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·综 述·

糖脂代谢异常与肿瘤发生发展的相关性

Correlation between abnormal glucose and lipid metabolism and occurrence and development of cancers

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[摘 要] 流行病学研究表明，糖尿病患者中肿瘤的发病风险显著提高，但两者的相关性及发生机制尚未完全阐明。有文献报道，个体的能量稳态、糖脂类代谢、炎症反应等在糖尿病相关肿瘤的发生和进展中发挥了重要作用。本文从糖脂代谢异常、相关信号通路基因表达异常对肿瘤发生发展的影响及其作用机制等方面进行综述，期望为与糖尿病相关肿瘤发生的预防和治疗提供相关依据。

[关键词] 糖脂代谢；肿瘤；高血糖；胰岛素；相关性

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随着人类生活方式的转变，糖尿病和糖脂代谢异常导致的相关疾病发生率在世界范围内逐渐上升，已成为影响人类生命健康的主要问题之一[1-2]。随着糖尿病和肿瘤研究的深入发展，糖脂代谢异常和肿瘤发生的相关性得到了广泛关注。最新的循证医学数据[3-5]显示，糖尿病、糖脂代谢障碍与许多恶性肿瘤的发生有较密切的关系，但是其发生机制尚不清楚。本文综述了糖尿病患者糖脂代谢通路相关基因表达异常对肿瘤发生发展的影响方面的最新研究，将为糖尿病和肿瘤的防治提供相关依据。

1 糖代谢异常与肿瘤的发生发展

有研究[6-9]显示，与非糖尿病组相比，糖尿病患者罹患多种肿瘤的风险增加。如其胃癌风险会增加20%,2型糖尿病患者组患结肠直肠癌(colorectal cancer，CRC)的风险要高27%，罹患肝癌的风险增加2倍，而空腹血糖每增加0.56 mmol/L会导致胰腺癌发生率增加14%。除消化道肿瘤外，糖尿病患者的性激素依赖性肿瘤发病风险也会增加，如糖尿病妇女罹患子宫内膜癌(endometrial cancer，EC)的风险较正常人增加3倍[10]；而患2型糖尿病超过1年的男性患者患前列腺癌的风险比非2型糖尿病男性低(*HR*=0.85)[11]。此外，2型糖尿病和葡萄糖耐量下降会使乳腺癌的预后变差[12]。

己糖激酶(hexokinase，HK)、磷酸果糖激酶(phosphofructokinase，PFK)和丙酮酸激酶(pyruvate kinase，PK)都是糖酵解过程中的关键酶。有研究[13]表明，HK-II的高表达水平与肿瘤的大小、侵袭成度、转移和TNM分期显著相关，同时也与复发率和总体死亡率的增加明显相关。而黄酮类化合物Gen-27可以通过抑制乳腺癌细胞中HK-II的表达来抑制糖酵解和诱导细胞的凋亡[14]。此外，使用PFK抑制剂能显著降低糖酵解水平，进而抑制膀胱癌细胞的生长和侵袭[15]。SHIROKI等[16]研究表明，PK的M2型同工酶(PKM2)在癌组织中的表达显著增高，抑制胃癌细胞中的PKM2的表达则能显著降低细胞的增殖、迁移和肝转移能力。

2 糖代谢异常与肿瘤发生发展的相关机制

2.1 高胰岛素血症

有研究[17-19]显示，高胰岛素血症患者的癌症死亡率显著高于非高胰岛素血症患者，如高胰岛素水平(空腹胰岛素水平>6.10 μU/ml)的人患前列腺癌的概率会增

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加2.55倍，高胰岛素血症还可通过增强由IL-17引起的下游促炎基因的表达增加导致前列腺癌侵袭性增强。另外，高胰岛素血症是促进乳腺癌的生长、转移、侵袭、复发和死亡率增加的重要因素[20]，其可通过增加胰岛素受体/胰岛素样生长因子-I-受体的活化以及激活PI3K)/AKT/ mTOR（雷帕霉素靶蛋白）通路加快乳腺癌的进展[21]。高胰岛素血症通过促进血管生成是导致结直肠癌的生长加速的重要原因之一[22]。

