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调节性细胞死亡在子痫前期中的作用

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摘　要

子痫前期是一种发病机制复杂的妊娠期疾病，可能涉及到多种调节性细胞死亡方式，如细胞凋亡、自噬、焦亡、铁死亡和铜死亡等。将子痫前期与调节性细胞死亡联系起来，有助于更加全面深入地了解子痫前期的病理进程，为子痫前期的发生提供潜在的预测指标和新型诊疗方法。本文就近年来调节性细胞死亡与子痫前期的研究进展进行综述。

关键词

子痫前期，调节性细胞死亡，凋亡，自噬，焦亡，铁死亡，铜死亡

The Role of Regulatory Cell Death in Preeclampsia

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Abstract

Preeclampsia is a pregnancy disease with a complex pathogenesis, which may involve multiple regulatory cell death modes such as apoptosis, autophagy, pyroptosis, ferroptosis, and copper death. Linking preeclampsia with regulatory cell death can help to gain a more comprehensive and in-depth understanding of the pathological process of preeclampsia, providing potential predictive indicators and novel diagnostic and therapeutic methods for its occurrence. This article reviews the research progress on regulatory cell death and preeclampsia in recent years.

Keywords

Preeclampsia, Regulated Cell Death, Apoptosis, Autophagy, Pyroptosis, Ferroptosis, Cuprotosis

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1. 引言

子痫前期(Preeclampsia)是妊娠期特发的高血压疾病，确诊需要孕妇在妊娠 20 周后出现新发高血压症状，且伴有至少一种其他相关并发症诊断，包括蛋白尿，水肿，胎盘功能异常等[1]。若子痫前期合并有母体心、脑、肾、肺等重要器官受累，可诊断为重度子痫前期[2]。子痫前期发病时，根据妊娠是否超过 34 周，可分为早发型和晚发型[3]，有研究证实了早发型子痫前期和重度子痫前期呈现相关性[4]。据统计，全球子痫前期发病率约为 2%~8% [5]，每年全球近八万名孕妇和五十万胎儿，会因包括子痫前期在内的妊娠高血压疾病丧失生命，每年因子痫前期导致的早产儿高达 15%。子痫前期的病因和发病机制尚不明确，可能与胎盘发育不良引发缺血缺氧，胎儿先天性缺陷，母体代谢紊乱，免疫功能异常，肠道菌群失调等多个因素有关[6]。

近数十年来，随着自然科学技术和细胞研究方法的进步，多种新的细胞死亡方式被发现和深入研究。总体来看，细胞死亡可分为意外性细胞死亡(accidental cell death, ACD)和调节性细胞死亡(Regulated cell death, RCD) [7] [8]。ACD 主要是由理化或外界损伤引起，细胞对着这些刺激无法通过自身功能进行调节，引发不受控制的细胞死亡过程，也可称为细胞坏死。RCD 则是一种主动性可受调控的细胞死亡方式，包括细胞凋亡、细胞自噬，细胞焦亡，铁死亡、铜死亡等。通过各种调节性细胞死亡方式，机体实现了清除多余、不可逆损伤的细胞的目的，对维持内稳态发挥重要作用[9]。RCD 是细胞可以发挥调控功能的细胞死亡方式，调控的方式多种多样，涉及信号分子及上下游通路，可表现出特殊的生化及形态特征和免疫学特点。

越来越多的证据表明，子痫前期作为一种作用机制复杂的妊娠期疾病，可能涉及到多种调节性细胞死亡方式[10]。通过对调节性细胞死亡的深入研究，有助于进一步加深对子痫前期疾病进程的理解，探索子痫前期的发病机制。

2. 调节性细胞死亡与子痫前期

2.1. 凋亡与子痫前期

细胞凋亡(apoptosis)是发现最早，研究最全面，也是最经典的调节性细胞死亡的方式。凋亡的形态学特征，包括细胞体积缩小、细胞膜出现囊泡、染色质聚集，细胞核固缩及破碎[11]。

细胞凋亡的内源性途径也被称为线粒体凋亡途径，是细胞通过改变线粒体外膜通透性来完成自杀的方式。细胞内稳态的破坏，如代谢障碍，氧化应激等，会引发细胞凋亡[12]。细胞稳态失衡刺激促凋亡因子分泌及释放，引发相关促凋亡蛋白的产生增加，推动凋亡小体的形成，激活 caspase-3 和 caspase-7 这两个细胞凋亡的“刽子手”，完成内源性途径的细胞凋亡过程[13]。

