抵抗素调控机制及其与慢性疾病关系的研究现状

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摘 要：抵抗素是在小鼠脂肪细胞中发现的激素，在炎症、代谢、免疫性疾病、慢性疾病中发挥重要作用。该文就抵抗素调控机制及其与慢性肾脏病、心血管疾病、肥胖及糖尿病、癌症的关系作一综述。

关键词：抵抗素；炎症因子；胰岛素抵抗；慢性疾病

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Research progress on regulatory mechanism of resistin and its relationship with chronic diseases

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Abstract: Resistin is a hormone found in mouse adipocytes, and plays an important role in inflammatory, metabolic, immune and chronic diseases. This article reviews the regulatory mechanism of resistin and its relationship with chronic kidney diseases, diabetes, cardiovascular diseases, and cancer.

Key words: resistin; inflammatory factor; insulin resistance; chronic disease

抵抗素是一种由脂肪细胞产生的分泌蛋白，通过胰岛素抵抗与肥胖、糖尿病建立联系。随着研究的深入，抵抗素亦被发现可通过刺激人体单核细胞而诱导低度炎症，其介导的慢性炎症可导致肥胖、动脉粥样硬化、代谢性疾病、慢性肾病等。本文拟就抵抗素调控机制及其与慢性肾脏病、心血管疾病、肥胖及糖尿病、癌症的关系作一综述，以了解抵抗素与慢性肾脏病、糖尿病与肥胖、心血管疾病等慢性疾病的关系。

1 抵抗素概述

抵抗素（又称脂肪细胞分泌因子，ADSF）是一种12.5 kDa的分泌性蛋白，其富含半胱氨酸，在小鼠和人类中分别由 94 和 108 个氨基酸组成。它属于抵抗素样分子（RELM）激素家族，该家族还包括RELMa、RELMb和RELMG，是参与炎症过程的一组蛋白质[1]。抵抗素最初由Steppan等[2]在研究噻唑烷二酮类（TZD）降糖药物时发现，被认为是肥胖与糖尿病之间的潜在联系。在小鼠哮喘模型的研究中，抵抗素被确定为与肺部炎症相关的蛋白质，在炎症区 3 中发现的蛋白质被命名为FIZZ3[3]。抵抗素组织分布和细胞来源在人类和小鼠中是不同的。在人类，抵抗素主要由巨噬细胞及单核细胞产生和释放[4]，被认为是一种促炎因子，通过调节肿瘤坏死因子α（TNF-α）、白细胞介素（IL）-1β、IL-6、IL-8、 IL-12 的释放，诱导单核细胞趋化蛋白-1（MCP-1）的表达和核因子B细胞k轻链（NF-κB）的激活[5-7]，从而发挥促炎反应，还可诱导线粒体功能障碍；可在各种器官或组织中表达，包括肾上腺、脑垂体、下丘脑、白色脂肪组织、肺、骨骼肌和血浆等[8]，造成相应器官损害，引起各种慢性疾病。

2 抵抗素调控

2.1 CCAAT/增强子结合蛋白（C/EBP）

小鼠抵抗素表达高度集中于脂肪细胞，C/EBP家族成员在脂肪因子生成的转录级联反应中起着重要作用，其有一个碱性激活区和一个亮氨酸拉链模体，通过DNA结合区与靶基因结合成调控元件。C/EBPα作为脂肪细胞基因转录的激活剂，反式激活在脂肪细胞中大量表达的启动子，包括 GLUT4、瘦素和 激活蛋白 2；

