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· 综述 ·

应激诱导蛋白 Sestrin2 在多种病理过程中的作用研究进展

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[摘要] Sestrins是高度保守的应激诱导蛋白, 可帮助维持代谢稳态并在应激条件下保护细胞。Sestrin2抑制氧化应激并调节AMP依赖的蛋白激酶-雷帕霉素靶点复合物(the AMP activated protein kinase - mammalian target of rapamycin complex, AMPK-mTORC)信号通路, 在机体发生肿瘤、衰老退行性疾病、代谢性疾病、免疫性疾病时发挥保护作用。

[关键词] Sestrin2; AMP依赖的蛋白激酶-雷帕霉素靶点复合物; 肿瘤; 衰老; 代谢; 免疫

Research progress on stress-induced protein Sestrin2 in several pathological process

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Abstract Sestrins are highly conserved stress-inducible proteins that help maintain metabolic homeostasis and protect cells under stress conditions. The role of Sestrin2 inhibits oxidative stress and regulates the AMP activated protein kinase - mammalian target of rapamycin complex (AMPK-mTORC) signaling pathway, which protects the body from tumors, aging and degenerative diseases, metabolic diseases, and immune diseases.

Keywords Sestrin2; AMP activated protein kinase-mammalian target of rapamycin complex; tumors; senility; metabolic; immune

Sestrins是应激(DNA损伤、缺氧、饥饿、生长因子耗竭、辐射和氧化应激)条件下诱导产生的蛋白质, 其家族由Sestrin1、Sestrin2和Sestrin3组成^[1]。人类Sestrin2蛋白质分子质量为52~57 kD, 包含两个结构相似的亚结构域, 即Sesn-A和Sesn-C, 通过螺旋-环-螺旋结构域(Sesn-B)连接。两个亚结构域属于烷基氢过氧化物酶家族具有显

著的同源性, 从而减少过氧化物酶^[2]。据文献[3]报道Sestrin2的表达受p53, Nrf2(NF-E2-related factor 2)、缺氧诱导因子1 α (hypoxia-inducible factor-1 α , HIF-1 α)的调控。活化的Sestrin2保护细胞免受活性氧(reactive oxygen species, ROS)的侵害, 并通过促进过氧化物酶的再循环来减少ROS的产生^[4]。Sestrin2通过激活AMPK-mTORC1信号通路在

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抵抗多种病理过程(肿瘤、衰老、代谢稳态、变态反应、脂质蓄积和胰岛素抵抗)中起重要作用^[5]。

mTORC存在mTORC1和mTORC2两种形式。其中mTORC1在抑制巨噬细胞自噬中起重要作用。首先, mTORC1导致p70S6K激酶的磷酸化和激活, 然后使胰岛素受体底物(insulin receptor substrate, IRS)的多个Ser/Thr残基磷酸化, 从而导致IRS降解, 并因此抑制PI3K和蛋白激酶B(protein kinase B, AKT)活化^[6], 其中AKT是代谢的关键调节因子和细胞死亡的抑制剂。而mTORC2通过使AKT和蛋白激酶C(protein kinase C, PKC)磷酸化来控制葡萄糖的代谢、细胞迁移、细胞骨架重塑、离子转运和细胞死亡^[6]。Sestrin2通过2种平行机制抑制mTORC1: 第1个机制是由结节性硬化症复合物(tuberous sclerosis complex, TSC)激活介导的, 随后对Rheb进行抑制, 最终达到对mTORC1抑制效应。在这过程中Sestrin2充当AMPK与肝激酶B1(LKB1)形成复合物的平台^[7], AKT是AMPK主要激活剂, 负责催化 α 亚基的磷酸化; 另一个重要机制是通过激活GATOR2途径, 从而增强GATOR1对mTORC1的抑制作用^[7]。另外, Sestrin2与GATOR2的相互作用可防止mTORC1易位至溶酶体, 并阻止Rheb激活mTORC1^[8]。

