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肝脏糖异生的调控

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摘要　肝脏糖异生是维持体内血糖稳态的重要代谢过程, 糖异生调控的失衡是2型糖尿病的典型特征。该综述重点描述了调控肝脏糖异生分子机制的研究进展和针对糖异生起作用的治疗2型糖尿病的药物及其靶点。

关键词　糖异生; 肝脏; 2型糖尿病; 胰岛素; 胰高血糖素

Regulation of Hepatic Gluconeogenesis

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Abstract　Gluconeogenesis in the liver maintains glucose homeostasis, while enhanced gluconeogenesis is one of the hallmarks of type 2 diabetes. Here, we review the molecular mechanisms controlling hepatic gluconeogenesis and assess the current drugs to treat type 2 diabetes, focusing on the therapeutically targeted pathways that are associated with hepatic gluconeogenesis.

Keywords　gluconeogenesis; liver, type 2 diabetes (T2D); insulin; glucagon

血液中的葡萄糖称为血糖。血糖浓度是反映机体内糖代谢状况的一项重要指标。正常情况下血糖浓度是相对恒定的, 要维持血糖浓度的相对稳定必须保持血糖的来源和去路的动态平衡。血糖的主要来源是食物、糖原分解以及糖异生等, 而血糖的主要去路包括糖原合成和糖酵解等。机体的葡萄糖稳态受到多层次的精细调控, 糖原代谢、葡萄糖代谢以及糖异生代谢等代谢通路及相关信号转导通路均

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参与机体的血糖稳态调控过程。

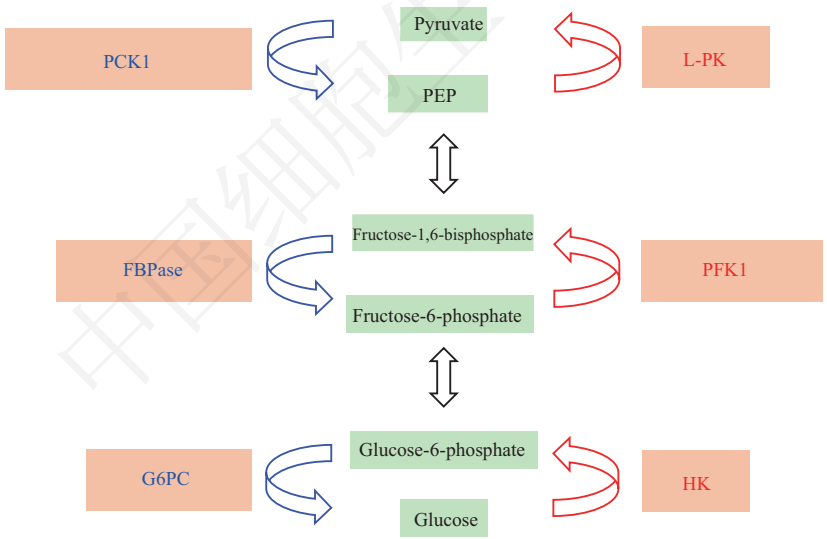
肝脏对葡萄糖稳态维持至关重要, 约90%的内源葡萄糖在肝脏生成[1-3]。在进食时, 葡萄糖会合成糖原或者经糖酵解–脂肪酸合成方式形成脂肪储存能量。在空腹饥饿状态下, 糖原分解和糖异生会随饥饿时间依次激活从而提供葡萄糖来维持正常血糖, 并且为神经元、红细胞和肾髓质等细胞提供能量[4-5]。肝葡萄糖代谢包括多种分解代谢和合成代谢通路, 它们对血糖的贡献最终由糖原合成、糖原分解、糖异生和糖酵解等途径共同决定, 通过肝细胞自主和非自主的方式响应环境和营养的变化调控葡萄糖代谢的动态平衡[5-7]。

糖异生负责正常人体空腹饥饿过夜后大约一半的葡萄糖生成, 以及2型糖尿病(type 2 diabetes, T2D)病人空腹后肝脏葡萄糖增量[8-12]。此外, 糖异生也是目前临床上治疗2型糖尿病药物的主要靶点[6-7,13-15]。肝糖异生受各种不同机制的调控, 包括底物水平调节、代谢产物变构调节和激素水平的调节等[6-7]。

1 糖异生

糖异生作用是指非糖物质如生糖氨基酸、乳酸、丙酮酸及甘油等转变为葡萄糖的过程。糖异生发生在肝脏、肾脏和小肠, 但肝脏是糖异生最主要的器官[1-3,6-7,15]。糖异生最重要的生理意义是在空腹或饥饿情况下维持血糖浓度的相对稳定, 使机体免于低血糖导致的休克或者死亡。

糖异生基本上是糖酵解反应的逆过程(图1)。葡萄糖-6-磷酸酶(glucose-6-phosphatase, G6PC)、果糖-1,6-二磷酸酶(fructose 1,6-bisphosphatase, FBPase)以及磷酸烯醇式丙酮酸羧激酶1(phosphoenolpyruvate carboxykinase 1, PCK1)是糖异生中的三个限速酶, 而己糖激酶(hexokinase, HK)、6-磷酸果糖激酶1(6-phosphofructokinase 1, PFK1)以及丙酮酸激酶(pyruvate kinase, L-PK)是肝脏中糖酵解的限速酶[6-7,15-17]。己糖激酶、6-磷酸果糖激酶1以及丙酮酸激酶催化的三个反应释放了大量的能量, 构成难以逆行的能障, 因此这三个反应是不可逆的[16-17]。



糖异生过程中有三个限速酶, 分别是磷酸烯醇式丙酮酸羧激酶(PCK1), 催化草酰乙酸(丙酮酸生成草酰乙酸由丙酮酸羧化酶)转化成磷酸烯醇式丙酮酸; 果糖-1,6-二磷酸酶(FBPase), 催化果糖-1,6-二磷酸形成果糖-6-磷酸; 葡萄糖-6-磷酸酶(G6PC), 催化葡萄糖-6-磷酸形成葡萄糖。糖酵解过程中也有三个相对应的限速酶, 分别是己糖激酶(HK), 催化葡萄糖形成葡萄糖-6-磷酸; 6-磷酸果糖激酶1(PFK1), 催化果糖-6-磷酸形成果糖-1,6-二磷酸; 肝脏特异性的丙酮酸激酶(L-PK), 催化磷酸烯醇式丙酮酸形成丙酮酸。

