·文献综述·

糖化与氧化应激交互下自噬对糖尿病性白内障的调控

王 融[1,2],李鹏飞[1,2],刘家伟[1,2],戴雨欣[1,2],周梦颖[1,2],钱晓曦[1,2],陈 威[1,2],季 敏[1,2]

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作者单位:[1](226019)中国江苏省南通市南通大学;[2](226006)中国江苏省南通市,南通大学附属医院眼科研究所
作者简介:王融,在读硕士研究生,研究方向:白内障和青光眼的诊治。
通讯作者:季敏,博士,主任医师,博士研究生导师,研究方向:白内障和青光眼的诊治. jimin_nteye@163.com;陈威,博士,主任医师,硕士研究生导师,研究方向:白内障、糖尿病视网膜病变. c280794406@126.com

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摘要

糖尿病性白内障是糖尿病患者常见的并发症之一,其发病机制复杂,主要涉及氧化应激和糖化应激等多种病理过程。自噬是细胞自我保护的重要机制之一,通过清除和处理受损的细胞器和蛋白质,维持细胞内环境的稳态,从而拮抗高糖环境下氧化应激和糖化应激所致的损伤。近来研究表明,糖化应激与氧化应激之间存在相互作用,这种交互影响可能加剧自噬功能的障碍,进而促进糖尿病性白内障的发生与发展,但具体机制并未完全阐明。文章系统综述了自噬在糖尿病性白内障发病中的调控作用,重点探讨糖化应激与氧化应激交互作用下自噬对疾病进展的影响,以期为糖尿病性白内障的分子诊断和靶向治疗提供新思路。

关键词:自噬;糖尿病性白内障;糖化应激;氧化应激
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Regulation of autophagy on diabetic cataract under the interaction of glycation and oxidative stress

Wang Rong[1,2], Li Pengfei[1,2], Liu Jiawei[1,2], Dai Yuxin[1,2], Zhou Mengying[1,2], Qian Xiaoxi[1,2], Chen Wei[1,2], Ji Min[1,2]

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[1]Nantong University, Nantong 226019, Jiangsu Province, China; [2]Eye Research Institute, Affiliated Hospital of Nantong University, Nantong 226006, Jiangsu Province, China

Correspondence to: Ji Min. Nantong University, Nantong 226019, Jiangsu Province, China; Eye Research Institute, Affiliated Hospital of Nantong University, Nantong 226006, Jiangsu Province, China. jimin_nteye@163.com; Chen Wei. Nantong University, Nantong 226019, Jiangsu Province, China; Eye Research Institute, Affiliated Hospital of Nantong University, Nantong 226006, Jiangsu Province, China. c280794406@126.com

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Abstract

• Diabetic cataract, a prevalent ocular complication of diabetes mellitus, arises from a complex interplay of pathological mechanisms, with oxidative stress and glycation stress playing central roles. Autophagy, a critical cellular self-protection mechanism, sustains intracellular homeostasis by selectively degrading damaged organelles and misfolded proteins, thereby counteracting the detrimental effects of oxidative and glycation stress under hyperglycemic conditions. Emerging evidence indicates a synergistic interaction between glycation stress and oxidative stress, which may exacerbate autophagic dysfunction and accelerate the onset and progression of diabetic cataract. However, the precise molecular mechanisms underlying this relationship remain incompletely understood. This review systematically examines the regulatory role of autophagy inthe pathogenesis of diabetic cataract, with a particular focus on how autophagic impairment influences disease progression under the combined effects of glycation and oxidative stress. By elucidating these mechanisms, the paper aims to provide novel insights into molecular diagnostic approaches and targeted therapeutic strategies for diabetic cataract.

• KEYWORDS: autophagy; diabetic cataract; glycative stress; oxidative stress

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0 引言

糖尿病(diabetes mellitus,DM)是一种以高血糖为特征的代谢性疾病[1]。随着病情的进展,许多糖尿病患者可能会出现眼部并发症,其中糖尿病性白内障(diabetic cataract,DC)是影响糖尿病患者视力的主要原因,病情严重者可致盲[2]。研究表明,糖尿病患者白内障的发病率是正常人的2-5倍,且白内障进展更快,手术并发症发生率更高[3]。近年来,研究者们逐渐认识到糖化应激(glycative stress[4]和氧化应激(oxidative stress)[5]在DC的发病机制

