微环境,最终在远处器官形成转移灶。内质网应激(endoplasmic reticulum stress, ER stress)引起的未折叠蛋白反应(unfolded protein response, UPR)是调节细胞适应不利微环境的最为重要的信号通路之一,在肿瘤细胞生长、存活、分化和维持蛋白质稳态等过程中发挥着至关重要的作用,参与到肿瘤转移的各个阶段。本文对内质网应激信号分子促进肿瘤细胞发生上皮间充质转化(epithelial-mesenchymal transition, EMT)、促进肿瘤存活、促进肿瘤的免疫逃逸、促进肿瘤血管新生、促进肿瘤细胞黏附以及促进肿瘤细胞从休眠中苏醒等转移相关特性及其机制进行综述,为开发治疗肿瘤转移的新靶标提供参考。

【关键词】 内质网应激 未折叠蛋白质反应 肿瘤转移

A Review of the Roles of Endoplasmic Reticulum Stress in Cancer Cell Metastasis ZHOU Jing-feng¹, ZHOU Qin², CHEN Chun², PAN Jing-xuan^{1△}. 1. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou 510060, China; 2. Division of Hematology/Oncology, Department of Pediatrics, the Seventh Affiliated Hospital, Sun Yat-Sen University, Shenzhen 518107, China

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【Abstract】 Metastasis is a multistep and low-efficiency biological process driven by acquisition of genetic and/or epigenetic alterations within tumor cells. These evolutionary alterations enable tumor cells to thrive in the inhospitable microenvironment they encounter in the process of metastasis and eventually lead to macroscopic metastases in distant organs. The unfolded protein response (UPR) induced by endoplasmic reticulum (ER) stress is one of the most important mechanisms regulating cellular adaptation to an adverse microenvironment. UPR is involved in all stages of metastasis, playing an important role in tumor cell growth, survival, and differentiation and the process of maintaining protein hemostasis. Sustained activation of ER stress sensors endows tumor cells with better epithelial-mesenchymal transition (EMT), survival, immune escape, angiogenesis, cellular adhesion, dormancy-to reactivation capacity in the process of metastasis. Here, we discussed the role of UPR in regulating the above-mentioned abilities of tumor cells during metastasis, providing a reference for development of new targets for the treatment of tumor metastasis. UPR in regulating the above-mentioned characteristics and mechanisms of tumor cells during metastasis, providing a reference for development of new targets for the treatment of tumor metastasis.

【Key words】 Endoplasmic reticulum stress Unfolded protein response Metastasis

内质网(endoplasmic reticulum, ER)是真核生物细胞中蛋白质合成、加工、修饰的场所,对维持蛋白质稳态(proteostasis)发挥举足轻重的作用^[1]。当细胞处在营养缺乏、低氧、钙失衡及氧化应激等压力条件下,将导致非折叠蛋白(unfolded proteins)或错误折叠蛋白(misfolded proteins)在内质网上积累,产生内质网应激(endoplasmic reticulum stress, ER stress)^[1]。为了应对内质网应激,细胞激活一系列适应性反应,以增强对蛋白的折叠和清除能力,从而恢复内质网蛋白稳态,这种自适应性反应机制被称为未折叠蛋白反应(unfolded protein response, UPR)^[2-4]。

UPR由位于内质网膜的至少3个主要的应力传感器

介导,即肌醇需求酶1(inositol requiring enzyme 1, IRE1)、蛋白激酶R样内质网激酶(PRKR-like endoplasmic reticulum kinase, PERK)和激活转录因子6(activating transcription factor 6, ATF6)^[2,5]。在非内质网应激条件下,他们与相对分子质量为78×10³的分子伴侣蛋白葡萄糖调节蛋白(glucose-regulated protein 78, GRP78/BiP)结合,处于非活性状态,当发生内质网应激时,非折叠蛋白或错误折叠蛋白竞争性结合至GRP78/BiP蛋白上,从而使GRP78/BiP与IRE1、PRKR、ATF6解离,激活下游信号通路^[2-3]。

肿瘤转移至少包括以下7个生物学步骤:①肿瘤细胞侵袭周围的正常组织;②肿瘤细胞内渗入血管(intravasation);③肿瘤细胞在循环系统中存活(survival);④肿瘤细胞外