In gluconeogenesis, there are three rate-limiting enzymes (blue) to control the flux. Oxaloacetate is generated from pyruvate by pyruvate carboxylase and further converted into phosphoenolpyruvate (PEP) by PEP carboxylase (PCK1). Fructose-1,6-bisphosphate is converted into fructose-6-phosphate by fructose-1,6-bisphosphatase (FBPase). Finally, the phosphate on glucose-6-phosphate is removed by glucose-6-phosphatase (G6PC) to generate glucose. In glycolysis, there are also three rate-limiting enzymes (red). The first is hexokinase (HK), which adds a phosphate group to glucose and generate glucose-6-phosphate. Phosphofructokinase 1 (PFK1) converts fructose-6-phosphate into fructose-1,6-bisphosphate, while the liver-specific pyruvate kinase (L-PK) generates pyruvate from phosphoenolpyruvate as the last step of glycolysis.

图1 糖异生与糖酵解的比较

Fig.1 Comparison of gluconeogenesis and glycolysis

糖异生能力的变化可以通过一系列实验来判断。在分子水平上可以通过葡萄糖-6-磷酸酶以及磷酸烯醇式丙酮酸羧激酶的表达(mRNA和蛋白)水平进行评估[18-19]; 在细胞水平可以直接测量单位时间内葡萄糖的生成量[20-21]; 在动物水平可以利用丙酮酸耐受实验或者高胰岛素−正葡萄糖钳夹实验来测量葡萄糖新生的能力[22-25]。

1.1 糖异生的调控

1.1.1 关键酶的别构调节　乙酰辅酶A(acetyl coenzyme A, acetyl-CoA)作为别构剂激活糖异生的丙酮酸羧化酶, 抑制糖有氧氧化中的丙酮酸脱氢酶复合体的活性, 促进糖异生作用[26-28]。当细胞能量足够时, 三羧酸循环被抑制、乙酰CoA堆积, 进而抑制丙酮酸脱氢酶复合体的活性, 减缓丙酮酸生成乙酰CoA的速率; 与此同时丙酮酸羧化酶被激活, 增加糖异生过程, 将多余的丙酮酸生成葡萄糖。

一磷酸腺苷(adenosine monophosphate, AMP)是糖异生途径中果糖-1,6-二磷酸酶的别构抑制剂, 是糖酵解中6-磷酸果糖激酶1的别构激活剂[16-17]。三磷酸腺苷(adenosine triphosphate, ATP)、柠檬酸是6-磷酸果糖激酶1的别构抑制剂。这两个酶相互协调共同调节糖异生和糖酵解过程。肝细胞内ATP/ADP比值增加时, 糖异生加强而糖酵解被抑制, 反之, 当ATP/ADP比值下降时, 糖酵解加速, 而糖异生被抑制[16-17]。

2,6-二磷酸果糖在糖酵解、糖异生的相互调节中起着重要作用[16-17]。2,6-二磷酸果糖是6-磷酸果糖激酶1最强的别构激活剂, 同时也是果糖-1,6-二磷酸酶的别构抑制剂。在葡萄糖供应充分时, 2,6-二磷酸果糖浓度增高激活6-磷酸果糖激酶1, 抑制果糖-1,6-二磷酸酶, 促进糖酵解。在葡萄糖供应缺乏时, 2,6-二磷酸果糖浓度降低, 减低对6-磷酸果糖激酶1的激活、降低对果糖-1,6-二磷酸酶的抑制, 从而增加糖异生[16-17]。

1.1.2 激素对糖异生的调控　在进食时, 胰岛的β细胞分泌胰岛素(insulin), 胰岛素激活肝脏中的胰岛素信号通路进而抑制糖异生过程; 在空腹饥饿时, 胰岛的α细胞分泌胰高血糖素(glucagon), 胰高血糖素结合肝细胞上的胰高血糖素受体(GCGR)并激活环化腺核苷一磷酸(cyclic adenosine monophosphate, cAMP)信号, 通过cAMP依赖的蛋白激酶A(PKA)激活肝糖异生[7]。研究表明, 胰高血糖素是T2D模型中高血糖发生的关键因素, 缺乏胰高血糖素受体的小鼠呈现出低血糖的症状, 而缺乏胰高血糖素受体的糖尿病小鼠(*db/db*)不表现出高胰岛素或高血糖症状[29-33]。

胰岛素调节胰腺α细胞中胰高血糖素的分泌, 而这一调节机制的丧失导致了糖尿病患者糖异生升高及高血糖症的发生[6-7]。对肝细胞胰岛素信号通路基因缺陷小鼠的研究证明了胰岛素信号对糖异生抑制机制。*AKT1*、*AKT2*和*FOXO1*是编码肝细胞胰岛素效应的三个关键基因, *AKT1*、*AKT2*和*FOXO1*在高胰岛素——正血糖钳夹研究中抑制糖异生[34-35]。

胰高血糖素在急性刺激条件下通过促进PKA的磷酸化、抑制肝脏丙酮酸激酶(L-PK)以及6-磷酸果糖–激酶2/2,6-二磷酸果糖磷酸酶2(PFK2/FBPase-2)刺激糖异生[17,36-38]。相对来讲, 胰岛素对糖异生的急性负调控作用不明显。高浓度的胰岛素会抑制cAMP信号对丙酮酸激酶以及6-磷酸果糖–激酶2/2,6-二磷酸果糖磷酸酶2的作用[17,39-40]。

