DCBLD2在疾病中的作用研究进展

刘燕杰 李燊俊 王晓桐 王震 杜亚悦 吴日娜 牛洪琳*

(河北医科大学护理学院, 石家庄 050017)

摘要 含盘状蛋白、CUB和LCCL结构域的蛋白2(discoidin, CUB and LCCL domain-containing protein 2, DCBLD2)是DCBLD受体家族中的一员, 在脊椎动物中高度保守。研究发现DCBLD2参与调控细胞内的多种生理过程, 包括细胞增殖、迁移以及信号转导等。目前针对DCBLD2的研究大多集中在心血管疾病和癌症上, 而在糖尿病肾病以及免疫性疾病方面的研究较少。该文主要对DCBLD2的结构和生物学功能以及该跨膜蛋白在心血管疾病和癌症中的病理生理作用及机制进行了综述, 同时也阐述了DCBLD2在糖尿病肾病以及免疫性疾病中的重要作用, 为其在临床领域的进一步研究提供参考。

关键词 DCBLD2; 心血管疾病; 肿瘤; 糖尿病肾病; 免疫系统

Research Progress on the Role of the DCBLD2 in Diseases

LIU Yanjie, LI Shenjun, WANG Xiaotong, WANG Zhen, DU Yayue, WU Rina, NIU Honglin*

(*School of Nursing, Hebei Medical University, Shijiazhuang 050017, China*)

Abstract DCBLD2 (discoidin, CUB, and LCCL domain-containing protein 2) is a member of DCBLD receptor family. It is highly conserved among vertebrates. Studies have found that it has participated in regulating various physiological processes, including cell proliferation, migration and signal transduction. Most current research on DCBLD2 focuses on both cardiovascular disease and cancer, while there are few studies on diabetic nephropathy or immunological disease. This review mainly describes the structure, functions of DCBLD2 as well as its pathophysiological roles and mechanisms in cardiovascular disease and cancer. Also, the important roles of DCBLD2 in diabetic nephropathy and immune diseases are also briefly summarized, which provides a reference for further studies on DCBLD2 in clinical diseases.

Keywords DCBLD2; cardiovascular diseases; tumor; diabetic nephropathy; immune system

含盘状蛋白、CUB和LCCL结构域的蛋白2(discoidin, CUB and LCCL domain-containing protein 2, DCBLD2)作为一种I型跨膜蛋白, 是DCBLD受体家族中的一员, 从人冠状动脉内皮细胞中首次被克隆出来[1]。人类蛋白图谱项目(www.proteinatlas.org)生成的RNA-seq数据表明DCBLD2主要表达在生殖和肌肉组织等中, 同时也发现其在肾脏内皮细胞中存在表达。近年来, 对于DCBLD2的研究逐渐深入, 对其结构和生物学功能的认识逐渐提高。然而迄今为止, 有关DCBLD2的研究仍旧较少, 但已发现其在心血管疾病和肿瘤等疾病中发挥重要作用。本文就DCBLD2的结构特征、生理功能及其在多种疾病中的最新研究进展作一综述, 为进一步探讨DCBLD2在相关疾病中的作用机制提供参考。

收稿日期: 2023-04-13 接受日期: 2023-09-19

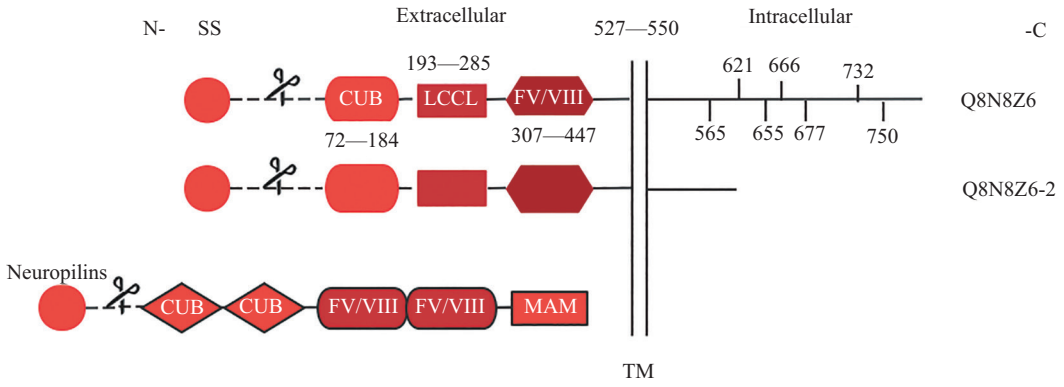
河北省自然科学基金(批准号: H2021206393)资助的课题

*通讯作者。Tel: 18533112282, E-mail: niuhonglin126@126.com

Received: April 13, 2023 Accepted: September 19, 2023

This work was supported by the Natural Science Foundation of Hebei Province (Grant No.H2021206393)

*Corresponding author. Tel: +86-18533112282, E-mail: niuhonglin126@126.com



SS: 信号序列; TM: 跨膜。

SS: signaling sequence; TM: transmembrane.

