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评 述

对葡萄糖转运蛋白GLUT5的分子见解

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摘要 葡萄糖转运蛋白5(glucose transporter 5, GLUT5)是人体唯一特异性转运果糖的膜转运蛋白, 其主要在小肠上皮细胞表达, 在膳食果糖摄取、代谢过程中有至关重要的作用. 近年来, 随着生活水平的不断提升, 全球人均果糖摄入量急剧增加, 由此导致的肥胖和代谢疾病也逐渐增多. 由于GLUT5在膳食果糖吸收和代谢中具有关键作用, 其与人类疾病的关系研究正受到越来越多的关注. 越来越多的证据表明, 从消化系统疾病到多种人类癌症, GLUT5都发挥了不可忽视的作用. 然而, 受限于各种困难和缺陷, GLUT5的分子结构研究尚未得到完全阐明. 深入揭示GLUT5分子结构及其生物学功能将有助于人们更好地理解GLUT5相关疾病的发生机制, 有利于设计针对性更强的靶向治疗药物. 本文主要介绍了哺乳动物GLUT5的分子结构和转运机制研究现状, 从最基础的分子生物学角度出发, 展望GLUT5的潜在应用价值, 以期能够为果糖代谢相关疾病的临床治疗提供更好的策略.

关键词 GLUT5, 果糖, 代谢疾病

GLUTs属于溶质载体2A(solute carrier 2A, *SLC2A*)基因家族成员, 目前在哺乳动物中共鉴定出14个成员: GLUT1~14, 均由*SLC2A*基因编码[1]. 根据序列相似性和底物特异性, 可以将GLUTs划分为三大类: Ⅰ类包括GLUT1~4和GLUT14; Ⅱ类包括GLUT5, 7, 9和11; Ⅲ类包括GLUT6, 8, 10, 12和13(HMIT1)[2]. 几乎所有的GLUTs都可以介导葡萄糖或果糖的易化扩散(被动转运), 只有GLUT13(HMIT1)例外, 它介导质子-肌醇同向主动转运[3]. 在14个成员中, 共有七个成员可以转运果糖, 但只有GLUT5是唯一特异性转运果糖的转运蛋白, 其编码基因为*SLC2A5*(1p36.23), 最初是从人类小肠cDNA文库中克隆得到[4]. 人GLUT5对果糖具有高度亲和力(K_m=6 mmol/L), 对葡萄糖和半乳糖没有运输活性.

在过去的几十年中, 由于制糖生产工艺的改进和扩展, 含有高浓度果糖的高果糖玉米糖浆(high fructose corn syrup)在全世界得到广泛应用[5]. 高果糖饮食与Ⅱ型糖尿病、高血压、高尿酸血症、肥胖、非酒精性脂肪肝和心血管疾病风险增加有关[6~9], 并且还会对动物大脑功能产生影响[10]. 世界卫生组织公布的数据显示, 全球约13%的成年人处于肥胖状态[11]. 更重要的是, 高果糖饮食不仅增加了人群代谢疾病的发生风险, 也给发展中国家带来了沉重的医疗和经济负担. 从分子水平看, 这些果糖代谢相关疾病的发生往往与

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GLUT5表达水平变化有密切联系[12,13]. 此外, 果糖不仅是机体代谢能量来源, 还可能作为信号分子参与某些生物活动的调节[14]. 因此, 深入描述人体唯一特异性转运果糖的转运蛋白GLUT5的分子结构、底物转运机制及其在细胞果糖代谢过程中的具体作用具有重要意义.