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抵抗素基因启动子的 224 bp片段携带C/EBPα结合位点，能与C/EBPα直接结合并进行自身调控，激活近端抵抗素启动子，使脂肪细胞中转录激活因子募集和组蛋白乙酰化[9]。C/EBPα还在 L6 肌细胞中诱导抵抗素的表达，控制抵抗素表达的不是脂肪细胞表型，而是C/EBPα 的存在。激活丝裂原活化蛋白激酶（MAPK）可减少C/EBPα的表达，从而使抵抗素的表达受到抑制，降低脂肪细胞的分化。C/EBPα有助于诱导抵抗素的表达，而C/EBPf具有相反的作用。C/EBPf与生长停滞DNA损伤（GADD153）相同，与生长和分化的调节有关，通过阻止 C/EBPα–C/EBPβ异二聚体与经典的CCAAT增强子序列结合，C/EBPf成为转录激活的显性失活抑制剂。C/EBPβ是启动转录级联反应的重要因子，在脂肪细胞中异位表达，在 3T3-L1 脂肪细胞分化过程中，C/EBPβ 早期被诱导以反激活两种末端脂肪细胞分化的主转录因子C/EBPα 和过氧化物酶体增殖物激活受体γ（PPARγ）的表达[10]。

2.2 过氧化物酶体增殖物激活受体（PPAR）

PPAR属于核激素受体超家族的配体激活受体，由 3 个不同基因编码的亚型组成，分别是PPARα、PPARδ和PPARγ，通过与靶基因增强子部位的特定识别序列–过氧化物酶体增殖物反应元件（PPRE）的结合调节基因转录。PPARγ与类视黄醇X受体一起作为异二聚体与DNA结合，充当转录因子调节参与脂质和葡萄糖代谢，在脂肪生成中发挥关键作用，与其他转录因子配合调节前脂肪细胞向脂肪细胞的分化。PPARγ是胰岛素增敏剂抗糖尿病药物中的噻唑烷二酮（TZD）类药物的分子靶点，可降低胰岛素抵抗，基于这种作用，目前罗格列酮、吡格列酮等药物已被批准用于治疗 2 型糖尿病。在人类中，抵抗素由单核–巨噬细胞分泌，当巨噬细胞暴露于TZD类药物大于 96 h后，抵抗素mRNA的表达将减少 80%[8]。PPARγ只在脂肪细胞中大量表达，可诱导脂肪细胞的合成，调控脂肪酸合成酶及乙酰辅酶A合成酶等的表达。Patel等[11]通过生物信息学分析在抵抗素转录起始点上游的基因组DNA序列中发现了PPRE2，其能够特异性地结合PPARγ，下调抵抗素表达，是抵抗素表达和功能的关键调节因子。

3 抵抗素与相关疾病

3.1 慢性肾脏病

肾脏是一个排泄代谢产物、调节水电解质和酸碱平衡、维持机体内环境稳定及分泌激素的器官。氧化应激、炎症和线粒体功能障碍等被认为是肾功能障碍的主要始动因素[12-13]。抵抗素可调控肾功能，可能通过氧化应激在增强内皮功能障碍中发挥重要作用，对肾小球有直接损害作用[14]。研究发现在慢性肾脏病（CKD）中血清抵抗素水平明显升高，其与肾小球滤过率（GFR）及炎症相关，而非胰岛素抵抗[15]，然而当GFR＞60 mL/（min·1.73m^2）时，抵抗素与GFR无相关性，表明除GFR以外的因素在影响轻度至正常范围内肾功能患者的抵抗素浓度[16]。此外，在CKD患者中TNF-α与抵抗素、C反应蛋白存在关联（P<0.05），抵抗素可能是CKD患者炎症反应的替代标记物，并且可能在CKD相关的亚临床炎症中起关键作用[17]。中性粒细胞是首要的非特异性免疫反应细胞，在CKD中抵抗素可干扰中性粒细胞的趋化，减弱吞噬作用；抵抗素储存在多形核白细胞（PMNL）颗粒中，并在炎症介质刺激后释放。由于抵抗素刺激$CD4^+$淋巴细胞的趋化性，PMNL可能会将淋巴细胞吸引到炎症部位，同时减弱自身的功能，导致CKD患者免疫功能紊乱[16，18]。抵抗素虽被认为是一种潜在的尿毒素，但血液透析和腹膜透析不能明显降低患者血清抵抗素水平[16，19]。