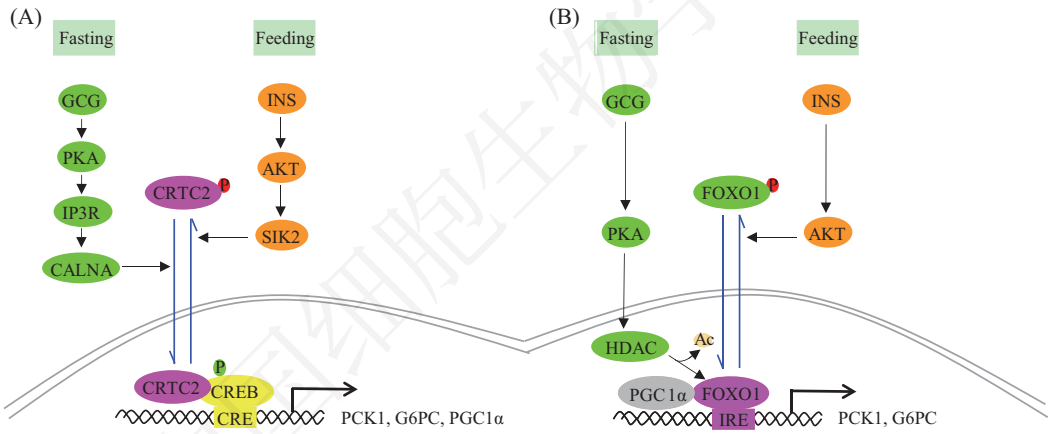
胰高血糖素和胰岛素对糖异生的转录调控相对缓慢, 主要通过转录激活或者转录抑制编码糖异生途径关键酶磷酸烯醇式丙酮酸羧激酶和葡萄糖-6-磷酸酶的基因。胰高血糖素通过刺激cAMP-PKA依赖的CREB/CRTC2转录复合物的激活参与了糖异生的转录调控[41-42]。CRTC2是该转录复合物激活与否的关键因子。饥饿时CRTC2被去磷酸化并定位于细胞核。胰岛素刺激后, CRTC2被磷酸化并出核[41-43]。在进食或者能量充足时, CRTC2被AMPK家族的激酶SIK2磷酸化, 结合14-3-3蛋白质并定位于细胞质或者导致CRTC2的降解[42]。CRTC2在饥饿过程中的去磷酸化涉及对依赖于PKA的丝氨酸/苏氨酸蛋白激酶SIK2的抑制; 以及对依赖于PKA的肌醇-1,4,5-三磷酸受体(IP3R)的磷酸化, IP3R磷酸化导致细胞内Ca^{2+}水平的增加, 而Ca^{2+}水平的增加激活了CRTC2特异性磷酸酶Calcineurin[20,44]。去磷酸化的CRTC2定位于细胞核, 从而结合并激活CREB依赖的*PCK1*和*G6PC*的基因转录[20]。*Crtc2*基因敲除小鼠表现出空腹低血糖, 而腺病毒(AAV)介导的组成性CRTC2过表达则表现为高血糖[18,45]。CRTC2对内质网应激和氨基酸信号的响应进一步表明CRTC2在糖代谢中的重要作用[21-22]。此外, CREB可以诱导PGC1α表达, 表明FOXO1和CRTC2通路之间的确

存在对话[41]。研究表明, CREB/CRTC2主要在小鼠空腹饥饿的前6 h对G6PC的表达进行主要调控, 而FOXO1-PGC1α在较长时间(~18 h)饥饿时对G6PC的表达发挥更大的作用, 这些结果表明了CREB/CRTC2与FOXO1-PGC1α之间的内在联系及其在不同饥饿时间对糖异生的交替调控作用[46](图2A)。

胰岛素依赖的糖异生基因转录表达调控涉及FOXO家族转录因子[7,47]。FOXO蛋白与转录激活因子PGC1α共同作用, 正调控PCK1和G6PC的表达[48-51]。cAMP信号促进了FOXO1的去磷酸化和细胞核滞留, 而胰岛素信号通过AKT磷酸化FOXO1使其停留在细胞质中[7,48,52]。除磷酸化的修饰外, FOXO1的酰基化修饰对其转录活性也有显著的影响。在空腹饥饿时, PKA导致SIK3的失活, 激活了HDAC, 使FOXO1去酰基化而激活其转录活性; 在进食时, AKT信号会导致HDAC磷酸化并停留在细胞质中, 无法去酰基化和激活FOXO1[53-54]。FOXO1-PGC1α轴的功能获得或缺失对PCK1和G6PC蛋白水平和血糖有显著影响[51,55-56]。FOXO1的肝脏敲除小鼠糖异生能力显著减弱, 而FOXO1的过表达降低了胰岛素对糖异生的抑制作用[57-58](图2B)。

血液中胰岛素与胰高血糖素的比例是控制肝脏糖异生的关键因素, 高比例的胰岛素/胰高血糖素表明能量处于充足状态, 因而糖异生会被抑制。反之, 则糖异生增强[6-7,15]。在2型糖尿病中, 胰岛素的直接和间接作用受损, 而胰高血糖素信号的增强进一步加剧了糖原降解以及糖异生的增强, 从而导致了葡萄糖的增多和血糖的升高[6-7,15]。

肝脏糖异生除了受到胰岛素和胰高血糖素的调控外, 儿茶酚胺也可以在应急状态时激活cAMP



A: 空腹饥饿时, 胰高血糖素(GCG)结合胰高血糖素受体(GCGR)激活cAMP依赖的PKA信号。PKA磷酸化内质网上的钙通道蛋白ITPR, 诱导钙离子从内质网到细胞质的释放, 激活钙离子依赖的磷酸酶CALNA。CALNA去磷酸化CRTC2, 导致CRTC2入核并结合被PKA磷酸化的转录因子CREB, 从而增强并激活启动子含有CRE位点基因的转录, 包括PCK1、G6PC和PGC1α等。进食时, 胰岛素信号激活AKT/SIK2进而磷酸化CRTC2, 磷酸化的CRTC2结合14-3-3停留在细胞质或者通过蛋白酶体途径降解。B: 空腹饥饿时, PKA导致HDAC入核并去酰基化FOXO1, 从而增强并激活启动子含有IRE位点基因的转录, 包括PCK1和G6PC等。PGC1α的结合进一步增强了FOXO1的转录活性。在进食情况下, AKT可以磷酸化FOXO1, 使其结合14-3-3停留在细胞质或者通过蛋白酶体途径降解。胰岛素信号也可以通过磷酸化HDAC并使其停留在细胞质中, 无法去酰基化和激活FOXO1。