1　膳食果糖代谢中的GLUT5

人体摄入的果糖是如何从肠腔进入血液循环并最终到达肝脏等各种组织器官的呢? 膳食果糖代谢从小肠吸收开始. 食物中的果糖会导致肠腔内果糖浓度升高, 从而推动果糖跨膜转运, 并且在GLUT5的K_m值附近波动[15]. 新合成的GLUT5在高尔基体加工成熟后, 在胞质Ras相关蛋白Rab11a介导形成的循环内体协助下运输至小肠上皮细胞顶端膜和基底外侧膜上. Rab11a是一种小GTP酶, 在顶端膜蛋白的运输过程中起关键作用[16,17]. 果糖经由GLUT5从肠腔易化扩散至上皮细胞内, 然后大部分经由基底侧膜上的GLUT2而不是GLUT5转运至胞外并进入循环, 小部分被胞质中的酮己糖激酶(ketohexokinase, KHK)磷酸化为果糖-1-磷酸(fructose-1-phosphate, F-1-P), 这不仅有利于保持从肠腔到胞质的果糖浓度梯度, 而且后续反应产物可刺激核内*SLC2A5*的转录和GLUT5 mRNA翻译(图1), 有利于胞膜持续转运果糖[18]. 进入循环的果糖经门静脉入肝, 在这里, 大部分果糖被代谢, 这也使得血清果糖水平始终维持在低水平状态[19]. 值得注意的是, 在生理情况下肝细胞膜上GLUT5表达水平较低, 主要通过GLUT2转运果糖. 可能还有GLUT8参与了果糖的肝细胞摄取[20], 但是GLUT8主要定位于细胞内部的内体和溶酶体上, 主要参与果糖在细胞内不同区室之间的转运[21,22]. 进入肝细胞的果糖由KHK催化形成F-1-P. F-1-P被醛缩酶B(aldolase B)水解为甘油醛(glyceraldehyde, GA)和磷酸二羟丙酮 (dihydroxyacetone phosphate, DHAP), 醛缩酶B的缺乏会导致遗传性果糖不耐受. GA进一步磷酸化产生3-磷酸甘油醛(glyceraldehyde-3-phosphate, GA-3-P). DHAP和GA-3-P这两种中间体都可以直接进入糖酵解途径进一步代谢, 或生成丙酮酸进入三羧酸(tricarboxylic acid, TCA)循环, 或转化为糖原, 或通过磷酸戊糖途径(pentose phosphate pathway)转化为磷酸丙糖. 果糖也可以被肝细胞内的己糖激酶(hexokinase)直接磷酸化为6-磷酸果糖(fructose-6-phosphate, F-6-P). 然而, 己糖激酶对果糖的亲和力远小于葡萄糖, 因此在肝脏中形成的F-6-P很少, 同时高水平的葡萄糖也会竞争性抑制果糖磷酸化. 小肠上皮细胞以类似的方式代谢约12%的果糖[23].