图1 DCBLD2蛋白的结构

Fig.1 The structure of DCBLD2 protein

1 DCBLD2的结构和生物学功能

2001年, KOBUKE等[1]利用改良的信号序列捕获技术, 成功从原代培养的人冠状动脉细胞中克隆出了一种新的跨膜蛋白, 该跨膜蛋白与神经纤毛蛋白结构相似, 从而将其命名为内皮和平滑肌细胞来源的neuropilin样分子(endothelial and smooth muscle cell-derived neuropilin-like molecule, ESDN)。由于ESDN特殊的分子结构, 因此其也被命名为CLCP1(CUB, LCCL homology and coagulation factor V/VIII-homology domains protein 1)和DCBLD2。通过Northern印迹分析检测DCBLD2在人胎儿和成人正常组织中的表达情况, 发现其在骨骼肌、胎盘、心脏、结肠、卵巢和前列腺中的表达相当丰富, 且在成人睾丸中表达量最高[2-3], 此外, 还发现DCBLD2转录本有6.5 Kb和4.5 Kb两种表达形式。

非哺乳类脊椎动物的DCBLD2信号序列均较短, 序列长度多接近平均信号肽长度(22个氨基酸), 而哺乳动物的DCBLD2信号序列却非常长且高度保守。目前研究显示, DCBLD2是真核生物中具有可切割的最长分泌信号序列(66个氨基酸)的I型跨膜蛋白[2]。RESCH等[4]描述了DCBLD2信号肽中具有不同功能的结构域, 包括C-端结构域、过渡区和N-端结构域。C-端结构域是一个功能完整的信号肽, 其具有带正电荷的氨基酸的特征序列、疏水延伸段和极性C-端。C-端结构域可以单独作为分泌途径的靶点。过渡区是由其自身形成β-转角的潜在能力来定义的。N-端结构域是DCBLD2糖基化所必需的, 在C-端结构域缺失的情况下, N-端结构域会将蛋白质定位到线粒体。DCBLD2的细胞外结构包含CUB结构域、LCCL结构域和凝血因子V/VIII结构域[5], 而其细胞内部分则包含多个磷酸化、乙酰化和泛素化位点以及Src同源结构域2(Src homology domain 2, SH2)结合基序(图1)。

DCBLD2胞外的CUB结构域被认为有助于蛋白质与蛋白质或蛋白质与碳水化合物之间的相互作用。研究表明, 含有CUB结构域的蛋白质通常参与细胞信号转导、补体激活、组织修复、炎症和肿瘤抑制等多种生物过程[6], 例如CUB结构域蛋白1(CUB domain-containing protein 1, CDCP1)是为数不多的包含3个胞外结构域的跨膜糖蛋白之一, 通过激活Src激酶调节非锚定生长和癌细胞迁移[7]; 而CUB结构域可以在胞外结构域分裂之前阻止胞外相互作用因子的结合。LCCL结构域是一个具有100个氨基酸的结构域, 该结构域是DCBLD2的组成部分并发挥了一定免疫作用, 但其特征性较差。凝血因子V/VIII同源结构域存在于膜蛋白[例如盘状蛋白结构域受体1(discoidin domain receptor 1, DDR1)]和细胞外蛋白中。DDR1参与细胞黏附、迁移、增殖、细胞因子分泌及细胞外基质的重塑。研究显示, DDR1分子在肿瘤细胞中的表达失调会导致肿瘤细胞的侵袭、增殖以及组织纤维化[8]。

另外, 不少研究表明*DCBLD2*基因突变会导致心肌炎的发生, 例如ALHAMOUDI等[5]的报道显示, *DCBLD2*基因纯合子突变是限制性心肌炎的潜在病因。

2 DCBLD2与心血管疾病

DCBLD2是从人冠状动脉和高度转移性肺癌

细胞中分离出来的I型跨膜蛋白。它通过调控血管内皮生长因子通路, 诱导内皮细胞增殖、迁移, 从而参与包括高血压、动脉粥样硬化和冠状动脉疾病在内的多种心血管疾病的发生发展。心血管疾病是危害人类生命健康的最严重的疾病之一, 其病理生理过程通常伴随着内皮功能障碍[9]。2019年贡悦等[10]利用cDNA芯片技术发现, DCBLD2在正常血管中低表达。而在动脉粥样硬化血管和发生血管重构的血管组织中, DCBLD2的表达量急剧增高。例如SADEGHI等[11]搭建了移植物动脉硬化模型, 并在重建的动脉中检测到了高水平的DCBLD2。同时, NIE等学者[12]的实验证明DCBLD2通过调节血管内皮生长因子(vascular endothelial growth factor, VEGF)信号转导影响小鼠体内血管生成。CHINTANAPHOL等[13]也通过临床病例及实验总结发现DCBLD2参与调节了细胞的增殖。这些研究均证实, DCBLD2表达水平的改变可能导致内皮细胞的增殖和迁移的异常, 诱发内皮功能障碍。