A: during fasting, the interaction of glucagon (GCG) with the glucagon receptor (GCGR) activates cAMP-dependent protein kinase A (PKA), which phosphorylates inositol 1,4,5-triphosphate receptor (IP3R), an ER calcium channel protein. This induces calcium release from the ER to the cytoplasm and activates calcineurin A (CALNA), a calcium-dependent phosphatase. CALNA dephosphorylates the CREB-regulated transcriptional coactivator 2 (CRTC2) and promotes its nuclear location. The dephosphorylated CRTC2 binds to cAMP-response element binding protein (CREB), which is phosphorylated by PKA, and promotes the transcription of CRE-containing genes, including phosphoenolpyruvate carboxylase (*PCK1*), glucose-6-phosphatase (*G6PC*) and PPARγ co-activator 1α (*PGC1α*). During feeding, activated salt inducible kinase 2 (SIK2) phosphorylates CRTC2 and thereby restricts phosphorylated CRTC2 to the cytoplasm via its association with 14-3-3 proteins, or promotes proteasome-dependent degradation of CRTC2. B: under fasting conditions, PKA enables nuclear translocation of HDAC, which deacetylates FOXO1, thereby promoting the occupancy of FOXO1 on the insulin response element (IRE) of gluconeogenic genes, such as *PCK1* and *G6PC*, and enhancing their transcription. The association of PGC1α and FOXO1 promotes FOXO1-targeted gluconeogenic gene expression. During feeding, AKT phosphorylates FOXO1, which sequesters FOXO1 in the cytoplasm via its binding to 14-3-3 protein or promotes FOXO1 degradation via a proteasome-dependent pathway.

图2 糖异生转录因子与激活因子活性的调控

Fig.2 Regulation of the activity of gluconeogenic transcription factors and co-activators

信号并促进糖异生[59]。最近来自于Chopra实验室[60]的结果表明, 在空腹饥饿时白色脂肪组织分泌激素Asprosin, 激活肝细胞中GPCR偶联的cAMP信号, 促进了糖异生。我们在筛选新的调控糖异生基因时发现嗅觉受体*OR4M1*(人源基因编码, 小鼠中是*OLFR734*)对糖异生基因的表达有显著的正调控作用。通过利用纯化的OLFR734在血清中寻找其配体, 我们筛选到Asprosin。进一步的实验证明, Asprison通过结合OLFR734激活了cAMP信号和糖异生[61]。

1.1.3 *氨基酸和游离脂肪酸对糖异生的调控* 激素是通过组织器官间对话调控糖异生的一种重要方式, 而来自于肝脏组织以外的氨基酸和游离脂肪酸也可以通过直接或者间接的方式影响肝脏的糖异生。饥饿状态下, 脂肪组织的甘油三酯通过脂解作用形成甘油和脂肪酸。甘油作为糖异生的底物通过底物推动的促进作用可以增强肝脏的糖异生。尽管饥饿状态下, 游离脂肪酸可以成为大部分组织的能量原料, 但大脑不能利用游离脂肪酸获得能量, 而是利用葡萄糖或者酮体产生能量。游离脂肪酸对糖异生的作用可能存在物种的特异性, 例如游离脂肪酸可以促进大鼠肝脏的糖异生, 但在狗和豚鼠中抑制糖异生[28,62-65]。此外, 游离脂肪酸在人体中的具体作用也存在争议[66]。脂肪酸或者脂肪酸氧化的产物不是糖异生的底物, 生成的乙酰辅酶A作为别构剂激活糖异生途径中的丙酮酸羧化酶, 同时抑制糖有氧氧化中的丙酮酸脱氢酶复合体的活性, 进而促进糖异生作用[26-28]。尽管这可以解释脂肪酸在某些物种中对糖异生的促进作用, 但无法回答在其他物种中的抑制作用。因此, 关于脂肪酸对糖代谢的调控作用有待进一步的阐明。

饥饿状态下, 来自于肌肉蛋白降解的氨基酸是糖异生的重要底物, 除了赖氨酸和亮氨酸外的18种常见氨基酸均可以转化成葡萄糖。在长时间饥饿或者某些低血糖疾病中, 由于来自于肌肉蛋白质降解的氨基酸水平下降从而减弱糖异生的能力[67]。高蛋白饮食增强了肝脏中磷酸烯醇式丙酮酸羧激酶的活性, 而对葡萄糖-6-磷酸酶的活性影响不大[68-69]。亮氨酸、缬氨酸和异亮氨酸等支链氨基酸可以通过激活mTOR信号抑制糖异生, 亮氨酸的缺乏激活了AMPK信号并抑制了mTOR信号从而促进了糖异生[70]。

1.1.4 *生物钟对糖异生的调控* 生物钟是生命体的内在计时系统, 机体中几乎所有细胞中都存在生物钟。脑中的视交叉上核(suprachiasmatic nuclei)是生物钟的中央调控系统, 感知光照并维持机体约24小时的生物钟周期性变化。肝脏中的生物钟系统不仅受视交叉上核生物钟的调控, 还受摄食/禁食周期的调控[71-73]。生物钟主要依赖于一个负反馈调节闭环的转录调控, BMAL1/CLOCK复合体促进*Per*和*Cry*基因的转录, 而PER和CRY蛋白抑制BMAL1/CLOCK复合物的转录活性进而抑制生物钟基因的表达[71-73]。