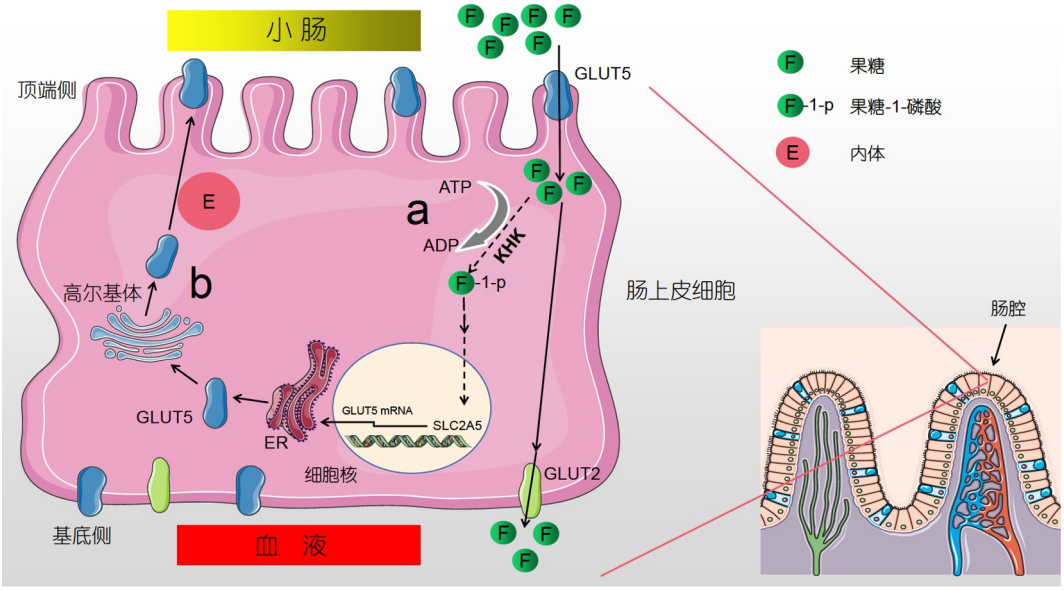

图 1　膳食果糖的肠道吸收过程
Figure 1　Intestinal absorption of dietary fructose

肝脏的首过代谢作用使其成为人体果糖代谢的主要场所, 但有观点认为, 内脏器官在个体果糖代谢中的重要性与其器官大小有关[24]. 另外, 不同的物种之间, 果糖在肝脏和肠道的代谢比也有所不同[25]. 但毫无疑问的是, 不论哪种代谢途径占优, GLUT5表达都是影响整个果糖代谢途径的首要因素.

2 哺乳动物GLUT5的生理性表达

每种GLUT蛋白都表现出独特的组织分布模式和基因调控. 人GLUT5主要在小肠上皮细胞顶端膜和基底外侧膜上高表达[26], 在肾脏、脂肪组织、精子、肌肉和大脑等细胞和器官中以较低水平表达[27,28]. 人GLUT5的生理性表达和活性在近端十二指肠最高, 沿小肠由近及远逐渐降低[29]. 但在反刍动物牛中, GLUT5 mRNA在肾脏和肝脏中含量最丰富[30]. 人和大鼠肠道GLUT5在出生时几乎不表达, 整个哺乳期(大鼠为0~14天)和断奶期(大鼠为14~28天)仅低水平表达, 断奶完成(大鼠为>28天)之后GLUT5 mRNA水平和活性显著增加[31]. 令人难以置信的是, 新生大鼠0~14天期间对果糖不敏感(具体原因尚未阐明), 给予果糖喂食并不能诱导小肠GLUT5表达, 只有14日龄以上大鼠才会对肠腔果糖刺激产生反应[32]. 那么, 是哪些因素导致了不同发育时期的肠道GLUT5表达差异呢? 研究显示, 新生大鼠和新生儿的肠道细胞果糖反应受到了糖皮质激素的调节[33,34]. 使用糖皮质激素类似物地塞米松人为刺激肠道, 可以显著、快速增加哺乳期幼崽肠道GLUT5表达[34]. 另外, 在GLUT5的−338/−272 bp启动子区域中存在甲状腺激素反应元件, 这意味着甲状腺激素很有可能参与了对GLUT5生理性表达的调节[35,36]. 值得注意的是, 成年大鼠GLUT5表达还表现出明显的昼夜节律, 并且与果糖的摄入无关[37]. 膳食果糖诱导的GLUT5表达是由碳水化合物反应元件结合蛋白(carbohydrate-responsive element-binding protein, ChREBP)介导的, 这是一种在肠上皮细胞中高表达的转录因子. 高果糖喂食全身或肠道特异性敲除*ChREBP*小鼠不能诱导GLUT5表达, 并且在一周内表现出吸收不良综合征[38]. 此外, *SLC2A5*敲除小鼠能够正常存活并且生育, 但给予高果糖饮食后, 这些小鼠也表现出低血压和吸收不良综合征(腹泻、肠膨胀)[39].

令人惊讶的是, 即便是体外培养的原代肠细胞也能够被果糖诱导表达GLUT5[40], 这说明GLUT5的营养感应是稳定的. 将果糖溶液灌入成年野生型小鼠肠腔, 观察到GLUT5 mRNA、蛋白质和活性水平增加了2~10倍, 然而在小肠黏膜靶向缺失Rab11a的小鼠, 果糖喂食不能诱导小肠中GLUT5表达, 这表明Rab11a对于GLUT5的表达不可或缺[41].