中发挥着重要作用。自噬(autophagy)作为一种细胞自我清除和保护机制,能够调节细胞内的糖化应激和氧化应激状态[6-7]。与现有综述多聚焦于单一应激(氧化或糖化应激)不同[8-10],本文着重探讨糖化应激与氧化应激的交互作用及其对自噬的协同调控,为深入了解 DC 病理过程及靶向干预提供新视角。

1 细胞自噬

1.1 自噬的分类和降解过程 自噬是一种细胞降解过程,其主要功能是清除细胞内的损伤器官和多余的细胞成分,以维持细胞的稳态。自噬的分类主要包括以下几种类型:(1)巨自噬(macroautophagy):这是最典型的自噬形式,涉及形成自噬体(autophagosome),将细胞内的成分包裹在双膜结构中,然后与溶酶体融合,最终降解这些成分并回收利用。(2)微自噬(microautophagy):在这种形式中,细胞膜直接向内凹陷,捕获细胞内成分并将其送入溶酶体进行降解。(3)选择性自噬(selective autophagy):这种方式针对特定的细胞成分,例如线粒体(mitophagy)、内质网(reticulophagy)或核糖体(ribosomes),以实现更精确的降解[11]。而自噬的降解过程主要包括以下几个步骤:(1)自噬体的形成:在营养缺乏或细胞受到压力的情况下,细胞内会发生自噬体的形成。相关的自噬相关基因(ATGs)会被激活,形成初始的自噬膜。(2)自噬体与溶酶体的融合:形成的自噬体会与溶酶体融合,形成自噬溶酶体(autolysosome)[7],在此环境中,内含物被降解。(3)降解与回收:自噬溶酶体内的酸性环境和溶酶体酶的作用使得自噬体内的成分被降解,最终产生氨基酸、脂肪酸等可被细胞再次利用的物质。

1.2 自噬的信号调控通路 自噬是维持细胞稳态的重要机制,其信号调控通路涉及多种生物学过程和疾病。目前,主要的自噬信号通路包括 PI3K-AKT-mTOR 通路、AMPK-mTOR 通路、AMPK-ULK 通路、Bcl-2 蛋白家族以及 NF-κB 通路。这些信号通路不仅调控自噬的发生,还在疾病的发生发展中扮演着重要角色。PI3K-AKT-mTOR 通路是自噬调节中的关键通路[12]。PI3K 通过产生 PIP3 激活 AKT[13],进而激活 mTOR,随后抑制自噬的启动[14]。近来,也有多项研究其在糖尿病性疾病中的作用。研究发现,PI3K-AKT-mTOR 信号通路影响自噬的发生,参与糖尿病肾脏[15-16]、糖尿病视网膜[17]等多器官损伤的发生发展过程。后续有学者利用药物如槲皮素[18]、钙多比赛[15]等药物抑制 PI3K-AKT-mTOR 通路的激活,进而增加自噬小体形成[19],恢复细胞的自噬功能,减轻高糖导致的肾脏、心脏等器官的损伤。这些研究表明PI3K-AKT-mTOR信号通路在糖尿病性疾病的自噬调控中发挥重要作用。

AMPK-ULK 通路是一个独立于 mTOR 的自噬调控途径。在能量缺乏或细胞应激状态下,AMPK 通过直接磷酸化 ULK1,激活自噬过程[20]。ULK1 是自噬启动的关键激酶,负责自噬体的形成和调节[21-22]。

此外,Bcl-2 蛋白家族不仅调控细胞凋亡,还通过多种机制影响自噬进程[23]。在营养充足条件下,抗凋亡蛋白 Bcl-2/Bcl-xL 可通过其 BH3 结构域与 Beclin-1 结合[24],抑制 Beclin-1/Vps34 复合体的形成[25],阻碍自噬起始。然而,在应激状态下,JNK1 等激酶可磷酸化 Bcl-2,使其与 Beclin-1 解离,促进自噬体形成[26]。此外,Bcl-2 还可通过调控内质网钙离子释放间接影响自噬相关信号通路[27],调控自噬流的进展。

NF-κB 通路作为调控应激反应的核心信号枢纽,通过多种分子机制对自噬过程进行双向调控。NF-κB 激活后,可通过诱导抗凋亡/抗氧化基因抑制 ROS 并上调 mTOR[28],从而抑制自噬;也可直接结合 Beclin1 等启动子或协同 E2F1、Skp2 等转录因子,促进 Beclin1、LC3、Atg5 等自噬基因表达,从而启动自噬[29]。同时,NF-κB 信号元件 IKK 及上游 TAK1 可绕过经典通路,通过 AMPK-mTOR 轴独立诱导自噬[29-30]。还有研究发现,NF-κB 通过 A20(NF-κB靶基因)去除 Beclin1 的 K63 泛素链,削弱其活性,从而限制 TLR4 所诱导的自噬[31]。