胰岛素和胰高血糖素的分泌受到胰岛细胞中生物钟的调控, 进而影响肝脏糖异生[74-75]。核心生物钟基因均直接或者间接地调控葡萄糖的稳态[71-73]。比如, CRY通过抑制cAMP的产生下调CREB复合物的转录活性, 进而抑制糖异生基因的表达[76]。小鼠模型中的相关研究发现, 肝脏中过表达CRY1可以降低糖尿病个体中的血糖水平并提高其对胰岛素的敏感性[76]。CRY1也可以与糖皮质激素受体(glucocorticoid receptor)结合并抑制磷酸烯醇式丙酮酸羧激酶基因的转录从而抑制糖异生[77]。AMPK磷酸化导致的CRY1蛋白降解或者细胞自噬导致的CRY1蛋白降解都可以解除CRY1对糖异生的抑制作用[78-79]。

1.2 糖异生的药物靶点

鉴于葡萄糖-6-磷酸酶、果糖-1,6-二磷酸酶以及磷酸烯醇式丙酮酸羧激酶在控制糖异生中的作用, 针对这些酶的抑制剂在理论上是降低血糖的重要手段。实际的动物和临床试验则产生了复杂的结果, 例如磷酸烯醇式丙酮酸羧激酶的抑制剂3-mercaptopicolinic acid导致低血糖[80-81]。尽管果糖-1,6-二磷酸酶的抑制剂MB07803可以很好地降低血糖, 但很多病人在临床试验中有恶心和呕吐的症状[82]。针对胰高血糖素受体(GCGR)的拮抗剂也没有取得预期的效果[15]。

二甲双胍是2型糖尿病的一线治疗方法[83]。抑制肝糖异生降低血糖是二甲双胍的主要作用机制[84-85]。目前二甲双胍在不同组织中作用的分子机制是糖异生调控研究的热点之一。二甲双胍可能的作用机制是激活AMPK, 而CREB/CRTC2转录复合物参与了二甲双胍对糖异生的调控[86-88]。二甲双胍激活AMPK, 活化的AMPK进而磷酸化CRTC2从而抑制糖异生[86]。研究也表明, 二甲双胍通过抑制线粒体复合物I的活性, 从而改变腺嘌呤核苷酸的能量

电荷(即细胞[AMP]:[ATP]和[ADP]:[ATP]比值)[89]。[AMP]:[ATP]比值的增加会激活AMPK并抑制糖异生关键酶果糖-1,6-二磷酸酶(FBPase)的活性[90]。此外, 二甲双胍在AMPK敲除的小鼠原代肝细胞中可以持续抑制葡萄糖产生, 并且可以增加AMPK敲除小鼠的葡萄糖耐受, 达到与对照野生型小鼠相似的水平[91]。所有这些证据表明, AMPK在二甲双胍抑制肝糖异生中起作用, 但不是唯一的作用。

在大鼠中, 二甲双胍可以增加细胞质还原状态并降低线粒体还原状态, 提示二甲双胍抑制了平衡细胞质和线粒体还原状态的穿梭蛋白[92]。二甲双胍可以抑制胰高血糖素诱导的cAMP信号或者抑制果糖-1,6-二磷酸酶减少糖异生[93-94]。尽管对二甲双胍抑制肝糖异生的分子机制已经做了大量的研究, 但具体的作用机制仍不清楚。主要原因是二甲双胍处理剂量的高低以及引起的急性或者慢性结果差异。如果考虑到二甲双胍在其他组织中起的作用[95-96]可能也影响肝糖异生, 那么其作用的机制将更复杂。

2 展望

随着经济的快速发展以及人们生活方式的改变, 糖尿病的发病率逐年上升, 成为严重影响人们健康和生活质量的重要疾病。仅在我国就有大约1亿的患者[97-98]。高血糖是糖尿病病人的重要病理特征, 糖异生调控紊乱是导致2型糖尿病高血糖的一个主要原因, 目前临床上针对糖尿病治疗的药物大多靶向糖异生的调节[6-7,99-100]。因而对糖异生调控机制的研究有利于我们认识糖尿病发病机理, 同时新发现的机制也有利于靶向药物的设计与开发。

尽管过去几十年糖异生的相关研究已取得了众多进展, 新药开发仍旧步履维艰。目前的研究表明, 通过影响底物或者产物对糖异生中关键酶的别构调控效应, 或者改变糖异生相关酶的表达, 在细胞和动物水平都有一定恢复血糖稳态的作用。但考虑到药物的安全性、有效性、专一性和价格优势, 发现新的调控糖异生的分子或者影响糖异生的通路是糖代谢研究领域基础研究的重要课题。激素是组织器官间对话并维持机体糖代谢稳态的重要方式, 新激素的发现是一个近期有可能取得突破的方向。另外, 代谢产物对糖代谢调控的研究也将极大地帮助我们理解糖异生过程, 并有可能为2型糖尿病预防或者治疗带来新的希望。

参考文献 (References)

1 Ekberg K, Landau BR, Wajngot A, Chandramouli V, Efendic S, Brunengraber H, *et al*. Contributions by kidney and liver to glucose production in the postabsorptive state and after 60 h of fasting. Diabetes 1999; 48(2): 292-8.

2 Moore MC, Coate KC, Winnick JJ, An Z, Cherrington AD. Regulation of hepatic glucose uptake and storage *in vivo*. Adv Nutr 2012; 3(3): 286-94.

3 Meyer C, Dostou JM, Welle SL, Gerich JE. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. Am J Physiol Endocrinol Metab 2002; 282(2): E419-27.

4 Rizza RA. Pathogenesis of fasting and postprandial hyper-glycemia in type 2 diabetes: implications for therapy. Diabetes 2010; 59(11): 2697-707.

5 Rui L. Energy metabolism in the liver. Compr Physiol 2014; 4(1): 177-97.

6 Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. Nat Rev Endocrinol 2017; 13(10): 572-87.

7 Lin HV, Accili D. Hormonal regulation of hepatic glucose production in health and disease. Cell Metab 2011; 14(1): 9-19.

8 Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI. Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13C NMR. Science 1991; 254(5031): 573-6.

9 Magnusson I, Rothman DL, Katz LD, Shulman RG, Shulman GI. Increased rate of gluconeogenesis in type II diabetes mellitus. A 13C nuclear magnetic resonance study. J Clin Invest 1992; 90(4): 1323-7.