近年来, DCBLD2在心血管分子调控机制方向的研究进展缓慢, 而随着VEGF作为各种动脉粥样硬化性疾病的关键因子[14]被熟知, 越来越多研究着眼于DCBLD2对VEGF信号通路的调控作用。VEGF是刺激血管生成强有力的生长因子之一, 是位于血管内皮细胞中的高度特异的丝裂原。它直接作用于内皮细胞, 促进内皮细胞增殖和新生血管生长[12]。VEGF的家族成员VEGF-A是调节血管发育的关键生长因子, 该家族成员主要通过高亲和力结合VEGF受体2(VEGF receptor-2, VEGFR-2)激活下游信号途径[15-16]。DCBLD2可以通过抑制VE钙黏蛋白、蛋白络氨酸磷酸酶1B和T细胞蛋白络氨酸磷酸酶与VEGFR-2的结合, 促进内皮细胞上VEGFR-2的磷酸化, 从而促进内皮细胞的增殖、迁移并使其渗透性增加。当*DCBLD2*基因被敲除后, 游离的VEGFR-2减少且VEGFR-2去磷酸化增强, VEGF信号活性减弱。此外, 也有研究显示DCBLD2具有调节血小板源性生长因子受体-β(platelet-derived growth factor receptor-β, PDGFR-β)活性的能力[17], 以上研究均提示DCBLD2很有可能成为心血管疾病临床治疗的新靶点。

3 DCBLD2与肿瘤疾病

DCBLD2参与血管重塑等多种生理功能, 血管重塑和血管再生则与肿瘤发生发展及不良预后密切相关。现有研究表明DCBLD2表达上调在胃癌中发挥抑制作用[18], 而在胰腺导管腺癌中, DCBLD2参与抑制细胞免疫和激活致癌信号通路的过程, 发挥癌基因的作用, 是胰腺导管腺癌预后不良的生物标志物[19]。因此, DCBLD2在不同类型的肿瘤中角色不同, 发挥的生物学功能也不同(表1)。

肺癌是全球确诊率最高的癌症, 其中肺腺癌(lung adenocarcinoma, LUAD)约占所有肺癌种类的40%, 临床标准一线治疗LUAD的方案多为含有两种或三种药物的铂类化疗方案。有学者利用生物信息学分析对经顺铂治疗的肺腺癌患者进行研究, 发

表1 DCBLD2的功能

Table 1 Function of DCBLD2

作用 Function	类别 Category
DCBLD2 up-regulation will have a positive effect and inhibit tumor progression	Gastric cancer Melanoma
DCBLD2 up-regulation will have a negative impact and promote the deterioration of tumors	Ductal adenocarcinoma of pancreas Adenocarcinoma of lung Colorectal cancer Hypopharyngeal squamous cell carcinoma Human glioblastoma Lung cancer
DCBLD2 participates in tumor invasion and migration, but the specific mechanism is still unclear	Neuroendocrine carcinoma Thyroid papillary carcinoma Mammary cancer Myxofibrosarcoma

现发生肿瘤远处转移患者体内的DCBLD2含量远高于未发生肿瘤远处转移的患者[20]。该学者又分析了来自TCGA数据库的515例LUAD患者癌组织中*DCBLD2*的mRNA表达情况，发现*DCBLD2*在LUAD组织中广泛上调，这些结果表明*DCBLD2*在肺腺癌中发挥致癌基因的作用。蛋白印迹法和细胞迁移实验不仅表明DCBLD2在顺铂诱导的肺腺癌的上皮–间质转化、迁移和转移中起重要作用，而且还发现DCBLD2可以通过介导糖原合成酶激酶3β(glycogen synthase kinase 3β, GSK3β)的磷酸化而使GSK3β失活并导致β-catenin破坏复合物的分解和β-catenin的稳定，从而促进细胞迁移，这说明在肺腺癌中DCBLD2通过Wnt/β-catenin信号通路促进上皮–间质转化和肿瘤的转移。研究还发现顺铂通过ERK/AP-1轴进一步上调DCBLD2的表达，促进肿瘤转移；综上所述，DCBLD2在顺铂诱导的肺腺癌上皮–间质转化和转移中起关键作用，提示DCBLD2可能是治疗铂类化疗诱导的转移的潜在靶点。

黑色素瘤(melanoma, MEL)是在人类中发现的最具侵袭性和耐药性的癌症之一，有研究已证实DCBLD2蛋白在原位人类黑色素瘤中高度表达，而在侵袭性黑色素瘤中表达下调，与肿瘤厚度增加呈负相关，并且与不良预后相关[21-22]；COPPO等[22]从*DCBLD2*$^{-/-}$和WT小鼠中分离和表征了晶状体上层细胞，并评估了绿色荧光蛋白(green fluorescence protein, GFP)转导的B16-F10细胞在晶状体上层细胞单层上的黏附情况，结果显示小鼠或人类内皮细胞中E-选择素和DCBLD2的表达量之间存在负相关关系，即内皮细胞中DCBLD2的表达量降低有利于黑色素瘤细胞黏附和E-选择素表达上调；生物信息学分析揭示了STAT3(signal transducer and activator of transcription 3)结合位点大多在E-选择素上游。此外还证明了在人脐静脉血管内皮细胞中，当STAT3被抑制时，E-选择素的转录也会减少，从而表明了E-选择素转录与STAT3的激活相关，这可能与细胞因子受体的激活有关。总之，DCBLD2上调后在黑色素瘤中起保护作用，它可以通过抑制STAT3来阻断内皮细胞中E-选择素的表达和肿瘤细胞的黏附从而抑制黑色素瘤的进展。