细胞凋亡的外源性途径是通过细胞外微环境的变化和死亡受体信号转导来激活的[14]。当死亡受体 FAS 与 FAS 配体(FasL)结合时，FAS 会被三聚化激活，导致 Fas 相关死亡域蛋白的构象发生变化，活化 caspase-8 以形成死亡诱导信号复合体。活化的 caspase-8 也可直接激活 caspase-3 和 caspase-7 诱导细胞凋亡，或将 BID 裂解为 tBID，触发细胞凋亡[15]。

在胚胎发育早期，滋养细胞有两种分化方向，一种是绒毛滋养细胞，另一种是绒毛外滋养细胞，两种分化成的细胞发挥不同的生物学功能。绒毛滋养细胞主要参与细胞生命代谢；绒毛外滋养细胞具有类

似“肿瘤细胞”的侵袭能力，可以向子宫间质和螺旋动脉浸润性生长，参与母体螺旋动脉的重铸[16]，以保证胎盘血供。因此，旧的滋养细胞必须通过凋亡被新生滋养细胞替代，胎盘才能正常发育[17]。若滋养细胞凋亡调控异常，会使子宫螺旋动脉重铸受阻，导致胎盘处于缺血缺氧的状态，发出现氧化应激和代谢异常[18]。

Zhou 等发现，一些环状 RNA 可通过 miR-126-3p/BAK1 轴调节子痫前期滋养细胞凋亡[19]。有研究证明，OLFML3 可能通过 PI3K/AKT 通路抑制滋养细胞凋亡，从而缓解子痫前期的发生[20]。阿司匹林作为经典的乙酰水杨酸类药物，是子痫前期的重要临床治疗药物，可调节 NF-κB 等多个信号通路，削弱 sFlt-1 在氧化应激和内皮细胞功能中的作用，抑制滋养细胞凋亡[21]。

2.2. 自噬与子痫前期

自噬(Autophagy)于 1963 年由 Christian 首次提出，并因此获得了诺贝尔生理学或医学奖[22] [23]。自噬在生物的进化上高度保守，参与饥饿反应及早期发育和细胞分化，分解衰老或损伤的蛋白质、细胞器，对维持和调节细胞稳态起重要作用。自噬可分为以下三种：1) 巨自噬：由内质网膜、高尔基体膜等包裹待降解的蛋白等形成自噬体，然后与溶酶体结合并进行分解；2) 微自噬：溶酶体的膜直接包绕长寿蛋白等，并在溶酶体内降解；3) 分子伴侣介导的自噬：胞质内待分解的蛋白结合分子伴侣后直接被转运到溶酶体内，继而被溶酶体酶分解和消化，完成自噬过程[24]。

有文献报道，TFEB 是溶酶体生成的主要调控因子，暴露在低氧环境中的原代人滋养细胞 TFEB 明显降低，提示 PE 患者滋养细胞自噬功能可能受到抑制[25]。也有研究表明子痫前期患者滋养细胞中溶酶体形成的主要转录调节因子及受其调节的蛋白 LAMP1，LAMP2，CTSD 等蛋白失调，可导致溶酶体结构缺陷，胎盘自噬功能受损[26]。Gu 等研究证实了环孢素 A 可通过上调小鼠胎盘中自噬相关蛋白的表达，减轻诱导的子痫前期小鼠的子痫前期样症状[27]。

2.3. 细胞焦亡与子痫前期

早在 1992 年，就有研究者发现被细菌感染巨噬细胞会发生特殊的细胞死亡[28]，进一步研究发现这类细菌感染巨噬细胞死亡不依赖于细胞凋亡相关的 caspase-3，而是依赖于 caspase-1 [29]。于是，这种细胞特殊的死亡方式被命名为细胞焦亡(Pyroptosis)，又称细胞炎性坏死[30]。在这个过程中细胞膜形成孔，引发膜破裂，细胞肿胀，细胞内容物释放，IL-1β、IL-18 等细胞因子会放大炎症效应并激活免疫反应[31]。