2 DC 的发病机制

2.1 糖化应激对 DC 的影响 糖化应激是糖尿病患者常见的生物学现象,是指细胞在高糖环境下,会产生过量的晚期糖化终末产物(advanced glycation end products,AGEs),从而诱发细胞的应激反应[10]。AGEs 主要是葡萄糖与蛋白质、脂质或核酸上的氨基基团发生非酶糖化,伴随其早期产物的进一步降解、重排,最终生成的不可逆性终末产物[32]。因此,AGEs 累积诱发的细胞应激是糖代谢性疾病中重要的发病机制。研究证实,糖化的高密度脂蛋白(HDL)在糖尿病患者中功能受损,降低了其对心脏的保护作用[33]。在糖尿病肾病的研究中,糖化蛋白的积累也被认为是导致肾脏功能衰退的重要因素。糖化反应引发的内源性氧化应激不仅导致细胞功能障碍,还可能通过影响细胞信号通路加速肾小管的炎症和纤维化过程。进一步研究发现,在体内加入抑制糖化反应的药物可能对改善糖尿病相关并发症的预后具有积极作用[34]。因此,糖化应激在糖尿病及其并发症中的作用越来越受到重视,未来的研究需要进一步探索糖化应激在糖尿病并发症中的其他作用,以及如何通过靶向干预来预防和治疗糖尿病相关的疾病。

此外,糖化应激同样在糖尿病性眼部并发症的发生发展中起关键作用。有研究显示在 DC 患者中,DC 的形成与 AKR1B1 的过度表达、氧化应激相关因子的上调密切相关,证实糖化应激在白内障形成中的重要作用[35]。还有学者发现,AGEs 的形成会导致 α-晶状体的糖化,降低其保护其他蛋白质的能力,进而影响晶状体的透明度和功能[36]。此外,AGEs 还会通过诱导细胞凋亡和纤维化,破坏晶状体上皮细胞的正常功能,导致晶状体的代谢失衡[37]。在高血糖环境下,AGEs 的生成与晶状体的硬化和混浊程度也密切相关,这一过程也与氧化应激和炎症反应相互作用,形成恶性循环,进一步加重 DC 的进展[5]。这表明针对 AGEs 的干预同样可能成为 DC 预防与治疗的重要策略。

2.2 氧化应激对 DC 的影响 氧化应激是指机体内产生的 ROS 和抗氧化防御系统之间的失衡状态,导致细胞和组织的损伤[38]。氧化应激的来源主要包括外部环境因素(如紫外线、污染物和辐射)以及内部代谢过程(如糖代谢和脂肪酸氧化)[39]。在糖尿病患者中,高血糖水平会通过多种途径增加氧化应激的发生,例如通过多元醇途径的糖代谢,导致细胞内甘露醇和果糖的积累,这些代谢产物会引起细胞损伤和凋亡[40]。此外,糖尿病患者的氧化应激水平通常较高,这与镁缺乏[41]、炎症反应[42]以及内源性抗氧化物质(如谷胱甘肽)[43]的不足密切相关。研究显示,DC 患者的血清中丙二醛水平显著升高,表明氧化应激

在糖尿病相关并发症中的重要作用[44-45]。因此,了解氧化应激的机制及其在 DC 形成中的作用,对于开发新的预防和治疗策略具有重要意义。

氧化应激通过多种机制对晶状体细胞造成损伤,主要包括氧化损伤、细胞凋亡和代谢失调:(1)氧化应激会导致晶状体蛋白质的氧化修饰,形成蛋白质-硫醇混合二硫化物,这种修饰会影响蛋白质的正常折叠与功能,最终导致晶状体混浊[46]。(2)氧化应激还会激活多条细胞凋亡信号通路,例如通过上调凋亡相关蛋白 Bax 和下调抗凋亡蛋白 Bcl-2,促进晶状体上皮细胞的凋亡,进而加速白内障的形成[47-48]。(3)氧化应激还会干扰细胞的能量代谢,导致线粒体功能障碍,增加细胞内活性氧的产生,形成恶性循环[49]。研究表明,抗氧化剂的补充可以减轻高糖诱导的晶状体细胞损伤,提示通过调节氧化应激可能是 DC 治疗的一个有效策略[50-51]。这表明深入研究氧化应激对晶状体细胞的影响机制将有助于揭示 DC 的发生发展过程。