3.2 心血管疾病

心血管疾病包括心脏病、血管疾病及动脉粥样硬化。抵抗素可触发各种细胞信号转导途径，引发炎症、内皮功能障碍以及促进血栓形成、血管生成和平滑肌细胞功能障碍等心血管疾病的病理状态；抵抗素由单核细胞分泌，分化成巨噬细胞，可累积致动脉粥样硬化蛋白，如极低密度脂蛋白（VLDL）、低密度脂蛋白（LDL）等，参与泡沫细胞的形成[20]；还可使基质金属蛋白酶（MMP）、内皮素-1、血管内皮生长因子受体、MCP-1 等的表达上调，导致细胞外基质分解和平滑肌细胞增殖迁移，从而使动脉粥样硬化进展加快并促使斑块不稳定，造成动脉粥样硬化破裂和心肌重构等各种损害[19，21-25]。在一项随机化研究中，消除了混杂因素后，高抵抗素水平与房颤、心肌梗死的发生风险成因果关系[26]。然而，抵抗素在房颤中的作用存在争议。在一项心血管疾病多种族的研究中，高抵抗素浓度与心力衰竭、冠心病及其他心血管疾病存在显著关联，但与房颤无关，可刺激TNF-α的分泌，影响缺血后心肌的恢复[27-28]。抵抗素水平升高还与左心室收缩功能下降有关，可能会增加心力衰竭的风险[29]，并与高血压呈正相关，在亚洲及糖尿病人群中的相关性最为显著，有可能是高血压的危险因素[30]。抵抗素亦可增加前白蛋白转化酶枯草溶菌素/Kexin9 型（PCSK9）的表达，增

强细胞内低密度脂蛋白受体（LDLR）溶酶体降解，降低肝脏对循环中LDL的清除能力，导致LDL蓄积，对心脏、脂肪细胞等靶器官产生有害影响[31]。

3.3　肥胖及糖尿病

抵抗素是由脂肪细胞分泌的蛋白，可抑制脂肪细胞分化，并可能作为脂肪形成的反馈调节剂，并与肥胖程度相关[25, 32]。抵抗素在肥胖和糖尿病之间具有重要联系。研究发现，在饮食诱导和遗传性肥胖的小鼠模型中，血清抵抗素水平显著升高，给正常小鼠注射抵抗素可损害葡萄糖耐量及致胰岛素抵抗，而降糖药物罗格列酮可降低抵抗素基因表达及分泌[2]，对饮食诱导的肥胖、胰岛素抵抗和高血糖的小鼠使用抗抵抗素抗体，可使血糖水平降至正常，并提高对胰岛素的敏感性[33]。这或许部分解释了TZD通过PPARγ途径改善胰岛素敏感性的机制。血清抵抗素水平与身体质指数（BMI）、内脏脂肪呈正相关，与瘦者相比，肥胖者具有更高的抵抗素mRNA表达[34-35]。有证据表明，通过运动减重可使血清抵抗素水平下降，可减少NF-KB信号通路、蛋白质分解、炎症及白色脂肪[36]。在一项纳入了10个研究的荟萃分析中，胰岛素抵抗程度与抵抗素水平呈正相关，证明了循环抵抗素在肥胖和2型糖尿病患者中起着桥梁作用[37]。另外，血清抵抗素水平与糖尿病微血管病变的发生密切相关[38]。在278例2型糖尿病患者中发现抵抗素可能通过氧化应激及亚临床炎症的机制影响糖尿病肾病的发生，并可能是糖尿病肾病的风险预测因子[39]。有研究者发现熊果苷（糖基化对苯二酚）可降低糖尿病患者血清抵抗素水平，改善糖耐量不良、胰岛素抵抗及炎症，但其机制及疗效有待进一步研究[40]。2型糖尿病病死率高，部分可由动脉粥样硬化介导，抵抗素可能有助于识别高风险患者[41-42]。