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渗出血管(extravasation),进入远处器官;⑤肿瘤细胞在远处靶器官发生驻留;⑥经过一段时间休眠后(dormancy),在远处器官苏醒(reactivation),形成微转移灶(micrometastases);⑦肿瘤细胞在靶器官发生定植(colonization),形成转移灶^[6-9]。在这些生物学过程中,肿瘤细胞可能发生一些遗传学(genetic)及表观遗传学(epigenetic)的改变,使肿瘤细胞适应转移过程中所面临的不利环境^[6-9],而内质网应激信号分子主要通过3条信号通路(图1)在肿瘤细胞生长、存活、分化和维持蛋白质稳态等过程中起着至关重要的作用,参与到肿瘤转移过程^[5,10-12]。

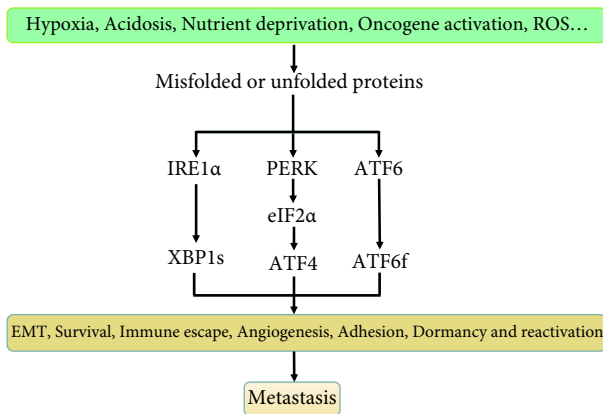


图1 UPR信号通路参与肿瘤转移

Fig 1 The roles of UPR in the process of metastasis

ROS: Reactive oxygen species; IRE1: Iositol requiring enzyme 1; XBP1s: X-box binding protein1spliced; PERK: PRKR-like endoplasmic reticulum kinase; eIF2α: Eukaryotic translation initiation factor 2 Alpha; ATF4: Activating transcription factor 4; ATF6: Activating transcription factor 6; ATF6f: ATF6 cytosolic domain.

1 内质网应激信号分子促进肿瘤细胞发生EMT及其机制

上皮间充质转化(epithelial-mesenchymal transition, EMT)是指上皮细胞失去细胞极性获得间充质细胞特性的生物学过程,被认为是肿瘤细胞内渗至血管的重要步骤^[7]。肿瘤细胞在进行EMT的过程中,E-cadherin表达减少,上皮细胞黏附能力降低,间充质细胞蛋白vimentin表达上升,肿瘤细胞运动能力增强^[13]。许多EMT相关转录因子(EMT-transcription factors, EMT-TFs)如Twist、Snail、Slug、Zeb1、Zeb2可以抑制E-cadherin基因的转录,促进肿瘤EMT的进程^[4]。

研究表明,内质网应激信号分子主要通过调节EMT-TFs的转录变化影响肿瘤细胞EMT进程^[14-15]。如IRE1α-XBP1信号通路激活可以诱导乳腺癌细胞Snail基因的

转录,促进乳腺癌细胞发生EMT,增强其迁移及侵袭能力^[16-17];化疗药物引起的肺腺癌细胞PERK-eIF2α通路激活,通过增加Snail、ZEB1基因转录水平,促使肺腺癌细胞发生EMT样改变^[18]。