3 自噬参与 DC 的发生发展

3.1 自噬在 DC 糖化应激中的调控作用 糖化应激是指在高糖环境下,糖与蛋白质发生非酶促反应形成的 AGEs 对细胞造成的损伤[52]。AGEs 的积累会导致细胞功能障碍,并引发一系列病理过程,包括炎症、氧化应激和自噬失调[53]。近年来的研究发现,自噬在应对糖化应激中也发挥了重要作用。AGEs 可以激活自噬信号通路,从而帮助细胞清除积累的 AGEs,减轻糖化引起的细胞损伤[54]。然而,过量的糖化应激可能会抑制自噬的正常功能,进一步加重细胞的氧化损伤和炎症反应。例如,糖化高密度脂蛋白(gly-HDL)可通过激活内源性应激通路,诱导巨噬细胞的自噬,从而减轻细胞凋亡[55]。过去一些研究发现,在 DM 和 DC 患者中 AGEs 的累积能够激活/抑制 LECs 的自噬[53,56-57]。如研究所示,积累的 AGEs 可以通过激活 AKT/mTOR 信号通路来抑制细胞自噬[58]。AGEs 还能够激活 NF-κB 信号通路,影响自噬起始相关基因的转录,从而可能导致 LECs 功能障碍,诱导白内障的发生[56]。此外,AGEs 对自噬的负面影响与沉默信息调节因子 1(sirtuin 1,SIRT1)密切相关[59]。SIRT1 是一种 NAD^+依赖性脱乙酰化酶,也是自噬的经典调节剂[60]。先前有研究证明,在代谢性疾病中,SIRT1 表达的高低可以调控 p38-MAPK[61]、FOXO3a[62]、AMPK-mTOR[63]、AKT-mTOR[61]等多个通路诱导或抑制自噬的发生。在 DC 中,也有学者发现,AGEs 通过减少 SIRT1 mRNA 的甲基化修饰,阻碍自噬的进程。在体内外诱导的 DC 模型中发现,自噬相关蛋白 Beclin1 和 LC3Ⅱ/Ⅰ的表达明显降低,而自噬底物识别蛋白 p62 的水平则升高,导致 LECs 自噬障碍,推动了 DC 的进程[64]。综上,自噬与糖化应激之间存在复杂的相互作用,既有保护作用,也可能在过度糖化的情况下导致细胞功能的进一步损害。未来有必要深入探讨 AGEs 通过多种信号通路对自噬功能的具体调控作用,明确其在 DC 发生和发展的病理学意义。

3.2 自噬在 DC 氧化应激中的调控作用 在糖尿病患者[65]以及糖尿病动物模型[66]LECs 中,ROS 对晶状体蛋白的破坏作用尤为显著,使得氧化应激成为 DC 发展的重要诱因[67]。ROS 能够诱导自噬的发生来调控 DC 的发生发展。过量的 ROS 能够阻碍自噬小体的形成,从而导致自噬起始阶段的失调[68]。如 Li 等[57]研究发现,在糖尿病大鼠模型中,高糖条件下 ROS 过度累积的同时,自噬起始基因 ULK1 的激活能力减弱,从而阻碍了自噬的启动。进一步研究发现,由于细胞内 ATP/AMP 比值异常升高,直接抑制了 AMPK 通路的活性,导致 ULK1 的激活失败。此外,还有学者发现 ROS 介导的氧化应激能够通过激活 AKT 信号通路以及 mTOR 信号通路,阻碍了自噬的发生阶段。Dong 等[69]构造的高糖细胞模型也进一步证实,高糖环境中,AKT 信号通路以及随后的 mTOR 信号通路的激活,增强了 mTORC1 对 ULK1 的抑制作用,阻碍了自噬小体的形成,提示氧化应激使 PI3K-AKT-mTOR 失活来抑制细胞自噬。