3.4　癌症

癌症是全世界第二大常见死因[43]。抵抗素除可介导炎症、代谢紊乱及胰岛素抵抗外，还可促进细胞增殖，调节血管内皮生长因子受体（VEGFRs）和MMP的表达，促进癌症发展，在肿瘤代谢中发挥关键作用[44-46]。抵抗素还可通过诱导上皮细胞转化为间充质细胞、调节细胞周期及凋亡来影响癌症的病理生理学[47]，但其详细机制还有待阐明。研究表明，高抵抗素水平与肥胖相关癌症（如子宫内膜癌、乳腺癌、结直肠癌等）的发病率增加有关，有可能是肥胖相关癌症的独立风险因素，但不是预测指标[46, 48-50]。在乳腺癌中，术后辅助放化疗患者的抵抗素水平明显高于初治时的水平，意味着抵抗素水平可能反映了乳腺癌术后辅助治疗引起的炎症状态，因而靶向抑制抵抗素可能是消除肿瘤微炎症的有效策略[51-53]。乳腺癌术后辅助治疗后抵抗素水平与胰岛素抵抗呈正相关，可能表明高抵抗素水平是肿瘤治疗后引起代谢紊乱的潜在原因[52]。与健康个体相比，结直肠癌（CRC）中的抵抗素水平明显升高[54-55]。一项meta分析结果表明，诊断CRC前的抵抗素浓度与CRC风险无关，但确诊2年内的患者抵抗素水平与CRC风险存在明显关联[56]。高抵抗素水平也与非肥胖相关癌症有关，如胃癌、肺癌、血液肿瘤、肝癌等。虽抵抗素与多种癌症相关，但其作为肿瘤标志物的能力有限[49]。

4　结语

抵抗素在炎症、线粒体功能障碍、细胞凋亡、血管平滑肌增殖等方面占据重要地位，与多种慢性疾病存在关联。其中，线粒体功能障碍被认为是一种新的机制。在细胞应激、心血管系统紊乱、癌症、肥胖、糖尿病等多种情况下，抵抗素可诱导蛋白激酶A（PKA）激活，使丝氨酸磷酸化，随后致线粒体分裂，导致三磷酸腺苷产量减少及线粒体功能障碍，使活性氧增加，引起细胞损伤并启动凋亡途径[57-59]。目前发现的抵抗素受体有核心蛋白聚糖、G蛋白偶联受体、酪氨酸激酶样孤儿受体1、Toll样受体4和腺苷酸环化酶相关蛋白1（CAP1），但有研究表明CAP1可能是抵抗素的真正受体，抵抗素直接与CAP1结合，上调环磷酸腺苷浓度、PKA活性和NF-KB相关转录[60]。基于抵抗素在代谢疾病中的作用，研究者发现了一种新型阻断肽，它模拟了与人抵抗素相互作用的核心肽序列，可抑制抵抗素与CAP1受体结合，减轻线粒体功能障碍，并消除抵抗素介导的炎症活性[57]。抵抗素-CAP1复合体有可能成为治疗代谢性疾病的潜在靶点。抵抗素作为促炎细胞因子，可激活单核细胞、巨噬细胞、中性粒细胞等免疫细胞，促进其黏附、浸润及迁移，加速炎症反应，然而在微生物的刺激下可表现出抗炎活性，防止微生物对宿主产生过度的炎症损伤，可能是一种双向免疫调节分子，但其机制有待进一步研究[61]。

参考文献：

[1] PINE G M, BATUGEDARA H M, NAIR M G. Here, there and everywhere: Resistin-like molecules in infection, inflammation, and metabolic disorders[J]. Cytokine, 2018, 110: 442-451.

[2] STEPPAN C M, BAILEY S T, BHAT S, et al. The hormone resistin links obesity to diabetes[J]. Nature, 2001, 409(6818): 307-312.

[3]KIM K H, LEE K, MOON Y S, et al. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation[J]. J Biol Chem, 2001, 276 (14): 11252-11256.

[4]CURAT C A, WEGNER V, SENGENÈS C, et al. Macrophages in human visceral adipose tissue: Increased accumulation in obesity and a source of resistin and visfatin[J]. Diabetologia, 2006, 49(4): 744-747.

[5]MCTERNAN P G, KUSMINSKI C M, KUMAR S. Resistin[J]. Curr Opin Lipidol, 2006, 17(2): 170-175.

[6]TRIPATHI D, KANT S, PANDEY S, et al. Resistin in metabolism, inflammation, and disease[J]. FEBS J, 2020, 287(15): 3141-3149.