2 内质网应激信号分子促进肿瘤存活及其机制

在脱离原发灶之后,肿瘤细胞会面临失巢凋亡、物理剪切压力(shear stress)、免疫杀伤等多种生存压力,在血流和宿主器官存活下来是后续形成转移灶的先决条件^[8-9]。实验表明内质网应激利于肿瘤细胞获得更强的生存能力^[19],如IRE1α及PERK可以激活STAT3及核因子(nuclear factor, NF)-κB信号通路,促进抗凋亡基因如BCL-2家族基因(如BCL-2、BCL-X_L等)、Caspase-8抑制基因(如c-FLIP、MCL-1)及凋亡抑制蛋白(inhibitor of apoptosis proteins, IAP)等的表达^[19-20]。PERK诱导的ATF4激活及NRF2蛋白稳定性增强,促进抗氧化基因NQO1、HO-1等的转录,减少活性氧(reactive oxygen species, ROS)对细胞的毒性作用,从而抑制肿瘤细胞失巢凋亡、促进肿瘤细胞生存及转移^[21-22]。内质网应激也可以通过诱导细胞自噬,清除对细胞产生毒性的胞浆蛋白及受损细胞器,从而促进肿瘤细胞生存^[23-26],如PERK通路激活诱导的ATF4-CHOP信号通路激活可以促进自噬小体形成及成熟相关基因如Atg5、Atg12及Beclin1等的转录^[19,27],是乳腺癌、结直肠癌、成纤维肉瘤细胞在转移过程中抵抗失巢凋亡所必需的^[22]。综上所述,内质网应激信号分子可以通过促进抗凋亡基因、抗氧化基因及诱导细胞自噬相关基因的转录促进肿瘤细胞的存活。

3 内质网应激信号分子促进肿瘤细胞免疫逃逸

躲避全身系统免疫和宿主器官局域免疫对肿瘤细胞的监控、识别和杀伤作用也是造成肿瘤细胞从原发灶转移至远处器官的重要因素^[12]。内质网应激信号分子可以通过多种途径介导肿瘤细胞免疫逃逸。内质网应激诱导的UPR可在肿瘤相关树突状细胞中(tumor associated dendritic cells, tDCs)发生,使tDCs IRE1α-XBP1信号通路激活,引起脂质积累,降低tDCs的抗原提呈能力,抑制肿瘤免疫反应^[19]。的确,在小鼠卵巢癌模型DCs细胞中选择性敲除XBP1基因可以显著抑制卵巢癌的进展及转移^[28]。在卵巢癌微环境T细胞中,IRE1α-XBP1通路激活可以降低T细胞谷氨酰胺转运蛋白的数量,下调CD4⁺T细胞内线粒体呼吸所需的谷氨酰胺水平,抑制CD4⁺T细胞内线粒

体呼吸,从而扰乱T细胞正常抗肿瘤免疫反应,促进肿瘤进展^[29]。在肿瘤相关髓系来源抑制细胞(tumor associated myeloid-derived suppressor cells, MDSCs)中,内质网应激导致PERK-AFT4信号通路激活,引起CHOP基因在MDSCs中高表达,抑制T细胞的功能,MDSCs中缺失CHOP可以下调IL-6-STAT3信号通路活性,恢复抗肿瘤免疫反应^[30]。UPR在其余免疫细胞中的功能尚需进一步研究。

4 内质网应激信号分子促进肿瘤血管新生

肿瘤细胞在转移灶快速生长,导致瘤灶中心缺乏氧气、葡萄糖和其他营养物质,迫使肿瘤细胞释放促血管新生因子以促进血管新生,增加氧气和营养的输送,从而维持肿瘤在远处器官生长^[6-9]。内质网应激信号分子能促进肿瘤血管生成^[5]。研究表明,在胶质瘤小鼠模型中抑制IRE1 α 可以显著下调促血管生成因子FGF2、IL-6、IL-8的表达,从而抑制肿瘤细胞生长及血管新生^[31]。在三阴性乳腺癌中,IRE1 α -XBP1s信号通路可以激活HIF1 α -VEGFA信号通路轴,促进乳腺癌血管新生^[32-33]。在头颈部鳞状细胞癌细胞系中,阻断PERK-eIF2 α -ATF4信号通路可以抑制促血管新生因子FGF2、VEGF及IL-6的表达,并抑制抗血管新生因子THBS1、CXCL14及CXCL10的表达^[19, 34]。在非小细胞肺癌细胞系中,ATF6f可以结合到EGF启动子上并促进EGF的转录,促进血管新生^[35]。综上所述,内质网应激信号分子XBP1s、ATF4及ATF6f主要通过直接结合到VEGF等促血管新生基因启动子上,上调其转录水平,促进肿瘤血管新生^[11, 36]。