2.2　高血糖

高血糖增加肿瘤发生的机制包括促进肿瘤细胞增殖、侵袭与迁移，诱导生长因子和炎症细胞因子的产生，进而影响肿瘤的发展过程[23]。过量的葡萄糖能够促进晚期糖基化终末产物(advanced glycationend products，AGEs)的形成和积累，导致ROS的生成增加，进一步引起各种细胞成分的损伤[23]。其中DNA的损伤则可以影响与细胞增殖和凋亡有关的基因（如p53和Ras），进而引发肿瘤的形成。研究[24]表明，高血糖症可通过激活细胞外调节蛋白激酶（extracellular regulated protein kinases，ERK）和AKT通路促进MCF-7乳腺癌细胞的增殖、侵袭和迁移。此外，高血糖还可能通过活化ERK和p38 MAPK（mitogen-activated protein kinase，丝裂原活化蛋白激酶）信号通路，进而促进EMT的表达，增强胰腺癌细胞的迁移和侵袭能力，使胰腺癌恶化[25]。高血糖状态还可通过己糖胺生物合成途径（hexosamine biosynthesis pathway，HBP）诱导结肠癌细胞异常糖基化、增殖和侵袭[26]；而随着血糖浓度的增加（10~30 mmol/L），CT-26结肠癌细胞的迁移和侵袭能力也逐渐增强，这种情况与STAT3诱导的基质金属蛋白酶-9（matrix metalloproteinase-9，MMP-9）信号通路表达增强相关[27]。另外，高血糖状态还能够降低胃癌细胞对化学药物的敏感性并促进其增殖[28]。

2.3　慢性炎症

高血糖导致不同器官的慢性炎症在糖尿病患者中非常普遍。有证据[23,29-31]表明，持续的炎症会增加遗传的不稳定性和肿瘤的风险，而慢性炎症与高水平的肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）具有关联性。TNF-α可激活MAPK和NF-κB信号通路；其中NF-κB不仅能促进恶性细胞的增殖、抑制其凋亡从而提高恶性细胞的存活率，还能促进血管新生和转移并介导激素和/或化疗药物的反应[23,32]。

3 糖脂代谢相关细胞因子表达异常与肿瘤的发生发展

3.1　脂联素

研究[33]显示，脂联素可以通过激活多种信号通路影响肿瘤的发生发展,低剂量的脂联素能够抑制细胞外信号调节激酶（ERK1/2）信号并且减弱乳腺癌细胞的细胞活力。脂联素还可通过下调c-Myc、细胞周期蛋白D和Bcl-2水平诱导细胞周期阻滞以及通过增加p53、p21和Bax的表达来诱导细胞凋亡。在乳腺癌细胞中，脂联素能降低PI3K/AKT的磷酸化，诱导AMP依赖的蛋白激酶（adenosine 5'-monophosphate-activated protein kinase，AMPK）活化，进而负相调节蛋白质合成和细胞增殖。AMPK是脂联素作用的关键分子，抑制LKB1/AMPK信号通路能够增强结肠癌细胞的存活能力[34]。另有研究[35]发现，卵巢癌患者血清的脂联素与瘦素的水平均明显低于对照组。低循环脂联素水平增加EC的风险，而绝经后妇女的高脂联素水平能够降低这个风险[36]。

3.2　瘦素

血清瘦素水平在不同肿瘤中的表达是不一致的，如血清瘦素水平在乳腺癌患者中表达明显升高[37]，而在肺癌患者[38]和卵巢癌患者[35]中表达下降。瘦素能够以时间和剂量依赖的方式上调尿激酶纤维蛋白溶酶原激活剂（uPA），从而诱导卵巢癌细胞侵袭[39]。而阻断瘦素可以显著地抑制卵巢恶性腹水引起的癌细胞转移性恶化。TONG等[40]的Meta分析显示，瘦素在组织中的高表达水平和肺癌之间有显著相关性。同时，高水平的血浆瘦素也与男性胰腺癌的风险升高有关[41];瘦素-Notch轴参与了胰腺癌的发生发展过程[42]。瘦素不仅能够加速细胞周期和增加细胞增殖，还能增加Notch受体、配体、靶向分子（Notch1-4，DLL4，JAG1，Survivin和Hey2）以及胰腺癌干细胞（pancreatic carcinoma stem cell，PCSC）标志（CD24/CD44/ESA、ALDH、CD133、Oct-4）和ABCB1蛋白等多种分子的表达，从而促进肿瘤的形成和发展。

3.3　网膜素

有研究[1]显示，前列腺癌、结肠癌、肝癌、结肠直肠癌与血清网膜素intelectin-1（ITLN-1）水平异常相关，而这种情况独立于BMI、血糖和血脂等因素。KARABULUT等[43]的研究发现，胰腺癌患者的血清网膜素水平显著升高，其在肿瘤尺寸≥4 cm的胰腺癌患者中的表达水平明显高于肿瘤尺寸小的患者，网膜素促进肿瘤生长的作用可能与激活PI3K/AKT（磷脂酰肌醇-3激酶的下游效应）信号通路有关。而SHEN等[44]的研究发现，肾细胞癌患者ITLN-1水平显著下降。高水平的ITLN-1能够显著改善胃癌患者的预后，ITLN-1可能够通过上调肝细胞核因子4α（hepatocyte nuclear factor 4α，HNF4α），抑制胃癌细胞内β-链蛋白的核转位与转录活性，从而抑制胃癌的进展[45]。MAEDA等[46]的研究显示，ITLN-1的下调与晚期结直肠癌的不良预后有关，其中穿膜蛋白