1 Sestrin2 在抗肿瘤中的保护作用

Sestrin2被认为是潜在的肿瘤抑制剂。尽管在营养缺乏或氧化应激的情况下, Sestrin2可以保护细胞, 但同时Sestrin2可以在某些刺激下诱导细胞死亡。例如, Sestrin2通过调节AMPK的表达和活性来诱导DNA损伤的细胞死亡^[9]。研究^[10]指出: Sestrin2还通过促进凋亡抑制剂(inhibitors of apoptosis, IAP)蛋白的溶酶体降解来促进细胞因子诱导的细胞死亡。研究^[10]发现在多种癌细胞系中诱导Sestrin2可抑制氧化应激并减缓肿瘤发生, 并且在结肠癌、肝癌、乳腺癌、神经母细胞瘤等多种恶性肿瘤中SESN2基因的遗传基因座1p35被删除, 同时Sestrin2表达降低表现出对化疗药物治疗的敏感性降低, 且被认为是结肠癌、肺癌、鼻咽癌等不良预后的因素之一^[11-13]。在胸部肿瘤方面, Tsilioni等^[14]发现恶性胸腔积液中Sestrin2的水平显著高于良性胸腔积液。在BEAS-2B细胞(肺支气管上皮细胞)中, 敲除的SESN2通过激活mTOR信号转导有效刺激了细胞的增殖和恶性转化, 而SESN2的异位表达再次抑制了恶性转化^[15]。在腹

部肿瘤方面, 与正常人肝细胞和癌症相邻肝组织相比, Sestrin2表达水平在肝细胞癌(hepatocellular carcinoma, HCC)细胞系和组织中均显著上调且发现Sestrin2可通过激活AKT信号促进肝癌细胞对新型多靶向性抗肿瘤药物索拉非尼原发性抵抗^[16]。然而最近也有研究^[17]表明: Sestrin2可能通过激活Nrf2/HO-1通路, 促进胃癌细胞生长并提高其耐药性。在泌尿系肿瘤方面, 膀胱癌研究中发现c-Jun氨基末端激酶(JNK)激活Sestrin2并刺激癌细胞自噬的机制, JUN与Sestrin2启动子区域中AP-1位点的结合对于Sestrin2的诱导和随之而来的自噬激活形成至关重要^[18]。众多肿瘤与Sestrin2的相关研究揭示: Sestrin2缺失有可能会诱导肿瘤的发生并且患者预后较差, 而Sestrin2过表达有消除肿瘤发生和改善预后的作用, 这将为我们通过基因方法治疗肿瘤提供了新的切入点, 通过过表达Sestrin2来预防或者治疗恶性肿瘤是一个不错的思路。

2 Sestrin2 在抗衰老退行性中的延缓作用

衰老是生物组织细胞积累损伤的过程, 最终导致器官功能紊乱, 生命机能受损和死亡。衰老与多种疾病的发展密切相关, 包括心脑血管疾病和神经退行性病等^[19]。2010年Lee等^[5]首次在*Science*上报导了Sestrin2基因与抗衰老有关, 该研究发现: 果蝇中Sestrin2基因可增强AMPK的作用, 并抑制mTORC1的过度激活, 通过负反馈机制抑制与衰老有关的病理过程。mTORC1激酶是衰老的关键激活因子, 抑制mTORC1可延长酵母、扁虫、果蝇和小鼠的寿命^[20]。研究^[21]证明: 失去Sestrin2会导致与衰老相关的病理过程, 包括三酰甘油积累、线粒体功能障碍、肌肉变性、心脏扩大、心功能不全和心律失常。

2.1 心血管疾病属于可以被 Sestrin2 抑制的衰老相关性疾病

Sestrin2通过激活血管内皮细胞中的AMPK通路来阻止动脉粥样硬化的发展^[22]。研究^[23]发现患有冠状动脉粥样硬化的患者血清中的Sestrin2水平与冠状动脉狭窄的程度成正相关。最近研究^[24]发现内源性Sestrin2参与抑制心肌缺血后内质网应激诱导的心肌细胞凋亡。随着年龄的增长心肌中Sestrin2的表达水平降低, 这导致老年个体对心肌梗死的敏感性增加。同时在小鼠的实验^[25]中发现: 当遭受缺血再灌注

(ischemia/reperfusion, I/R)损伤时,与正常组相比,SESN2基因敲除组出现更大的心肌梗死面积和更差的心功能。此外研究^[26]证明:永久性房颤患者Sestrin1、Sestrin2和Sestrin3的表达均明显高于窦性心律者,这可能由于房颤性氧化应激导致Sestrins表达升高,而Sestrins反馈性对房颤引起的心房重构有抑制作用。

2.2 在急性脑缺血事件中, Sestrin2 可保护脑细胞

在急性脑缺血事件中, Sestrin2表达水平与脑缺血严重程度相关,并发挥保护脑细胞的作用^[27]。急性脑缺血后Sestrin2通过AMPK激活的蛋白激酶信号通路发挥重要的神经保护作用, Sestrin2不仅可减少脑梗死面积和脑萎缩,而且还有显著改善神经功能的作用^[28]。在大鼠实验中, Sestrin2在短暂性全脑缺血后1~48 h内,在24 h达到最高水平,此后下降。用siRNA下调Sestrin2表达可以增强短暂性脑I/R后诱导的神经元凋亡^[29]。相反,过表达Sestrin2可改善I/R损伤,这证明了Sestrin2在急性脑缺血事件中的保护作用^[30]。