子痫前期由于子宫螺旋动脉形成不良，胎盘血管因灌注不足诱发了氧化应激反应，导致 ROS 过度积累，诱发大量炎症因子释放，从而促进细胞焦亡的发生[32]。有文献表明，HOXA9 可以通过 CMKLR1/AMPK/TXNIP/NLRP3 通路，诱导滋养细胞焦亡，加重子痫前期症状[33]。有研究证实，子痫前期胎盘组织中 HDAC2 下调，激活 FOXO3 PERK，并且伴随 IL-1β、IL-18 等焦亡相关的细胞因子上调，可导致细胞焦亡的发生[34]。Wu 等证明了非编码 RNA LINC00240 通过调控 miR-155/Nrf2 轴，抑制氧化应激导致的焦亡，改善滋养层细胞功能和促进 M2 巨噬细胞的极化，抑制子痫前期症状[35]。

2.4. 铁死亡与子痫前期

铁死亡(Ferroptosis)的主要形态特征为线粒体体积变小、线粒体嵴减少或消失、线粒体外膜破裂、细胞核大小正常[36] [37]。铁死亡的关键机制是细胞内氧化还原稳态失衡，抗氧化系统如谷胱甘肽和谷胱甘肽过氧化物酶 4 (GPX4)水平下降，引起亚铁离子和 ROS 水平升高，脂质过氧化，导致质膜损伤最终引发铁死亡[38]。过量铁可以储存在线粒体铁蛋白中，线粒体呼吸链在产生 ATP 的同时生产 ROS。ROS 可以与铁硫簇蛋白相互作用，催化线粒体中的芬顿反应，从而产生更多的 ROS，加剧氧化应激和铁死亡的发生[39]。

研究表明，子痫前期孕妇血清及胎盘组织铁含量均高于正常孕妇，这可能是由于铁代谢异常导致滋养细胞发生铁死亡[40]。子痫前期患者胎盘中谷胱甘肽含量和谷胱甘肽过氧化物酶活性降低，铁死亡特异性标志物明显上升，提示子痫前期发病伴随铁死亡增强[41]。Yang 等发现妊娠期间滋养细胞铁蛋白轻链(FLT)降低引发铁死亡，进而引起子宫螺旋动脉重铸障碍，导致子痫前期的发生[42]。有研究证实，抑制 Nox2 表达可通过 STAT3/GPX4 途径抵抗滋养层细胞铁死亡，改善滋养细胞功能及子痫前期症状[43]。

2.5. 铜死亡与子痫前期

2022 年，Tsvetkov 等首次提出了铜死亡(Cuprotosis)并阐述了铜死亡的相关机制[44]。铜死亡会表现出一系列形态学特征，包括线粒体的收缩、细胞膜的破裂、内质网的损伤以及染色质的破裂，虽然这些特征与凋亡过程相似，但发生机制不同于其它凋亡等调节性细胞死亡[45]。铜死亡是由于铜离子过度积累，通过芬顿反应，导致 ROS 生成过多，触发氧化应激，促进 DLAT 寡聚化，破坏了泛素－蛋白酶体系统，引起铁硫簇蛋白活性下降，干扰线粒体正常呼吸，最终导致细胞死亡[44]。

多项研究表明，子痫前期的发生可能与孕妇血清及胎盘组织的铜代谢异常有关[46]-[48]。Tang 等通过数据库对子痫前期胎盘组织中铜死亡相关基因进行分析，筛选出五个与子痫前期发病机制密切相关的基因，包括 NFE2L2、PDHA1、PDHB、DLD 和 GLS，其中 NFE2L2 与最高妊娠血压及脐血流量呈负相关[49]。也有研究表明，子痫前期患者胎盘组织乳酸水平升高，可增强铜离子转运体关键蛋白 SLC31A1 的表达，从而增加细胞内铜含量，提示降低乳酸可能有助于抑制铜死亡的发生、预防和治疗子痫前期[50]。目前，铜死亡与子痫前期具体致病机制的相关研究尚浅，需要进一步深入研究。

3. 展望

子痫前期作为发病率相对较高的妊娠期疾病之一，严重威胁母婴健康。因此，为了更好地预防和治疗子痫前期，对于子痫前期发病机制的研究显得尤为重要。但是，不同的细胞调节性死亡方式之间的关系，以及对子痫前期发病机制的详细作用，仍有待更深入的研究。

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