3 哺乳动物GLUT5的结构

GLUTs转运蛋白属于主要促进因子超家族(major facilitator superfamily, MFS)中的糖转运蛋白亚家族. MFS超家族成员的一个共同结构特征是MFS折叠结构. GLUT5具有一个典型的MFS折叠结构: 12个疏水跨膜α-螺旋(transmembrane helice, TM)构成了4个三聚体亚结构, 这些三聚体再组成两个分开的TM束(TM bundle), 即一个N-端六TM束(TM1-6)和一个C-端六TM束(TM7-12), 两个六TM束通过围绕穿过转运蛋白中心并垂直于质膜平面的假双对称轴旋转约180°呈镜像表现[42]. 12个TM之间由不同长度的亲水环相连, 并且在TM6和TM7之间有一个大细胞质环将两个六TM束分隔开来[43]. 值得注意的是, TM1-3与反向TM4-6具有序列相似性, 而TM7-9与反向TM10-12具有序列相似性, 这可能是由于基因复制和融合导致的[44]. 此外, 与人类GLUT5具有81%序列同一性的大鼠和牛GLUT5在胞内结构域还有五个螺旋, 一个在C-端, 四个位于N-端六TM束和C-端六TM束之间[45].

GLUT5是第一个被发现的Ⅱ类GLUT. Ⅱ类GLUT与其他两类GLUT的一个显著差异是在TM10的GXXXXP序列中不存在色氨酸残基, 这也是包括GLUT5在内的Ⅱ类GLUT对细胞松弛素B不敏感的原因[43]. 人类GLUT5共含有501个氨基酸(残基), 通过查询蛋白质数据库UniProt(https://www.uniprot.org/), 得到人类GLUT5拓扑结构域和12个TM沿氨基酸序列在质膜及其两侧的分布特征, 以及多肽链上发生翻译后修饰的位点(图2).

已经运用X射线衍射分析了大鼠和牛GLUT5晶体结构. GLUT5底物结合位点位于N-端六TM束和C-端六TM束之间的中央腔内, 排列在此的氨基酸残基与底物结合活性相关. 388和412位点上的色氨酸残基对于GLUT1的转运活性至关重要[46], 而在大鼠