结直肠癌(colorectal cancer, CRC)是一种高发病率和高死亡率的胃肠道恶性肿瘤，在结直肠癌治疗中5-氟尿嘧啶(5-fluorouracil, 5-FU)是临床推广的一线药物，但由于患者本身的耐药性使其疗效显著降低。XIE等[23]通过体内和体外研究阐明了DCBLD2对结直肠癌恶性程度及5-FU治疗敏感性的影响和机制。通过研究GEO(Gene Expression Omnibus)基因数据库的结直肠癌数据，他们发现*DCBLD2*基因在结直肠癌肿瘤组织中高表达且与预后不良相关。CCK-8细胞增殖实验与克隆形成实验结果表明，DCBLD2可能通过抑制肿瘤细胞增殖来增强CRC细胞对5-FU的敏感性，其中体内和体外实验结果表明，DCBLD2可以促进上皮–间质转化和血管生成，从而促进结直肠癌的发展。此外，DCBLD2还可以与黏着斑(黏着斑是已知调节上皮–间质转化的重要途径)通路的关键信号因子整合素β1结合；换言之，抑制DCBLD2可以抑制CRC细胞的增殖和迁移，增强CRC细胞对5-FU的药物敏感性，这项研究的结果可能有助于开发结直肠癌患者的生物标志物和治疗策略。

黏液纤维肉瘤(myxofibrosarcoma, MFS)是最具有侵袭性的软组织肿瘤之一，其主要的治疗方式为手术切除，但手术切除后存在复发率高、复发后肿瘤细胞的增生与转移能力更强的问题。对于黏液纤维肉瘤的侵入特性临床中主要使用磁共振成像(magnetic resonance imaging, MRI)进行评估，然而其检查结果与组织学检查的范围有一定差距，尤其对于浸润生长的肿瘤，MRI难以确定其生长范围、评估其侵袭潜力。KIKUTA等日本学者[24]利用MRI与二维凝胶电泳在原发MFS肿瘤组织中进行蛋白质谱分析，鉴定了DCBLD2在识别MFS侵袭潜力中的生物标志物作用。结果显示，DCBLD2在MFS的不同肿瘤组织中的表达水平一致，并且其表达对MFS的侵袭特征有着较高的阳性预测水平。虽然该研究中使用的病例样本量较小，但利用免疫组织化学方法研究DCBLD2在组织中的表达情况已经得到了多个实验室的技术认可。上述研究对40余种蛋白质进行了相关分析，发现DCBLD2是MFS中与肿瘤细胞侵袭相关的新因子，其作为MFS预后的生物标志物具有潜在的临床应用价值。

DCBLD2不仅在胰导管腺癌和结直肠癌中扮演着推动癌症发展的负面角色，在其他肿瘤中也发挥同样作用。例如实验表明DCBLD2上调还会诱发下咽鳞状细胞癌、人胶质母细胞瘤和肺癌中癌细胞的增殖和迁移，进而促进癌症的发生发展[25-27]。另外，

XIE等[28]推测DCBLD2可能通过T细胞排斥来逃避免疫杀伤, 从而导致肿瘤的恶化。虽然最新研究显示, DCBLD2作为一种潜在的致癌性、免疫学性和预后性的生物标志物, 在肿瘤靶向治疗和临床观察肿瘤预后的过程中发挥着重要作用, 但是关于DCBLD2在肿瘤和其他疾病中作用的现有证据仍十分有限(表2), 而且DCBLD2的具体生物学作用以及其在肿瘤疾病中的潜在分子机制尚待进一步研究。

表2 DCBLD2与肿瘤

Table 2 DCBLD2 and the tumor

癌症类型 Cancer type	内在机制 Intrinsic mechanism	临床应用 Clinical application	文献 References
Gastric cancer	DCBLD2 expression is significantly down-regulated in gastric cancer tissues, and its promoter region is frequently hypermethylated	DCBLD2 may inhibit the proliferation and invasion of gastric cancer cells and be identified as a novel epigenetic target of gastric cancer	[18]
Ductal adenocarcinoma of pancreas	DCBLD2 up-regulates in PDAC and highly expressed in patient extracellular vesicles, and may inhibit cellular immunity and participate in oncogenic signaling pathways	Play a carcinogenic role as a diagnostic and prognostic biomarker for PDAC	[19]
Adenocarcinoma of lung	DCBLD2 promotes epithelial-to-stromal transition and tumor cell migration in LUAD	Act as an oncogene, blocking *DCBLD2* may play a preventive role in metastasis induced by platinum-based chemotherapy	[20]
Melanoma	DCBLD2 expression is inversely correlated with tumor thickness; DCBLD2 inhibits melanoma development by blocking E-selectin expression and tumor cell adhesion in endothelial cells by inhibiting STAT3	DCBLD2 has a protective role in melanoma dissemination and has therapeutic potential	[21-22]
Colorectal cancer	DCBLD2 up-regulates in CRC, promoting epithelial-stromal transition and angiogenesis, and reducing sensitivity to drugs, which can be used as an independent adverse prognostic factor in CRC	*DCBLD2* may act as an oncogene in CRC and can serve as a prognostic biomarker and a novel therapeutic target in CRC	[23,29]
Myxofibrosarcoma	DCBLD2 is identified as a novel factor associated with tumor cell invasion in MFS	It has potential clinical utility as biomarkers of MFS prognosis	[24]
Hypopharyngeal squamous cell carcinoma	DCBLD2 is up-regulated in HSCC and contributes to the migration and invasion of cancer cells	*DCBLD2* functions as an oncogene, is regulated by miR-451a, and can serve as a target of tumor suppressor miR-451a in HSCC	[25]
Human glioblastoma	The expression of the *DCBLD2* gene is up-regulated in clinical GBM and plays a role in signaling in mediating EGFR-driven tumorigenesis, activating the epithelial-to-stromal transition process to stimulate cancer cell proliferation and metastasis	High expression of DCBLD2 is closely associated with poor prognosis in glioblastoma and can be used as a potential therapeutic target in human cancers associated with EGFR activation	[26,30]
Lung cancer	DCBLD2 up-regulates in highly metastatic lung cancer cells, and may promote the motility and migration of lung cancer cells	May be a therapeutic target to inhibit lung cancer metastasis	[27]
Neuroendocrine carcinoma	*DCBLD2* gene is involved in tumor invasion, progression and metastasis	May become a new tumor diagnostic marker	[31]
Thyroid papillary carcinoma	DCBLD2 is involved in cell proliferation and invasion in PTC, and can target DCBLD2 and AKT1 by up-regulating miR-451a, thus weakens the proliferation and invasion of cancer cells, accelerates cell apoptosis, and reduces vascular endothelial growth factor	PTC can be treated by targeting DCBLD2 in the future, but whether it has a direct effect on PTC cells needs further investigation	[32]
Mammary cancer	DCBLD2 participates in the invasion and migration of breast cancer cells	Can be used as a diagnostic biomarker for the stratification of breast cancer subtypes	[33]