10 Katz J, Tayek JA. Gluconeogenesis and the Cori cycle in 12-, 20-, and 40-h-fasted humans. Am J Physiol 1998; 275(3): E537-42.

11 Landau BR, Wahren J, Chandramouli V, Schumann WC, Ekberg K, Kalhan SC. Contributions of gluconeogenesis to glucose production in the fasted state. J Clin Invest 1996; 98(2): 378-85.

12 Bogardus C, Lillioja S, Howard BV, Reaven G, Mott D. Relationships between insulin secretion, insulin action, and fasting plasma glucose concentration in nondiabetic and noninsulin-dependent diabetic subjects. J Clin Invest 1984; 74(4): 1238-46.

13 Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab 2014; 20(6): 953-66.

14 Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333(9): 550-4.

15 Rines AK, Sharabi K, Tavares CD, Puigserver P. Targeting hepatic glucose metabolism in the treatment of type 2 diabetes. Nat Rev Drug Discov 2016; 15(11): 786-804.

16 Hers HG, Hue L. Gluconeogenesis and related aspects of glycolysis. Annu Rev Biochem 1983; 52: 617-53.

17 Pilkis SJ, Claus TH. Hepatic gluconeogenesis/glycolysis: regulation and structure/function relationships of substrate cycle enzymes. Annu Rev Nutr 1991; 11: 465-515.

18 Wang Y, Inoue H, Ravnskjaer K, Viste K, Miller N, Liu Y, *et al*. Targeted disruption of the CREB coactivator Crtc2 increases insulin sensitivity. Proc Natl Acad Sci USA 2010; 107(7): 3087-92.

19 Perry RJ, Wang Y, Cline GW, Rabin-Court A, Song JD, Dufour S,

et al. Leptin mediates a glucose-fatty acid cycle to maintain glucose homeostasis in starvation. Cell 2018; 172(1/2): 234-48,e17.

20 Wang Y, Li G, Goode J, Paz JC, Ouyang K, Screaton R, *et al*. Inositol-1,4,5-trisphosphate receptor regulates hepatic gluconeogenesis in fasting and diabetes. Nature 2012; 485(7396): 128-32.

21 Wang Y, Vera L, Fischer WH, Montminy M. The CREB coactivator CRTC2 links hepatic ER stress and fasting gluconeogenesis. Nature 2009; 460(7254): 534-7.

22 Han J, Li E, Chen L, Zhang Y, Wei F, Liu J, *et al*. The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. Nature 2015; 524(7564): 243-6.

23 Li P, Fan W, Xu J, Lu M, Yamamoto H, Auwerx J, *et al*. Adipocyte NCoR knockout decreases PPARgamma phosphorylation and enhances PPARgamma activity and insulin sensitivity. Cell 2011; 147(4): 815-26.

24 Ayala JE, Bracy DP, Malabanan C, James FD, Ansari T, Fueger PT, *et al*. Hyperinsulinemic-euglycemic clamps in conscious, unrestrained mice. J Vis Exp 2011; 16(57): pii: 3188.

25 Zhang Y, Xu L, Liu X, Wang Y. Evaluation of insulin sensitivity by hyperinsulinemic-euglycemic clamps using stable isotope-labeled glucose. Cell Discov 2018; 4: 17.

26 Perry RJ, Zhang XM, Zhang D, Kumashiro N, Camporez JP, Cline GW, *et al*. Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. Nat Med 2014; 20(7): 759-63.

27 Keech DB, Utter MF. Pyruvate carboxylase. II. properties. J Biol Chem 1963; 238: 2609-14.

28 Williamson JR, Kreisberg RA, Felts PW. Mechanism for the stimulation of gluconeogenesis by fatty acids in perfused rat liver. Proc Natl Acad Sci USA 1966; 56(1): 247-54.

29 Lee Y, Berglund ED, Yu X, Wang MY, Evans MR, Scherer PE, *et al*. Hyperglycemia in rodent models of type 2 diabetes requires insulin-resistant alpha cells. Proc Natl Acad Sci USA 2014; 111(36): 13217-22.

30 Longuet C, Robledo AM, Dean ED, Dai C, Ali S, McGuinness I, *et al*. Liver-specific disruption of the murine glucagon receptor produces alpha-cell hyperplasia: evidence for a circulating alpha-cell growth factor. Diabetes 2013; 62(4): 1196-205.

31 Parker JC, Andrews KM, Allen MR, Stock JL, McNeish JD. Glycemic control in mice with targeted disruption of the glucagon receptor gene. Biochem Biophys Res Commun 2002; 290(2): 839-43.

32 Gelling RW, Du XQ, Dichmann DS, Romer J, Huang H, Cui L, *et al*. Lower blood glucose, hyperglucagonemia, and pancreatic alpha cell hyperplasia in glucagon receptor knockout mice. Proc Natl Acad Sci USA 2003; 100(3): 1438-43.

33 Conarello SL, Jiang G, Mu J, Li Z, Woods J, Zycband E, *et al*. Glucagon receptor knockout mice are resistant to diet-induced obesity and streptozotocin-mediated beta cell loss and hyperglycaemia. Diabetologia 2007; 50(1): 142-50.

34 Perry RJ, Camporez JG, Kursawe R, Titchenell PM, Zhang D, Perry CJ, *et al*. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell 2015; 160(4): 745-58.

35 Lu M, Wan M, Leavens KF, Chu Q, Monks BR, Fernandez S, *et al*. Insulin regulates liver metabolism *in vivo* in the absence of hepatic Akt and Foxo1. Nat Med 2012; 18(3): 388-95.

36 Blair JB, Cimbala MA, Foster JL, Morgan RA. Hepatic pyruvate kinase. Regulation by glucagon, cyclic adenosine 3′-5′-monophosphate, and insulin in the perfused rat liver. J Biol Chem 1976; 251(12): 3756-62.

37 Pilkis SJ, El-Maghrabi MR, McGrane M, Pilkis J, Claus TH. Regulation by glucagon of hepatic pyruvate kinase, 6-phosphofructo 1-kinase, and fructose-1,6-bisphosphatase. Fed Proc 1982; 41(10): 2623-8.