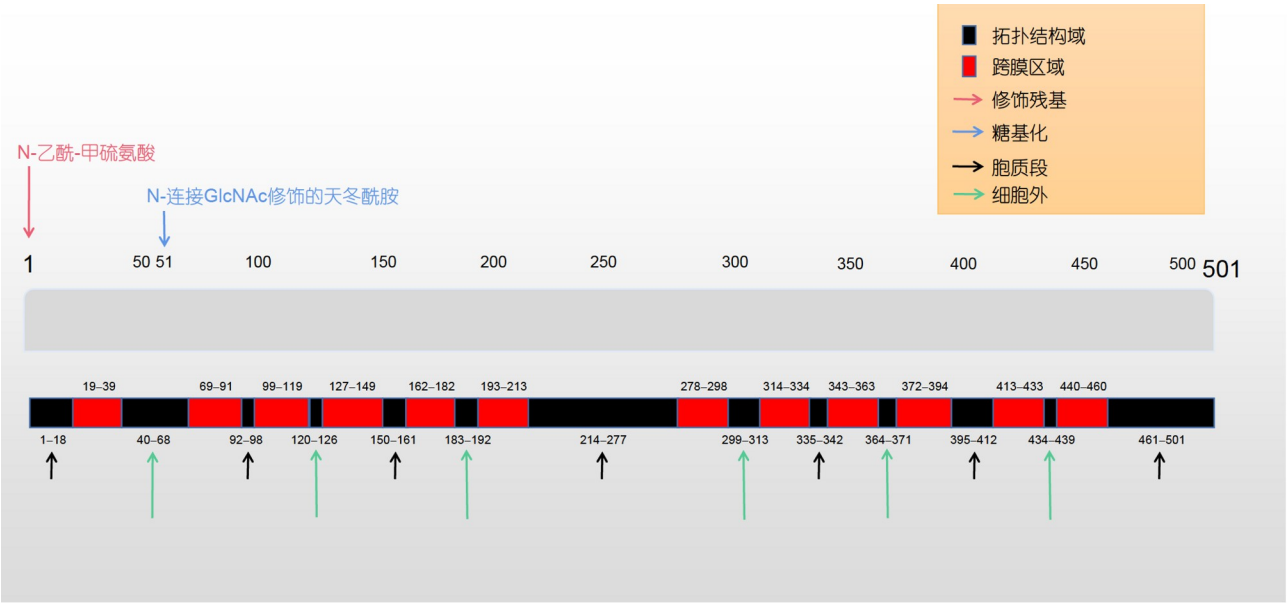

图 2　UniProt数据库中显示的智人GLUT5沿氨基酸序列排列的胞质、胞外拓扑结构域及膜上12个TM区，两种翻译后修饰分别发生在1和51位点

Figure 2　The cytoplasmic and extracellular topological domains and 12 TM regions on the membrane of GLUT5 of *Homo sapiens* displayed in UniProt database are arranged along the amino acid sequence, and the two post-translational modifications occur at positions 1 and 51, respectively

GLUT5中，419位点上的色氨酸残基(Trp419)是唯一位于中央腔底物结合位点的色氨酸残基. 当添加底物为D-果糖时, 可以观察到中央腔色氨酸残基荧光强度剧烈消失; 而当添加底物为其他单糖时，中央腔色氨酸残基荧光强度无明显变化，这代表了GLUT5对D-果糖的底物结合活性[45]. 此外，人类GLUT5底物结合位点中的Tyr31, His386, His418, Ser391和Ala395的丙氨酸定点突变体都会导致强烈的底物结合活性减弱, 并且除Tyr31外, 其余氨基酸残基都属于C-端六TM束, 这表明GLUT5中N-端六TM束和C-端六TM束不对称结合果糖[45].

在MFS转运蛋白的运输过程中，TM束间盐桥(inter-TM bundle salt-bridges)在中央腔内不断地破坏和形成[47]. 在大鼠GLUT5中, N-端六TM束中的Glu151和Arg97同C-端六TM束中的Arg407形成TM束间盐桥, N-端六TM束中的Arg158同C-端六TM束中的Glu400和Arg340形成TM束间盐桥. 此外, 还有C-端六TM束中的 Glu336通过与Arg340形成TM束内盐桥进而同TM束间盐桥相连. 这些盐桥仅在外部构象中观察到，并且均远离中央腔，但它们所构成的跨TM束盐桥网络起到了维持外部构象稳定的作用[45].

4　GLUT5的底物识别-转运机制

构成MFS折叠的4个三聚体亚结构能够相对彼此移动，从而交替打开和关闭膜两侧的通道. 交替通道(alternating access)转运机制是转运蛋白最普遍和最常用的解释模型. 转运蛋白经历一系列构象变化, 产生向外开放(空载)、向外封闭(底物结合)、向内开放(底物释放)、向内封闭(空载)、向外开放(空载)的瞬时状态循环, 四种主要构象交替暴露于膜的每一侧, 以便通过脂质双层运输和释放底物[48]. N-端和C-端六TM束在中央腔底物结合位点周围与底物的对称结合和两个六TM束的刚体运动构成了MFS转运蛋白“摇杆开关”机制的结构基础, 并以此完成交替通道转运[49,50]. GLUT5的底物运输可能不仅受到N-端和C-端六TM束的“摇杆开关”运动控制，因为其两个六TM束与底物显示不对称结合. 通过对大鼠和牛GLUT5的晶体结构分析, Nomura等人[45]提出C-端六TM束中的TM7和TM10在局部通过相互作用进行门控运动，并与底物的结合和释放耦合(图3). 此外, 在MFS超家族的所有蛋白质中, 在TM2和TM3的细胞质环之间具有高度保守的盐桥序列RXGRR, 在TM8和TM9的细胞质环之间重复该盐桥序