[7]PARK H K, KWAK M K, KIM H J, et al. Linking resistin, inflammation, and cardiometabolic diseases[J]. Korean J Intern Med, 2017, 32(2): 239-247.

[8]ADEGHATE E. An update on the biology and physiology of resistin[J]. Cell Mol Life Sci, 2004, 61(19-20): 2485-2496.

[9]SONG H, SHOJIMA N, SAKODA H, et al. Resistin is regulated by C/EBPs, PPARs, and signal-transducing molecules[J]. Biochem Biophys Res Commun, 2002, 299(2): 291-298.

[10]GUO L, LI X, TANG Q Q. Transcriptional regulation of adipocyte differentiation: A central role for CCAAT/enhancer-binding protein (C/EBP) β[J]. J Biol Chem, 2015, 290(2): 755-761.

[11]PATEL L, BUCKELS A C, KINGHORN I J, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators[J]. Biochem Biophys Res Commun, 2003, 300(2): 472-476.

[12]LIN T A, WU V C, WANG C Y. Autophagy in chronic kidney diseases[J]. Cells, 2019, 8(1):61.

[13]O'SULLIVAN E D, HUGHES J, FERENBACH D A. Renal aging: Causes and consequences[J]. J Am Soc Nephrol, 2017, 28(2): 407-420.

[14]MENZAGHI C, SALVEMINI L, FINI G, et al. Serum resistin and kidney function:A family-based study in non-diabetic, untreated individuals[J]. PloS One, 2012, 7(6): e38414.

[15]AXELSSON J, BERGSTEN A, QURESHI A R, et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance[J]. Kidney Int, 2006, 69(3): 596-604.

[16]COHEN G, HORL W H. Resistin as a cardiovascular and atherosclerotic risk factor and uremic toxin[J]. Semin Dial, 2009, 22(4): 373-377.

[17]YATURU S, REDDY R D, RAINS J, et al. Plasma and urine levels of resistin and adiponectin in chronic kidney disease[J]. Cytokine, 2007, 37(1): 1-5.

[18]COHEN G, ILIC D, RAUPACHOVA J, et al. Resistin inhibits essential functions of polymorphonuclear leukocytes[J]. J Immunol, 2008, 181(6): 3761-3768.

[19]MUNJAS J, SOPIĆ M, BOGAVAC-STANOJEVIĆ N, et al. Serum resistin, adenylate cyclase-associated protein 1 gene expression, and carotid intima-media thickness in patients with end-stage renal disease and healthy controls[J]. Cardiorenal Med, 2020, 10(1): 51-60.

[20]ROMEJKO K, RYMARZ A, SZAMOTULSKA K, et al. Resistin contribution to cardiovascular risk in chronic kidney disease male patients[J]. Cells, 2023, 12(7)：999.

[21]JAMALUDDIN M S, WEAKLEY S M, YAO Q, et al. Resistin: Functional roles and therapeutic considerations for cardiovascular disease[J]. Br J Pharmacol, 2012, 165(3): 622-632.

[22]YUXIANG L, FUJIU K. Human resistin and cardiovascular disease[J]. Int Heart J, 2020, 61(3): 421-423.

[23]ZHOU L, LI J Y, HE P P, et al. Resistin:Potential biomarker and therapeutic target in atherosclerosis[J]. Clin Chim Acta, 2021, 512: 84-91.

[24]ACQUARONE E, MONACELLI F, BORGHI R, et al. Resistin:A reappraisal [J]. Mech Ageing Dev, 2019, 178: 46-63.

[25]WOLF G. Insulin resistance and obesity:Resistin, a hormone secreted by adipose tissue[J]. Nutr Rev, 2004, 62(10): 389-394.

[26]CHEN D, ZHANG Y, YIDILISI A, et al. Causal associations between circulating adipokines and cardiovascular disease: A mendelian randomization study[J]. J Clin Endocrinol Metab, 2022, 107(6): e2572-e2580.

[27]MUSE E D, FELDMAN D I, BLAHA M J, et al. The association of resistin with cardiovascular disease in the multi-ethnic study of atherosclerosis [J]. Atherosclerosis, 2015, 239(1): 101-108.