LUAD: 肺腺癌; CRC: 结直肠癌; HSCC: 下咽鳞状细胞癌; PDAC: 胰腺导管腺癌; MFS: 黏液纤维肉瘤; PTC: 甲状腺乳头状癌; GBM: 人胶质母细胞瘤; EGFR: 表皮生长因子受体。

LUAD: lung adenocarcinoma; CRC: colorectal cancer; HSCC: hypoharyngeal squamous cell carcinoma; PDAC: pancreatic ductal adenocarcinoma; MFS: mucofibrosarcoma; PTC: papillary thyroid carcinoma; GBM: human glioblastoma; EGFR: epidermal growth factor receptor.

4 DCBLD2与糖尿病肾病

糖尿病肾病(diabetic nephropathy, DN)是糖尿病最常见且最严重的微血管并发症之一, 常因发病隐匿而被患者忽视, 最终导致肾功能衰竭[34]。其发病机制复杂, 尚未被完全阐明。新的流行病学和临床研究表明其与异常血管生成、糖脂代谢紊乱、氧化应激、血液动力学异常等密切相关[35-36]。其中, 当出现糖脂代谢异常即肾小球内皮细胞(glomerular endothelial cells, GECs)暴露于循环高血糖水平以及发生胰岛素抵抗时, 高血糖可以导致GECs糖代谢饱和, 多元醇通路、己糖胺通路、AGE/RAGE轴和PKC通路等激活, 内源性ROS生产过多, 晚期糖基化终末产物生成, 从而造成GECs功能障碍[37-39]; 同时, 早期DN存在异常的血管生成, 可致肾小球肥大及肾小球毛细血管基底膜增厚[35]。研究显示, 异常血管生成主要与糖尿病状态下GECs上的VEGF/VEGFR等调节血管生成的信号途径被激活有关[40]。

人类蛋白图谱项目(www.proteinatlas.org)的最新数据表明, DCBLD2在肾脏内皮细胞上存在表达。研究显示下调DCBLD2表达后, 细胞表面胰岛素受体的敏感性升高, 细胞内的葡萄糖被加速利用[41], 进而延缓糖尿病肾病所致的内皮细胞损伤。此外, DCBLD2可以通过调控异常血管生成[40], 减轻高血糖导致的早期肾脏损伤。同时还有研究表明, DCBLD2可以通过调节细胞表面多种受体酪氨酸激酶(receptor tyrosine kinases, RTKs)包括VEGFR、PDGF-BB和胰岛素受体(insulin receptor, INSR)[2]的信号转导从而发挥作用。NIE等[12]发现上调人类和小鼠内皮细胞中DCBLD2的表达会显著促进VEGF介导的细胞生长和迁移; LI等[41]发现, 下调DCBLD2表达会提高INSR的敏感性, 改善细胞内的葡萄糖稳态, 这一作用被认为是通过增强INSR泛素化, 并改变INSR调节机制之间的平衡来实现的[2]。SH2B2(SH2B adapter protein 2)是SH2B接头蛋白家族的一个成员, 其C末端SH2结构域可以与酪氨酸磷酸化的蛋白结合, 而胰岛素受体INSR[41]即为酪氨酸受体家族中的一员。Grb10是胰岛素受体的负调控因子, 属于一种与胰岛素受体结合的接头蛋白, *Grb10*基因的敲除增强了人肌肉细胞中胰岛素诱导的PI3K/AKT信号和葡萄糖摄取[42]。研究显示, DCBLD2通过调节胰岛素受体与SH2B2和生长因子受体结合蛋白10(growth factor receptor bound protein 10, Grb10)的相互作用, 调节胰岛素信号转导[41]。研究表明SH2B2可以通过与泛素连接酶c-Cbl(c-casitas B-lineage lymphoma)结合延缓INSR受体的去磷酸化进而促进胰岛素信号转导[41]。但也有研究发现, SH2B2是可以独立于DCBLD2调控胰岛素信号的, 在没有Grb10参与下, DCBLD2是INSR激活所必需的[41]。同时DCBLD2可以作为INSR胞质酪氨酸激酶的支架, 促进INSR酪氨酸磷酸化速率提升、信号传播和INSR下调[2], 上述实验结果均提示DCBLD2可以直接抑制胰岛素信号转导。另外, 有研究表明, DCBLD2表达的缺失可以释放可用的接头蛋白/E3连接酶复合物或其他通常与DCBLD2相互作用的INSR阳性调节因子, 具体来说, 当DCBLD2表达下调时, 可以通过招募INSR的某些正调节因子例如c-Cbl[2,43-44]来调节胰岛素信号通路。这些机制均提示, DCBLD2极有可能成为糖尿病肾病临床治疗的潜在干预靶点。