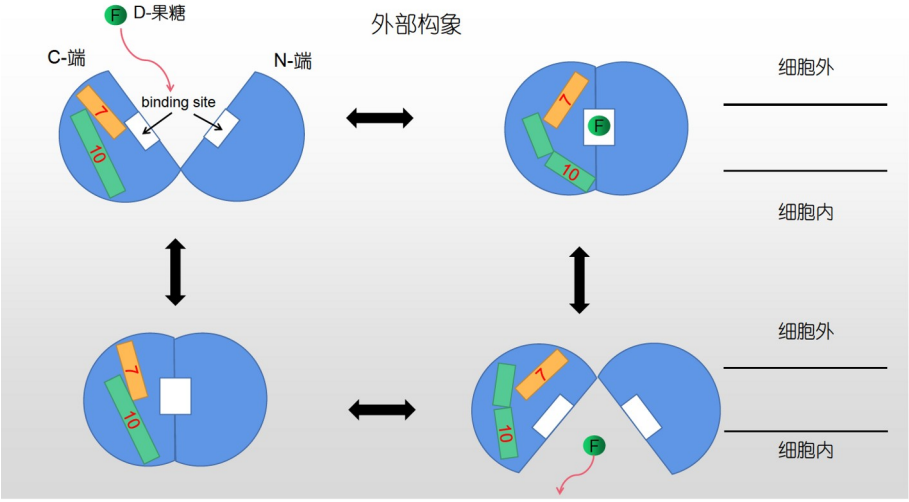

图 3 GLUT5外部构象中的交替通道机制示意图. 两个六TM束的刚体运动构成了“摇杆开关”运动控制, 还有TM7和TM10的相互作用在局部形成了门控机制

Figure 3 Schematic illustration of the alternating access mechanism in the outward conformation of GLUT5. The rigid body motion of the two six-TM bundles constitutes the “rocker switch” motion control, and the interaction of TM7 and TM10 locally forms the gating mechanism

列, 这些盐桥序列与底物转运过程中发生的构象变化有关[51].

尽管在不同的物种, GLUT5对D-果糖的K_m值有所不同, 但D-果糖始终是其最佳底物. 那么GLUT5是如何做到特异性识别果糖的呢? 在水溶液中, 葡萄糖和果糖均以吡喃糖或呋喃糖构象存在, 其中葡萄糖99%为吡喃糖, 果糖31.5%为呋喃糖[52]. 在结合了葡萄糖的蛋白质晶体结构中, 以吡喃葡萄糖为主要形式; 在结合了果糖的蛋白质晶体机构中, 以呋喃果糖为主要形式(Protein Data Bank). GLUT5识别呋喃糖和吡喃糖构象的果糖, 结合涉及与果糖的C_1, C_2, C_3和C_4位置的相互作用[53]. 此外, 氨基酸残基不仅在底物结合活性方面起作用, 在GLUT5的底物识别过程中, 一些氨基酸残基也是必要的结构基础. 只运输葡萄糖的GLUT1, 3, 4在TM7中具有QLS序列, 该区域能与D-葡萄糖的C_1位相互作用, 密切参与外表面底物结合位点对底物的识别; 能够运输葡萄糖和果糖的GLUT2的TM7含有HVA序列, 而特异性运输果糖的GLUT5则为MGG序列[54](表1).

表 1 人类GLUT1~5中的TM7序列[54]

Table 1 Sequence alignments of TM7 in human GLUT1–5[54]

GLUTS	TM7序列比对
GLUT1	... A V V L Q L S Q Q L S G I N A ...
GLUT2	... A L M L H V A Q Q F S G I N G ...
GLUT3	... S I V L Q L S Q Q L S G I N A ...
GLUT4	... A V V L Q L S Q Q L S G I N A ...
GLUT5	... I I V L M G G Q Q L S G V N A ...