[28]BHALLA V, KALOGEROPOULOS A, GEORGIOPOULOU V, et al. Serum resistin:Physiology, pathophysiology and implications for heart failure[J]. Biomark Med, 2010, 4(3): 445-452.

[29]MCMANUS D D, LYASS A, INGELSSON E, et al. Relations of circulating resistin and adiponectin and cardiac structure and function:The Framingham Offspring Study[J]. Obesity (Silver Spring), 2012, 20(9): 1882-1886.

[30]ZHANG Y, LI Y, YU L, et al. Association between serum resistin concentration and hypertension:A systematic review and meta-analysis[J]. Oncotarget, 2017, 8(25): 41529-41537.

[31]MELONE M, WILSIE L, PALYHA O, et al. Discovery of a new role of human resistin in hepatocyte low-density lipoprotein receptor suppression mediated in part by proprotein convertase subtilisin/kexin type 9[J]. J Am Coll Cardiol, 2012, 59(19): 1697-1705.

[32]EMAMALIPOUR M, SEIDI K, JAHANBAN-ESFAHLAN A, et al. Implications of resistin in type 2 diabetes mellitus and coronary artery disease: Impairing insulin function and inducing pro-inflammatory cytokines[J]. J Cell Physiol, 2019, 234(12): 21758-21769.

[33] STEPPAN C M, LAZAR M A. Resistin and obesity-associated insulin resistance[J]. Trends Endocrinol Metab, 2002, 13(1): 18-23.

[34] DEGAWA-YAMAUCHI M, BOVENKERK J E, JULIAR B E, et al. Serum resistin (FIZZ3) protein is increased in obese humans[J]. J Clin Endocrinol Metab, 2003, 88(11): 5452-5455.

[35] AZUMA K, KATSUKAWA F, OGUCHI S, et al. Correlation between serum resistin level and adiposity in obese individuals[J]. Obes Res, 2003, 11(8): 997-1001.

[36] ALIZADEH PAHLAVANI H. Exercise therapy for people with sarcopenic obesity: Myokines and adipokines as effective actors[J]. Front Endocrinol (Lausanne), 2022, 13: 811751.

[37] SU K Z, LI Y R, ZHANG D, et al. Relation of circulating resistin to insulin resistance in type 2 diabetes and obesity:A systematic review and meta-analysis[J]. Front Physiol, 2019, 10: 1399.

[38] WANG L K, WANG H, WU X L, et al. Relationships among resistin, adiponectin, and leptin and microvascular complications in patients with type 2 diabetes mellitus[J]. J Int Med Res, 2020, 48(4): 300060519870407.

[39] LI M, FAN R, PENG X, et al. Association of ANGPTL8 and resistin with diabetic nephropathy in type 2 diabetes mellitus[J]. Front Endocrinol (Lausanne), 2021, 12: 695750.

[40] ABDUH M S, ALZOGHAIBI M A, ALZOGHAIBI A M, et al. Arbutin ameliorates hyperglycemia, dyslipidemia and oxidative stress and modulates adipocytokines and PPARγ in high-fat diet/streptozotocin-induced diabetic rats[J]. Life Sci, 2023, 321: 121612.

[41] SCARALE M G, ANTONUCCI A, CARDELLINI M, et al. A serum resistin and multicytokine inflammatory pathway is linked with and helps predict all-cause death in diabetes[J]. J Clin Endocrinol Metab, 2021, 106(11): e4350-e4359.

[42] DEL CRISTO RODRÍGUEZ PÉREZ M, GONZÁLEZ D A, RODRÍGUEZ I M, et al. Resistin as a risk factor for all-cause (and cardiovascular) death in the general population[J]. Sci Rep, 2022, 12(1): 19627.

[43] WANG H D, NAGHAVI M, ALLEN C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the Global Burden of Disease Study 2015[J]. Lancet (London, England), 2016, 388(10053): 1459-1544.

[44] DI SIMONE N, DI NICUOLO F, SANGUINETTI M, et al. Resistin regulates human choriocarcinoma cell invasive behaviour and endothelial cell angiogenic processes[J]. J Endocrinol, 2006, 189(3): 691-699.