38 Rider MH, Bertrand L, Vertommen D, Michels PA, Rousseau GG, Hue L. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase: head-to-head with a bifunctional enzyme that controls glycolysis. Biochem J 2004; 381(Pt 3): 561-79.

39 Edgerton DS, Ramnanan CJ, Grueter CA, Johnson KM, Lautz M, Neal DW, *et al*. Effects of insulin on the metabolic control of hepatic gluconeogenesis *in vivo*. Diabetes 2009; 58(12): 2766-75.

40 Ramnanan CJ, Edgerton DS, Rivera N, Irimia-Dominguez J, Farmer B, Neal DW, *et al*. Molecular characterization of insulin-mediated suppression of hepatic glucose production *in vivo*. Diabetes 2010; 59(6): 1302-11.

41 Koo SH, Flechner L, Qi L, Zhang X, Screaton RA, Jeffries S, *et al*. The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism. Nature 2005; 437(7062): 1109-11.

42 Altarejos JY, Montminy M. CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. Nat Rev Mol Cell Biol 2011; 12(3): 141-51.

43 Dentin R, Liu Y, Koo SH, Hedrick S, Vargas T, Heredia J, *et al*. Insulin modulates gluconeogenesis by inhibition of the coactivator TORC2. Nature 2007; 449(7160): 366-9.

44 Screaton RA, Conkright MD, Katoh Y, Best JL, Canettieri G, Jeffries S, *et al*. The CREB coactivator TORC2 functions as a calcium- and cAMP-sensitive coincidence detector. Cell 2004; 119(1): 61-74.

45 Hogan MF, Ravnskjaer K, Matsumura S, Huising MO, Hull RL, Kahn SE, *et al*. Hepatic insulin resistance following chronic activation of the CREB coactivator CRTC2. J Biol Chem 2015; 290(43): 25997-6006.

46 Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, *et al*. A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange. Nature 2008; 456(7219): 269-73.

47 Accili D, Arden KC. FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. Cell 2004; 117(4): 421-6.

48 Nakae J, Kitamura T, Silver DL, Accili D. The forkhead transcription factor Foxo1 (Fkhr) confers insulin sensitivity onto glucose-6-phosphatase expression. J Clin Invest 2001; 108(9): 1359-67.

49 Puigserver P, Rhee J, Donovan J, Walkey CJ, Yoon JC, Oriente F, *et al*. Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1alpha interaction. Nature 2003; 423(6939): 550-5.

50 Schmoll D, Walker KS, Alessi DR, Grempler R, Burchell A, Guo S, *et al*. Regulation of glucose-6-phosphatase gene expression by protein kinase Balpha and the forkhead transcription factor FKHR. Evidence for insulin response unit-dependent and -independent effects of insulin on promoter activity. J Biol Chem 2000; 275(46): 36324-33.

51 Yoon JC, Puigserver P, Chen G, Donovan J, Wu Z, Rhee J, *et al*. Control of hepatic gluconeogenesis through the transcriptional