5 GLUT5抑制剂

深入分析GLUT5晶体结构和底物识别-转运机制对设计特异性抑制剂具有指导意义. 虽然GLUTs成员之间具有很高的序列相似性, 但已知的一些GLUTs蛋白抑制剂(例如细胞松弛素B、根皮素或毛喉素)并不能抑制GLUT5对果糖的特异性转运. 已经发现了几种GLUT5天然抑制剂, 比如绿茶儿茶素(green tea catechins)[55]和来自中国甜茶叶提取物中的甜茶苷(rubusoside)[56]. 然而这些天然抑制剂都是非特异性的, 并且结合抑制效力低(IC_{50} ~5 mmol/L). 目前, 人们已经将计算机高通量配体筛选手段运用于开发具有治疗潜力的新型抑制剂[57]. 例如N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3-benzodioxol-5-amine(MSNBA), 该抑制剂对GLUT5是特异性的, 不影响人GLUT2的果糖转运或人GLUT1~4的葡萄糖转运, 是目前已知最强的GLUT5特异性抑制剂[58]. 新型GLUT5抑制剂的开发对于果糖代谢相关疾病的治疗策略意义重大.

6　观点和展望

代谢紊乱是困扰人类健康的长期难题之一. 如今, 癌症成为人类死亡的主要原因之一, 对癌症的发生发展机制已经做了大量研究, 但其代谢途径的改变及调控机制仍然有待深入阐明. 癌细胞的代谢失调是癌症的标志之一, 因为许多癌基因或抑癌基因的功能是维持癌细胞中改变的代谢状态[59]. 正如1920年代德国生物化学家Warburg等人[60]所提出的, 肿瘤细胞更倾向于将葡萄糖用于糖酵解产生乳酸而非进行TCA循环, 即便是在有氧情况下. 然而, 由于糖酵解每分子葡萄糖所能产生的ATP明显少于TCA循环, 因此肿瘤细胞必须摄取更多的葡萄糖来满足自身需求, 这意味着负责转运葡萄糖和果糖的GLUTs在肿瘤细胞代谢变化过程中发挥了重要作用. 过往的大量研究也证明, GLUTs在众多类型的癌症中都有高表达[61].

细胞/机体代谢的强烈变化往往驱动或加剧癌症的进展, 正如GLUT5在人类恶性肿瘤中表达显著增加[62]. 因此, 还需要对GLUT5进行更充分、更深入的结构和机制研究, 在蛋白分子水平上阐述GLUT5表达相关病理变化机制, 不仅是代谢疾病, 某些代谢相关/诱发的癌症都可以获得更具特异性的治疗.

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Molecular insights into the glucose transporter GLUT5

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Glucose transporter 5 (GLUT5) is the only membrane transporter that specifically transports fructose in the human body. GLUT5 is mainly expressed in small intestinal epithelial cells and plays an important role in dietary fructose uptake and metabolism. In recent years, with the continuous improvement of living standards, the global per capita fructose intake has increased dramatically, resulting in a gradual increase in obesity and metabolic diseases. Due to the critical role of GLUT5 in dietary fructose absorption and metabolism, the relationship between GLUT5 and human diseases is receiving increasing attention. Increasing evidence suggests that GLUT5 plays a significant role in diseases ranging from digestive system diseases to a variety of human cancers. However, due to various difficulties and shortcomings, the molecular structure of GLUT5 has not been fully elucidated. Further understanding of the molecular structure and biological function of GLUT5 will help us to better understand the mechanism of GLUT5-related diseases and design more targeted therapeutic drugs. In this review, we mainly introduce the molecular structure and transport mechanism of mammalian GLUT5, and provide an outlook for potential application of GLUT5 from the perspective of basic molecular biology, in order to provide a better strategy for the clinical treatment of fructose metabolism-related diseases.

GLUT5, fructose, metabolic diseases

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