[45] MU H, OHASHI R, YAN S, et al. Adipokine resistin promotes in vitro angiogenesis of human endothelial cells[J]. Cardiovasc Res, 2006, 70(1): 146- 157.

[46] PHAM D V, PARK P H. Tumor metabolic reprogramming by adipokines as a critical driver of obesity-associated cancer progression[J]. Int J Mol Sci, 2021, 22(3) :1444.

[47] SUDAN S K, DESHMUKH S K, POOSARLA T, et al. Resistin:An inflammatory cytokine with multi-faceted roles in cancer[J]. Biochim Biophys Acta Rev Cancer, 2020, 1874(2): 188419.

[48] GONG W J, ZHENG W, XIAO L, et al. Circulating resistin levels and obesity- related cancer risk:A meta-analysis[J]. Oncotarget, 2016, 7(36): 57694-57704.

[49] YANG G, FAN W, LUO B, et al. Circulating resistin levels and risk of colorectal cancer: A meta-analysis[J]. Biomed Res Int, 2016, 2016: 7367485.

[50] SPYROU N, AVGERINOS K I, MANTZOROS C S, et al. Classic and novel adipocytokines at the intersection of obesity and cancer: Diagnostic and therapeutic strategies[J]. Curr Obes Rep, 2018, 7(4): 260-275.

[51] WANG Y Y, HUNG A C, LO S, et al. Adipocytokines visfatin and resistin in breast cancer: Clinical relevance, biological mechanisms, and therapeutic potential[J]. Cancer Lett, 2021, 498: 229-239.

[52] COSKUN T, KOSOVA F, ARI Z, et al. Effect of oncological treatment on serum adipocytokine levels in patients with stage II-III breast cancer[J]. Mol Clin Oncol, 2016, 4(5): 893-897.

[53] AVGERINOS K I, SPYROU N, MANTZOROS C S, et al. Obesity and cancer risk: Emerging biological mechanisms and perspectives[J]. Metabolism, 2019, 92: 121-135.

[54] DEB A, DESHMUKH B, RAMTEKE P, et al. Resistin: A journey from metabolism to cancer[J]. Transl Oncol, 2021, 14(10): 101178.

[55] DURAIYARASAN S, ADEFUYE M, MANJUNATHA N, et al. Colon cancer and obesity: A narrative review[J]. Cureus, 2022, 14(8): e27589.

[56] PHAM T T, NIMPTSCH K, ALEKSANDROVA K, et al. Pre-diagnostic circulating resistin concentrations are not associated with colorectal cancer risk in the european prospective investigation into cancer and nutrition study[J]. Cancers, 2022, 14(22):1627.

[57] YANG H M, KIM J, SHIN D, et al. Resistin impairs mitochondrial homeostasis via cyclase-associated protein 1-mediated fission, leading to obesity-induced metabolic diseases[J]. Metabolism, 2023, 138: 155343.

[58] ROVIRA-LLOPIS S, BAÑULS C, DIAZ-MORALES N, et al. Mitochondrial dynamics in type 2 diabetes:Pathophysiological implications[J]. Redox Biol, 2017, 11: 637-645.

[59] VÁSQUEZ-TRINCADO C, GARCÍA-CARVAJAL I, PENNANEN C, et al. Mitochondrial dynamics, mitophagy

（下转第 114 页）

[23]DZAMA MM, STEINER M, RAUSCH J, et al. Synergistic targeting of FLT3 mutations in AML via combined Menin-MLL and FLT3 inhibition[J]. Blood, 2020, 136(21): 2442-2456.

[24]CHEN W L, Li D D, CHEN X, et al. Proton pump inhibitors selectively suppress MLL rearranged leukemia cells via disrupting MLL1-WDR5 protein-protein interaction[J]. Eur J Med Chem, 2020, 188: 112027.

[25]CHEN W, CHEN X, LI D, et al. Discovery of ddo-2213 as a potent and orally bioavailable inhibitor of the wdr5-mixed lineage leukemia 1 protein-protein interaction for the treatment of mll fusion leukemia[J]. J Med Chem, 2021, 64(12): 8221-8245.