5 DCBLD2与泛素化调节

多种免疫疾病与泛素化失调密切相关, DCBLD2可以通过调节泛素化过程进而参与细胞增殖、凋亡、自噬、内吞、DNA损伤修复以及免疫应答等[45]各种生理过程。泛素化是指将泛素分子共价结合到靶蛋白上, 是蛋白质组中最普遍的翻译后修饰之一。c-Cbl属于胞质泛素连接酶, 已被认为是PDGFR-β信号的负调节剂, c-Cbl酶的表达即受DCBLD2的调节[46]。研究显示, 在用DCBLD2 siRNA转染的血管平滑肌细胞中, 相比于DCBLD2的降低程度, c-Cbl蛋白水平的降低更为显著。所以, XIAO等[47]得出DCBLD2在PDGF诱导的血管平滑肌细胞信号转导中具有泛素化调节作用。同时, 他们还发现DCBLD2下调增加了PDGF的结合位点的数量, 而细胞表面受体的总表达水平却没有显著变化, 从而提示DCBLD2改变受体泛素化这一可能性。同时, 我们已知盘状蛋白结构域会影响白介素参与的免疫反应[48-49], CDCP1是属于先天免疫补体系统的蛋白质, 这均提示DCBLD2可能与免疫性疾病密切相关。

6 总结与展望

*DCBLD2*基因的过表达和敲除研究揭露了DCBLD2发挥的调节血管内皮细胞迁移和增殖的作用及其与常见心血管疾病的关系。许多研究表明, DCBLD2在肿瘤细胞中存在表达上调或下调的现象, 而在不同肿瘤中DCBLD2的作用不具有一致性[18-20,22], 因此, 造成DCBLD2在不同类型肿瘤中作用存在差异性的本质还有待进一步研究。另外, 虽然有证据证明

下调DCBLD2可以加速细胞内的葡萄糖利用, 但是其具体的作用机制尚未被阐释清楚。而对肾小球内皮细胞上的RTKs途径的研究可能有助于对糖尿病肾病的发病机制进行进一步的揭示。

目前, 对于DCBLD2的结构和生物学功能的研究正在不断完善, 但是异常表达的DCBLD2造成多种疾病的发病机制尚不清楚, 未来对DCBLD2和DCBLD家族其他成员的研究将为临床上揭示相关疾病的发病机制以及寻找治疗靶点提供新的思路。

参考文献 (References)

[1] KOBUKE K, FURUKAWA Y, SUGAI M, et al. ESDN, a novel neuropilin-like membrane protein cloned from vascular cells with the longest secretory signal sequence among eukaryotes, is up-regulated after vascular injury [J]. J Biol Chem, 2001, 276(36): 34105-14.

[2] SCHMOKER A M, EBERT A M, BALLIF B A. The DCBLD receptor family: emerging signaling roles in development, homeostasis and disease [J]. Biochem J, 2019, 476(6): 931-50.

[3] KOSHIKAWA K, OSADA H, KOZAKI K, et al. Significant up-regulation of a novel gene, CLCP1, in a highly metastatic lung cancer subline as well as in lung cancers *in vivo* [J]. Oncogene, 2002, 21(18): 2822-8.

[4] RESCH E, HISS J A, SCHREINER A, et al. Long signal peptides of RGMa and DCBLD2 are dissectible into subdomains according to the NtraC model [J]. Mol Biosyst, 2011, 7(3): 942-51.

[5] ALHAMOUDI K M, BARHOUMI T, AL-EIDI H, et al. A homozygous nonsense mutation in DCBLD2 is a candidate cause of developmental delay, dysmorphic features and restrictive cardiomyopathy [J]. Sci Rep, 2021, 11(1): 12861.

[6] HUANG Y, HUI K M, REN Q. Expression and functional characterization of the CUB domain-containing protein from the triangle sail mussel (*Hyriopsis cumingii*) in response to pathogenic infection [J]. Comp Biochem Physiol B Biochem Mol Biol, 2021, 251: 110521.

[7] PREDES D, CRUZ J V R, ABREU J G, et al. CUB domain-containing protein 1 (CDCP1) bindstransforming growth factor beta family members and increase TGF-β1 signaling pathway [J]. Exp Cell Res, 2019, 383(1): 111499.