5 内质网应激信号分子促进肿瘤细胞驻留

肿瘤细胞在靶器官驻留是肿瘤转移的又一重要步骤,已有证据表明,UPR可调节细胞骨架重塑和细胞黏附^[2, 8-9]。细丝蛋白A(filamin A)是参与细胞骨架重塑的肌动蛋白交联因子,也是内质网应激诱导的UPR通路中IRE1 α 的主要结合伴侣,IRE1 α 通过直接结合细丝蛋白A来控制肌动蛋白细胞骨架动力学并促进肿瘤细胞黏附^[37]。在前列腺癌中,内质网应激分子GRP78可以激活细胞黏附关键分子FAK(focal adhesion kinase)信号通路,促进肿瘤细胞侵袭^[38]。血管细胞黏附分子(vascular cell adhesion molecule 1, VCAM-1)可以与整合素 $\alpha 4\beta^+$ (integrin $\alpha 4\beta^+$)结合,介导肿瘤细胞与微环境细胞黏附,在乳腺癌中,靶向VCAM-1-integrin $\alpha 4\beta^+$ 信号轴可以显著抑制乳腺癌骨转移^[39]。研究表明,在多发性骨髓瘤中,XBP1s可以促进VCAM-1的表达,XBP1s是否能促进肿瘤

细胞高表达VCAM-1并促进肿瘤细胞黏附还需进一步研究^[39-40]。

6 内质网应激信号分子与休眠、苏醒

休眠(dormancy)是指肿瘤细胞阻滞在G₀/G₁期,不进行有丝分裂但处于存活状态,遇到合适的微环境刺激可进入苏醒(reactivation)^[10, 41-42]。研究表明,肿瘤细胞进入靶器官后,会进行一段时间的休眠,当微环境合适时,休眠肿瘤细胞重新苏醒,进行克隆增殖^[8, 9, 43]。目前认为肿瘤细胞休眠和苏醒状态转换与p38 MAPK和ERK信号通路的平衡密切相关,当ERK活性下降,p38 MAPK被激活时,肿瘤细胞进行休眠;当ERK被激活,而p38 MAPK活性下降时,肿瘤细胞重新苏醒^[41, 44-46]。研究表明,UPR信号通路参与调解肿瘤休眠及苏醒过程^[10]。p38 MAPK被激活后,不仅可以抑制ERK的活性,还可以激活PERK及IRE1 α , PERK激活后可以磷酸化NRF2及eIF2 α ,抑制cyclin D1等周期蛋白的表达,引起细胞周期阻滞在G₀/G₁期^[10, 47]。IRE1 α 激活可引起XBP1s的剪切,促进Grp78/BiP、抗凋亡基因的转录,维持肿瘤细胞存活状态^[10, 47]。此外,肿瘤细胞中ATF6的激活可以活化Rheb及mTOR信号通路,也是肿瘤细胞维持休眠状态的重要原因^[3]。不难看出,UPR在维持细胞休眠状态中扮演举足轻重的作用^[10]。UPR在肿瘤细胞苏醒中的作用机制仍然不清楚,还需进一步研究。

7 未来研究方向

虽然目前已有的研究结果指出UPR信号通路可能是治疗肿瘤转移的有效靶标,但UPR在肿瘤转移中的作用及分子机制仍需更为深入的研究。主要有以下几个方面:①UPR在肿瘤EMT及MET中的作用及分子机制需要进一步明确;②UPR既可以促进细胞生存也可以诱导肿瘤细胞死亡,在肿瘤转移阶段调控UPR促进生存或导致死亡的分子开关是什么?该分子开关的时空变化、调节通路是什么?以及如何正确地使用UPR调节化合物来最大程度地提高癌症治疗的效果?③UPR如何重塑肿瘤免疫抑制微环境?和现有免疫治疗手段是否有协同作用?④UPR可以诱导肿瘤细胞休眠,其是否参与到肿瘤苏醒过程中?具体分子机制是什么?⑤目前对UPR介导肿瘤细胞与转移靶器官微环境细胞之间黏附的功能及机制知之甚少,尚需深入研究。因此,深入了解内质网应激及UPR与肿瘤转移之间的关系,对阐明肿瘤转移分子机制、开发肿瘤转移治疗的新靶标具有重要意义。

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