[26]ROCHA-VIEGAS L, SILBERMINS M, OGARA M F, et al. Glucocorticoids uncover a critical role for ASH2L on BCL-X expression regulation in leukemia cells[J]. Biochim Biophys Acta Gene Regul Mech, 2020, 1863(1): 194475.

[27]WU Y J, LI L X, LIU L, et al. ASH2L-promoted HOXC8 gene expression plays a role in mixed lineage leukemia-rearranged acute leukemia[J]. Onco Targets Ther, 2020, 13: 381-387.

[28]MECHAAL A, MENIF S, ABBES S, et al. EZH2, new diagnosis and prognosis marker in acute myeloid leukemia patients[J]. Adv Med Sci, 2019, 64(2): 395-401.

[29]PORAZZI P, PETRUK S, PAGLIAROLI L, et al. Targeting chemotherapy to de-condensed H3K27me3-marked chromatin of AML cells enhances leukemia suppression[J]. Cancer Res, 2022, 82(3):458-471.

[30]YANG X, WAN M, YU F, et al. Histone methyltransferase EZH2 epigenetically affects CCNA1 expression in acute myeloid leukemia[J]. Cell Signal, 2021, 87: 110144.

[31]KEMPF J M, WESER S, BARTOSCHEK M D, et al. Loss-of-function mutations in the histone methyltransferase EZH2 promote chemotherapy resistance in AML[J]. Sci Rep, 2021, 11(1): 1-13.

[32]LAM U T F, CHEN E S. Molecular mechanisms in governing genomic stability and tumor suppression by the SETD2 H3K36 methyltransferase[J]. Int J Biochem Cell Biol, 2022, 144: 106155.

[33]LI J, PENG Z, LUO F, et al. SET domain containing 2 deficiency in myelodysplastic syndrome[J]. Front Genet, 2020, 11: 794.

[34]DONG Y, ZHAO X, FENG X, et al. SETD2 mutations confer chemoresistance in acute myeloid leukemia partly through altered cell cycle checkpoints[J]. Leukemia, 2019, 33(11): 2585-2598.

[35]SUN J, YU W, ZHANG X. Recurrent SETD2 mutation in NPM1-mutated acute myeloid leukemia[J]. Biomark Res, 2020, 8(1): 1-4.

[36]MARKOULI M, STREPKOS D, PIPERI C. Structure, activity and function of the SETDB1 protein methyltransferase[J]. Life, 2021, 11(8): 817.

[37]STREPKOS D, MARKOULI M, KLONOU A, et al. Histone methyltransferase SETDB1: A common denominator of tumorigenesis with therapeutic potential[J]. Cancer Res, 2021, 81(3): 525-534.

[38]ROPA J, SAHA N, HU H, et al. SETDB1 mediated histone H3 lysine 9 methylation suppresses MLL-fusion target expression and leukemic transformation[J]. Haematologica, 2020, 105(9): 2273.

[39]SARNO F, NEBBIOSO A, ALTUCCI L. DOT1L: A key target in normal chromatin remodelling and in mixed-lineage leukaemia treatment[J]. Epigenetics, 2020, 15(5): 439-453.

[40]LONETTI A, INDIO V, LAGINESTRA M A, et al. Inhibition of methyltransferase DOT1L sensitizes to sorafenib treatment AML cells irrespective of MLL-rearrangements: A novel therapeutic strategy for pediatric AML[J]. Cancers, 2020, 12(7): 1972.

[41]HEIMBRUCH K E, FISHER J B, STELLOH C T, et al. DOT1L inhibitors block abnormal self-renewal induced by cohesin loss[J]. Sci Rep, 2021, 11(1): 7288.

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（上接第 109 页）

and cardiovascular disease[J]. J Physiol, 2016, 594(3): 509-525.

[60]LEE S, LEE H C, KWON Y W, et al. Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes[J]. Cell Metab, 2014, 19(3): 484-497.

[61]LI Y, YANG Q, CAI D, et al. Resistin, a novel host defense peptide of innate immunity[J]. Front Immunol, 2021, 12: 699807.

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