TMEM207的低表达能够导致ITLN-1形成不足，进而促进直肠结肠癌的发生。另有研究[47]表明，ITLN-1能够通过上调人肝细胞癌中的p21蛋白进而增加肿瘤抑制基因p53蛋白，抑制肝细胞癌的增殖。

3.4 趋化素

XU等[48]研究发现，非小细胞肺癌患者的血清趋化素水平显著升高，并与晚期TNM分期、淋巴结转移及远处器官转移相关。胃癌患者血浆中的趋化素水平明显高于健康对照，趋化素能够增加胃癌细胞的侵袭性，并通过诱导p38和ERK1/2 MAPK磷酸化，上调VEGF、MMP-7和IL-6，促进肿瘤侵袭和转移[49-50]。同时，这个过程能够通过抑制ERK1/2的磷酸化来阻止或消除趋化素增加导致的侵袭效果。KUMAR等[51]的研究表明，食管鳞状细胞癌肌成纤维细胞可以释放趋化素，进而刺激癌细胞的侵袭，而这一过程可以被趋化素受体拮抗剂CCX832所抑制。

3.5 抵抗素

GONG等[52]的研究显示，高抵抗素水平与肥胖相关的癌症风险增加有关。ILHAN等[53]的研究表明，EC患者的高抵抗素水平与淋巴结转移增加有关，提示血清抵抗素水平可用于预测EC晚期病变的风险。然而，GEORGIOU等[54]的研究却发现，乳腺癌绝经前患者抵抗素水平下降。其中，抵抗素与乳腺导管内癌风险的降低有关联，而这种现象只在绝经前妇女中发现，提示抵抗素对于绝经前女性的肿瘤发生可能是一个保护因素。DESHMUKH等[55]的研究表明，抵抗素能增强STAT3的表达和磷酸化进而促进BC细胞的生长和侵袭。而在使用抵抗素刺激前运用IL-6来处理BC细胞能够阻止STAT3的磷酸化。另外，LEE等[56]的研究发现，抵抗素主要通过增加c-Src、蛋白激酶Cα（protein kinase Cα，PKCα）和埃兹蛋白的磷酸化以及增加波形蛋白的表达来促进乳腺癌的侵袭。

3.6 内脂素

有研究[33,57]表明，乳腺癌患者的高血清内脂素与乳腺癌病人的不良预后有关，并且可能作为乳腺癌的预后标志物。EC患者高水平的内脂素与肌层浸润风险相关，内脂素能够通过IR以及PI3K/AKT和MAPK/ERK信号的激活来促进EC的恶性发展[53,58-59]。另外，NSCLC患者血浆内脂素水平高于健康人群，高水平的血浆内脂素与TNM分期、淋巴结转移及远处转移有关[60]。CHEN等[61]的研究结果显示，在晚期和早期的CRC患者中，内脂素水平均高于对照组，提示高水平血浆内脂素可能是CRC检测的潜在生物标志物。内脂素可以通过c-Abl和STAT3的活化来促进乳腺癌的发展，而这一过程可以被伊马替尼（c-Abl抑制剂）和stattic（STAT3抑制剂）抑制[62]。内脂素-Notch1轴还可通过对NF-κB通路的激活来促进乳腺癌的生长[63]。来源于腹水的内脂素能够通过Rho/ROCK信号介导的肌动蛋白聚合来促进卵巢癌细胞的迁移[64]。此外，内脂素可以通过NF-κB/Snail-1/EMT通路来增强骨肉瘤细胞的迁移和侵袭[65]。

4 结 语

综上所述，糖脂代谢与肿瘤的关系仍有许多方面值得进一步探索。目前的证据已经表明糖脂代谢异常会导致胰腺癌、肝癌、乳腺癌、结肠直肠癌、胃癌和女性生殖系统癌症的发病风险增加。尤其是多种脂肪细胞因子与肿瘤发生有较密切的关系，如脂联素、网膜素与多种肿瘤发生呈负相关，而瘦素、趋化素、抵抗素和内脂素与多数肿瘤发生呈正相关。通过对糖尿病和糖脂代谢障碍的致癌机制的进一步研究，将会发现更多共同的信号通路，为新药物的研发和糖尿病患者的癌症防治提供更多的理论依据。

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