[8] 陈力, 朱梦柳, 孔祥溢, 等. 盘状蛋白结构域受体1在乳腺癌及其他恶性肿瘤中的研究进展[J]. 中国医学科学院学报(CHEN L, ZHU M L, KONG X Y, et al. Research progress of discoidin domain receptor 1 in breast cancer and other malignant tumors [J]. Acta Academiae Medicinae Sinicae), 2021, 43(4): 634-41.

[9] GIMBRONE M A JR, GARCÍA-CARDEÑA G. Endothelial cell dysfunction and the pathobiology of atherosclerosis [J]. Circ Res, 2016, 118(4): 620-36.

[10] 贡悦, 王齐松, 王凡轲, 等. 跨膜蛋白ESDN的表达与血管内膜增生的初步研究[J]. 河北医科大学学报(GONG Y, WANG Q S, WANG F K, et al. The preliminary study on correlation between transmembrane protein ESDN and vascular hyperplasia [J]. Journal of Hebei Medical University), 2019, 40(7): 753-7,98.

[11] SADEGHI M M, ESMAILZADEH L, ZHANG J, et al. ESDN is a marker of vascular remodeling and regulator of cell proliferation in graft arteriosclerosis [J]. Am J Transplant, 2007, 7(9): 2098-105.

[12] NIE L, GUO X, ESMAILZADEH L, et al. Transmembrane protein ESDN promotes endothelial VEGF signaling and regulates angiogenesis [J]. J Clin Invest, 2013, 123(12): 5082-97.

[13] CHINTANAPHOL M, ORGIL B O, ALBERSON N R, et al. Restrictive cardiomyopathy: from genetics and clinical overview to animal modeling [J]. Rev Cardiovasc Med, 2022, 23(3): 108.

[14] RASMUSSEN H S, RASMUSSEN C S, MACKO J. VEGF gene therapy for coronary artery disease and peripheral vascular disease [J]. Cardiovasc Radiat Med, 2002, 3(2): 114-7.

[15] KOCH S, TUGUES S, LI X, et al. Signal transduction by vascular endothelial growth factor receptors [J]. Biochem J, 2011, 437(2): 169-83.

[16] SIMONS M, GORDON E, CLAESSON-WELSH L. Mechanisms and regulation of endothelialVEGF receptor signalling [J]. Nat Rev Mol Cell Biol, 2016, 17(10): 611-25.

[17] WANG S, LIU X, MENG Z, et al. DCBLD2 regulates vascular hyperplasia by modulating the platelet derived growth factor receptor-β endocytosis through Caveolin-1 in vascular smooth muscle cells [J]. Faseb J, 2022, 36(9): e22488.

[18] KIM M, LEE K T, JANG H R, et al. Epigenetic -regulation and suppressive role of DCBLD2 in gastric cancer cell proliferation and invasion [J]. Mol Cancer Res, 2008, 6(2): 222-30.

[19] FENG Z, LI K, WU Y, et al. Transcriptomic profiling identifies DCBLD2 as a diagnostic and prognostic biomarker in pancreatic ductal adenocarcinoma [J]. Front Mol Biosci, 2021, 8: 659168.

[20] CHEN X, LÜ Y, XU K, et al. DCBLD2 mediates epithelial-mesenchymal transition-induced metastasis by cisplatin in lung adenocarcinoma [J]. Cancers, 2021, 13(6): 1403.

[21] OSELLA-ABATE S, NOVELLI M, QUAGLINO P, et al. Expression of AP-2α, AP-2γ and ESDN in primary melanomas: correlation with histopathological features and potential prognostic value [J]. J Dermatol Sci, 2012, 68(3): 202-4.

[22] COPPO R, ORSO F, VIRGA F, et al. ESDN inhibits melanoma progression by blocking E-selectin expression in endothelial cells via STAT3 [J]. Cancer Lett, 2021, 510: 13-23.

[23] XIE P, YUAN F Q, HUANG M S, et al. DCBLD2 affects the development of colorectal cancer via EMT and angiogenesis and modulates 5-FU drug resistance [J]. Front Cell Dev Biol, 2021, 9: 669285.

[24] KIKUTA K, KUBOTA D, YOSHIDA A, et al. Discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2) is a novel biomarker of myxofibrosarcoma invasion identified by global protein expression profiling [J]. Biochim Biophys Acta Proteins Proteom, 2017, 1865(9): 1160-6.

[25] FUKUMOTO I, KINOSHITA T, HANAZAWA T, et al. Identification of tumour suppressive microRNA-451a in hypopharyngeal squamous cell carcinoma based on microRNA expression signature [J]. Br J Cancer, 2014, 111(2): 386-94.

[26] CHENG S, WANG L Y, WANG C H, et al. Transmembrane protein DCBLD2 is correlated with poor prognosis and affects phenotype by regulating epithelial-mesenchymal transition in human glioblastoma cells [J]. Neuroreport, 2021, 32(6): 507-17.

[27] NAGAI H, SUGITO N, MATSUBARA H, et al. CLCP1 interacts with semaphorin 4B and regulates motility of lung cancer cells [J].