2.3 Sestrin2 可以延缓神经退行性疾病的进展

神经退行性疾病是中枢神经系统神经元逐渐退化和死亡的结果。关于阿尔茨海默病(Alzheimer's disease, AD)研究^[31]表明:淀粉样蛋白 β 肽是AD的生物标志物,而淀粉样蛋白 β 肽可诱导Sestrin2的表达,通过自噬激活保护细胞免于死亡,从而表明Sestrin2有延缓AD进展的作用。帕金森病(Parkinson's disease, PD)患者脑中Sestrin2的表达水平比正常人高,表明它是PD潜在的血清标志物之一,并且Sestrin2阻止了神经元中突触核蛋白的积累^[32]。在PD的小鼠模型中, Sestrin2降低了用于PD建模的物质(MPP+)的神经毒性^[33]。

2.4 Sestrin2 可以延缓椎间盘退变的进展

椎间盘退变(intervertebral disc degeneration, IDD)是一种由压力防御能力受损所介导的与衰老相关的病理过程。研究^[34]发现: Sestrin2在降解的退化髓核(nucleus pulposus, NP)细胞中的表达被抑制,另外, Sestrin2通过增强自噬来抑制应激诱导的细胞凋亡和细胞外基质(extracellular matrix, ECM)降解。而ECM降解是IDD发展所必须的过程,这些表明Sestrin2可以延缓IDD的进展。

综上, Sestrins对细胞死亡保护的作用与AMPK激活和mTORC1抑制有关,通过降低合成代谢过程的强度,并增加能量积累,以求生存和修复。

3 Sestrin2 在调节免疫中的平衡作用

Sestrin2通过控制免疫反应从而减弱炎症过度反应对机体的损伤^[35]。研究揭示溃疡性结肠炎患者结肠中的Sestrin2和Sestrin3的表达水平高于对照人群,体内数据显示内源性Sestrin2对于结肠炎损伤后抑制结肠内质网(endoplasmic reticulum, ER)应激至关重要^[36]。在结肠炎发展至肿瘤的过程中, Sestrin2缺乏会通过激活mTORC1途径促进结肠癌的生长^[37]。然而,最近研究^[38]证明Sestrin2作为免疫刺激剂会对免疫系统产生负面影响。大多数研究证明Sestrin2能够调节免疫延缓疾病发展,少数研究证明Sestrin2对免疫调节产生负面影响。

4 Sestrin2 在代谢紊乱中的保护作用

代谢性疾病的发生与主要营养物传感机制AMPK和mTOR1发生变化有关。Sestrin2抑制mTORC1,从而抑制p70S6K,随后稳定IRS,并激活激酶PDK1和mTORC2,从而调节葡萄糖和脂质的代谢^[39]。在过度表达或沉默Sestrin2的实验中,高糖介导的单核细胞极化和单核细胞与内皮细胞的黏附通过Sestrin2-AMPK-mTOR途径实现^[40]。在营养过剩期间, mTORC1的长期激活会增加蛋白质和脂质的合成,并抑制细胞中的自噬分解代谢,而Sestrin2激活AMPK继而抑制mTORC1途径,刺激细胞中的自噬^[7,41]。关于糖尿病的研究^[42]表明Sestrin2的过表达逆转AMPK-mTORC1途径而有效恢复受损的胰岛细胞。Sestrin2-AMPK-mTORC1信号转导在抵抗高糖诱导的损害和胰岛素抵抗中起显著作用,特别在2型糖尿病患者中, Sestrin2水平与胰岛素抵抗和体内脂肪百分比呈负相关^[43]。Lee等^[41]研究证明:在2型糖尿病和肥胖症小鼠模型中, Sestrin2在肌肉、肝和脂肪等组织中表达上调。综上所述,代谢性疾病诱导Sestrin2表达, Sestrin2抑制mTORC1引起的代谢紊乱。

5 结语

近年来,对Sestrin2病理生理机制的了解已取得一定的进展。Sestrin2是一种应激反应蛋白,调控AMPK-mTORC1通路,对抗细胞毒性和氧化应激,具有细胞保护作用。此外, Sestrin2可以激活自噬反应,进而导致癌细胞死亡。但需要进一步研究和发掘Sestrin2作为生物标志物和治疗靶标对抗这些疾病尤其是癌症的潜力。

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