氧化应激导致自噬障碍的另一重要因素是阻断自噬溶酶体的降解[70]。暴露于高糖环境后,ROS 通过激活 mTOR 信号通路,抑制自噬体的正常降解,导致其异常累积。研究发现,氧化应激诱导内质网 Ca^{2+}耗竭和细胞质 Ca^{2+}过载,从而激活溶酶体中的 mTOR 信号通路,进一步加剧自噬体的堆积[71]。TFEB 作为调节溶酶体生物生成和自噬体清除的关键转录因子,其活性受 ROS 水平的显著影响[72]。当 ROS 过度积累时,TFEB 的功能被抑制,溶酶体的降解能力受损,影响自噬体的清除效率。已有研究发现,在 DC 大鼠中,高糖诱导 LECs 内 ROS 过载,破坏了 TFEB 介导的溶酶体功能,使 LECs 无法清除异常聚集物,进一步加剧自噬障碍[73]。再者,线粒体是 ROS 的主要来源之一[74],而氧化应激能损伤线粒体膜的完整性。既往研究表明,在糖尿病条件下,氧化应激能损伤线粒体膜的完整性,线粒体功能的丧失会导致 ROS 的产生,从而损害溶酶体并阻断细胞中的自噬通量。因此,溶酶体降解的缺陷被认为是 DC 形成期间晶状体混浊的关键因素[75]。

3.3 糖化应激与氧化应激的交互影响 DC 的发病过程中,糖化应激与氧化应激并非独立存在,而是通过复杂的交互作用共同加剧晶状体损伤,从而导致 DC 的患病率和致盲率的显著增加。如研究所示,糖化应激产物 AGEs 通过其受体(RAGE)激活 NADPH 氧化酶,导致大量的 ROS 生成[76],造成细胞的进一步损伤。Kong 等[77]进一步研究也发现,在胰岛 β 细胞中,AGEs 激活 NADPH 氧化酶复合体(上调 p67phox/p22phox 表达及酶活性),触发以超氧阴离子和过氧化氢为主的 ROS 过量生成,进而诱导氧化应激依赖性 β 细胞凋亡,最终导致胰岛素分泌功能障碍。该现象也在临床 DM 患者和 T2DM 大鼠模型中进一步观察到[78]。反之,当 ROS 过剩时,也会正反馈导致糖化应激产物 AGEs 的产生。如研究所示,高血糖会导致细胞的线粒体电子传递链异常,产生大量 ROS;它们会进一步抑制甘油醛-3-磷酸脱氢酶(GAPDH),使得糖酵解中间体积累并转化为 AGEs 中间产物反应性羰基化合物(RCS),再导致 AGEs 的累积[79-81]。此外,也有研究发现 ROS 的激活还会导致脂质过氧化生成丙二醛(MDA)、和 4-羟基壬烯(4-HNE),这些 RCS 与蛋白质赖氨酸/精氨酸残基结合,导致 AGEs 的累积[82]。近年有研究发现,白藜芦醇抗氧化剂能够显著降低 ROS 和 MDA 水平,同时部分恢复 sRAGE 水平,进一步证实 ROS 减少可抑制 AGEs 形成或后续损伤[83]。如在高糖诱导的 LECs 中,ROS 和 MDA 过量累积,白藜芦醇可以减轻高葡萄糖诱导的 LECs 的氧化损伤[84]。除此之外,ROS 还能通过 AGE-RAGE-NOX4 轴放大氧化应激,形成恶性循环,持续推动 AGEs 累积[85],而在 DC 中有待进一步验证。

综上,DC 的发生发展中,糖化应激与氧化应激通路相互交织的同时相互影响,而自噬的调控是两者协同作用的关键节点。AGEs 和 ROS 通过调控自噬的不同发生阶段的关键蛋白,导致自噬溶酶体的降解功能受损。未来可通过探寻糖化应激和氧化应激的调控自噬的关键通路,开发防治白内障的药物。

4 小结与展望

自噬作为 DC 发病机制的重要环节,展现出复杂的双重作用机制:适度激活时,其通过 mTOR-ULK1 通路动态平衡维持细胞稳态,清除氧化应激损伤的细胞器、错误折叠蛋白,发挥保护作用;但过度激活则可能通过溶酶体超载或 Beclin-1 依赖性凋亡途径导致晶状体上皮细胞死亡。因此,一些学者强调自噬的激活与细胞保护作用密切相关;然而,亦有学者指出自噬的过度激活可能导致晶状体上皮细胞死亡。综上,进一步明确自噬在不同情况下的双重角色是未来研究的重要方向。本研究旨在初步整合氧化应激和糖化应激的协同调控来解释自噬的不同作用,试图归纳找出共同的调控通路。未来再通过药物模拟筛选、基因编辑技术(如 CRISPR-Cas9 靶向 ATG 基因)等,以滴眼液形式,干预双重应激环境下激活的自噬调控通路,从而实现自噬活性的动态的、精准的调控,为 DC 患者的临床诊疗提供新的药物干预方案。

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