Oncogene, 2007, 26(27): 4025-31.
[28] XIE P, LIU J Y, YAN H, et al. Pan-cancer analyses identify DCBLD2 as an oncogenic, immunological, and prognostic biomarker [J]. Front Pharmacol, 2022, 13: 950831.
[29] HE J, HUANG H, DU Y, et al. Association of DCBLD2 upregulation with tumor progression and poor survival in colorectal cancer [J]. Cell Oncol, 2020, 43(3): 409-20.
[30] FENG H, LOPEZ G Y, KIM C K, et al. EGFRphosphorylation of DCBLD2 recruits TRAF6 and stimulates AKT-promoted tumorigenesis [J]. J Clin Invest, 2014, 124(9): 3741-56.
[31] HOFSLI E, WHEELER T E, LANGAAS M, et al. Identification of novel neuroendocrine-specific tumour genes [J]. Br J Cancer, 2008, 99(8): 1330-9.
[32] TAN J, LI C, REN L, et al. miR-451a suppresses papillary thyroid cancer cell proliferation and invasion and facilitates apoptosis through targeting DCBLD2 and AKT1 [J]. Mol Cell Probes, 2022, 66: 101863.
[33] MOTIEGHADER H, MASOUDI-SOBHANZADEH Y, ASHTIANI S H, et al. mRNA and microRNA selection for breast cancer molecular subtype stratification using meta-heuristic based algorithms [J]. Genomics, 2020, 112(5): 3207-17.
[34] 马锋锋, 范增慧. 糖尿病肾病中医病因病机研究进展[J]. 中国中医基础医学杂志(MA F F, FAN Z H. Research progress on etiology and pathogenesis of diabetic nephropathy in Chinese medicine [J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine), 2022, 28(8): 1373-7.
[35] 陈碧霞, 张利, 吴玲玲, 等. 糖尿病肾病内皮细胞损伤机制的研究进展[J]. 解放军医学杂志(CHEN B X, ZHANG L, WU L L, et al. Research progress on the mechanism of endothelial cells injury in diabetic nephropathy [J]. Medical Journal of Chinese People's Liberation Army), 2020, 45(8): 876-83.
[36] REN L, CUI H, WANG Y, et al. The role of lipotoxicity in kidney disease: from molecular mechanisms to therapeutic prospects [J]. Biomed Pharmacother, 2023, 161: 114465.
[37] LASSÉN E, DAEHN I S. Molecular mechanisms in early diabetic kidney disease: glomerular endothelial cell dysfunction [J]. Int J Mol Sci, 2020, 21(24): 9456.
[38] DOU L, JOURDE-CHICHE N. Endothelial toxicity of high glucose and its by-products in diabetic kidney disease [J]. Toxins, 2019, 11(10): 578.
[39] YING L, LI N, HE Z, et al. Fibroblast growth factor 21 ameliorates diabetes-induced endothelial dysfunction in mouse aorta via activation of the CaMKK2/AMPKα signaling pathway [J]. Cell Death Dis, 2019, 10(9): 665.
[40] PANDEY A K, SINGHI E K, ARROYO J P, et al. Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease [J]. Hypertension, 2018, 71(2): e1-e8.
[41] LI X, JUNG J J, NIE L, et al. The neuropilin-like protein ESDN regulates insulin signaling and sensitivity [J]. Am J Physiol Heart Circ Physiol, 2016, 310(9): H1184-93.
[42] EDICK A M, AUCLAIR O, BURGOS S A. Role of Grb10 in mTORC1-dependent regulation of insulin signaling and action in human skeletalmuscle cells [J]. Am J Physiol Endocrinol Metab, 2020, 318(2): E173-e83.
[43] LIU J, DEYOUNG S M, HWANG J B, et al. The roles of Cbl-b and c-Cbl in insulin-stimulated glucose transport [J]. J Biol Chem, 2003, 278(38): 36754-62.
[44] LIU J, KIMURA A, BAUMANN C A, et al. APS facilitates c-Cbl tyrosine phosphorylation and GLUT4 translocation in response to insulin in 3T3-L1 adipocytes [J]. Mol Cell Biol, 2002, 22(11): 3599-609.
[45] 王翔, 魏潇凡, 张宏权. 泛素化的功能及其意义[J]. 中国科学: 生命科学(WANG X, WEI X F, ZHANG H Q. Role of protein ubiquitination and its functional importance [J]. Science China, Life Sciences), 2015, 45(11): 1074-82.
[46] JOAZEIRO C A, WING S S, HUANG H, et al. The t yrosine kinase negative regulator c-Cbl as a RING-type, E2-dependent ubiquitin-protein ligase [J]. Science, 1999, 286(5438): 309-12.
[47] GUO X, NIE L, ESMAILZADEH L, et al. Endothelial and smooth muscle-derived neuropilin-like protein regulates platelet-derived growth factor signaling in human vascular smooth muscle cells by modulating receptor ubiquitination [J]. J Biol Chem, 2009, 284(43): 29376-82.
[48] KLATT A R, ZECH D, KÜHN G, et al. Discoidin domain receptor 2 mediates the collagen II-dependent release of interleukin-6 in primary human chondrocytes [J]. J Pathol, 2009, 218(2): 241-7.
[49] MATSUYAMA W, WANG L, FARRAR W L, et al. Activation of discoidin domain receptor 1 isoform b with collagen up-regulates chemokine production in human macrophages: role of p38 mitogen-activated protein kinase and NF-kappa B [J]. J Immunol, 2004, 172(4): 2332-40.