coactivator PGC-1. Nature 2001; 413(6582): 131-8.
52 Nakae J, Kitamura T, Ogawa W, Kasuga M, Accili D. Insulin regulation of gene expression through the forkhead transcription factor Foxo1 (Fkhr) requires kinases distinct from Akt. Biochemistry 2001; 40(39): 11768-76.
53 Mihaylova MM, Vasquez DS, Ravnskjaer K, Denechaud PD, Yu RT, Alvarez JG, *et al*. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. Cell 2011; 145(4): 607-21.
54 Wang B, Moya N, Niessen S, Hoover H, Mihaylova MM, Shaw RJ, *et al*. A hormone-dependent module regulating energy balance. Cell 2011; 145(4): 596-606.
55 Haeusler RA, Kaestner KH, Accili D. FoxOs function synergistically to promote glucose production. J Biol Chem 2010; 285(46): 35245-8.
56 Matsumoto M, Han S, Kitamura T, Accili D. Dual role of transcription factor FoxO1 in controlling hepatic insulin sensitivity and lipid metabolism. J Clin Invest 2006; 116(9): 2464-72.
57 Matsumoto M, Pocai A, Rossetti L, Depinho RA, Accili D. Impaired regulation of hepatic glucose production in mice lacking the forkhead transcription factor Foxo1 in liver. Cell Metab 2007; 6(3): 208-16.
58 Nakae J, Biggs WH, 3rd, Kitamura T, Cavenee WK, Wright CV, Arden KC, *et al*. Regulation of insulin action and pancreatic beta-cell function by mutated alleles of the gene encoding forkhead transcription factor Foxo1. Nat Genet 2002; 32(2): 245-53.
59 Exton JH, Park CR. Control of gluconeogenesis in liver. II. Effects of glucagon, catecholamines, and adenosine 3′,5′-monophosphate on gluconeogenesis in the perfused rat liver. J Biol Chem 1968; 243(16): 4189-96.
60 Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, Xia F, *et al*. Asprosin, a fasting-induced glucogenic protein hormone. Cell 2016; 165(3): 566-79.
61 Li E, Shan H, Chen L, Long A, Zhang Y, Liu Y, *et al*. OLFR734 mediates glucose metabolism as a receptor of asprosin. Cell Metab 2019; doi: org/10.1016/j.cmet.2019.05.022.
62 Gonzalez-Manchon C, Ayuso MS, Parrilla R. Control of hepatic gluconeogenesis: role of fatty acid oxidation. Arch Biochem Biophys 1989; 271(1): 1-9.
63 Morand C, Remesy C, Demigne C. Fatty acids are potent modulators of lactate utilization in isolated hepatocytes from fed rats. Am J Physiol 1993; 264(5 Pt 1): E816-23.
64 Arinze IJ, Hanson RW. Mitochondrial redox state and the regulation of gluconeogenesis in the isolated, perfused cat liver. FEBS Lett 1973; 31(3): 280-2.
65 Jomain-Baum M, Hanson RW. Regulation of hepatic gluconeogenesis in the guinea pig by fatty acids and ammonia. J Biol Chem 1975; 250(23): 8978-85.
66 Chen X, Iqbal N, Boden G. The effects of free fatty acids on gluconeogenesis and glycogenolysis in normal subjects. J Clin Invest 1999; 103(3): 365-72.
67 Ruderman NB. Muscle amino acid metabolism and gluconeogenesis. Annu Rev Med 1975; 26: 245-58.
68 Azzout-Marniche D, Gaudichon C, Blouet C, Bos C, Mathe V, Huneau JF, *et al*. Liver glyconeogenesis: a pathway to cope with postprandial amino acid excess in high-protein fed rats? Am J Physiol Regul Integr Comp Physiol 2007; 292(4): R1400-7.
69 Azzout-Marniche D, Gaudichon C, Tome D. Dietary protein and blood glucose control. Curr Opin Clin Nutr Metab Care 2014; 17(4): 349-54.
70 Xiao F, Huang Z, Li H, Yu J, Wang C, Chen S, *et al*. Leucine deprivation increases hepatic insulin sensitivity via GCN2/mTOR/S6K1 and AMPK pathways. Diabetes 2011; 60(3): 746-56.
71 Bass J, Lazar MA. Circadian time signatures of fitness and disease. Science 2016; 354(6315): 994-9.
72 Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science 2010; 330(6609): 1349-54.
73 Panda S. Circadian physiology of metabolism. Science 2016; 354(6315): 1008-15.
74 Ruiter M, La Fleur SE, van Heijningen C, van der Vliet J, Kalsbeek A, Buijs RM. The daily rhythm in plasma glucagon concentrations in the rat is modulated by the biological clock and by feeding behavior. Diabetes 2003; 52(7): 1709-15.
75 Boden G, Ruiz J, Urbain JL, Chen X. Evidence for a circadian rhythm of insulin secretion. Am J Physiol 1996; 271(2 Pt 1): E246-52.
76 Zhang EE, Liu Y, Dentin R, Pongsawakul PY, Liu AC, Hirota T, *et al*. Cryptochrome mediates circadian regulation of cAMP signaling and hepatic gluconeogenesis. Nat Med 2010; 16(10): 1152-6.
77 Lamia KA, Papp SJ, Yu RT, Barish GD, Uhlenhaut NH, Jonker JW, *et al*. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. Nature 2011; 480(7378): 552-6.
78 Toledo M, Batista-Gonzalez A, Merheb E, Aoun ML, Tarabra E, Feng D, *et al*. Autophagy Regulates the Liver Clock and Glucose Metabolism by Degrading CRY1. Cell Metab 2018; 28(2): 268-81.
79 Lamia KA, Sachdeva UM, DiTacchio L, Williams EC, Alvarez JG, Egan DF, *et al*. AMPK regulates the circadian clock by cryptochrome phosphorylation and degradation. Science 2009; 326(5951): 437-40.
80 DiTullio NW, Berkoff CE, Blank B, Kostos V, Stack EJ, Saunders HL. 3-mercaptopicolinic acid, an inhibitor of gluconeogenesis. Biochem J 1974; 138(3): 387-94.
81 Robinson BH, Oei J. 3-Mercaptopicolinic acid, a preferential inhibitor of the cytosolic phosphoenolpyruvate carboxykinase. FEBS Lett 1975; 58(1): 12-5.
82 Aicher TD, Boyd SA, McVean M, Celeste A. Novel therapeutics and targets for the treatment of diabetes. Expert Rev Clin Pharmacol 2010; 3(2): 209-29.
83 American Diabetes A. 7. Approaches to Glycemic Treatment. Diabetes Care 2016; 39(Suppl 1): S52-9.
84 Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, *et al*. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; 49(12): 2063-9.
85 Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, *et al*. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 1998; 338(13): 867-72.
86 Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, *et al*. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005; 310(5754): 1642-6.
87 Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, *et al*. Role of AMP-activated protein kinase in mechanism of met-

在机体利用先天免疫系统对抗病原菌感染的过程中, 脯氨酸代谢起着至关重要的作用。Tang等[61]发现, 脯氨酸分解代谢酶的调节影响宿主对细菌病原体铜绿假单胞菌的易感性, 其依赖于脯氨酸分解代谢控制活性氧(reactive oxygen species, ROS)稳态和随后的SKN-1活化, SKN-1是调节外源生物应激反应和病原体防御的关键性转录因子。该研究结果揭示了动物如何利用单一氨基酸的代谢来抵御病原体, 并将脯氨酸分解代谢鉴定为先天免疫信号的组成部分。

此外, 支链氨基酸(branched-chain amino acids, BCAAs)也被证明与免疫调节有关。20世纪70年代中期和80年代, 首次研究评估了BCAAs——亮氨酸、异亮氨酸和缬氨酸等的免疫调节能力。证据表明, BCAAs可以直接促进免疫细胞功能、帮助恢复受损的免疫系统以及改善癌症和肝脏疾病的营养状况[62]。支链氨基酸也可以在脓毒症或创伤患者的治疗中发挥作用改善临床结果和生存, 特别是亮氨酸, 是哺乳动物mTOR的激活剂[63]。Bonvini等[64]提到BCAAs激活mTOR主要与促炎症相关, 其在临床实践中对败血症和炎症的治疗能够起到很好的作用。

氨基酸代谢影响免疫细胞活化和炎症反应, 氨基酸缺乏严重时将导致疾病。因此, 在应激和炎症反应下, 可以通过外源途径补充特殊氨基酸如谷氨酰胺、精氨酸和苏氨酸等, 增强机体防御体系。

4 肿瘤代谢物对免疫细胞的影响

1927年, Otto Warburg等[65]发现, 肿瘤细胞消耗葡萄糖的速率为正常细胞的20倍左右, 这表现出肿瘤细胞与正常细胞显著不同的代谢表型。但随着癌基因的发现, 学界观点逐渐认为肿瘤是一种基因缺陷疾病。而近年代谢物组学的蓬勃发展则重新让人们认识到肿瘤其实也是一种代谢性疾病。

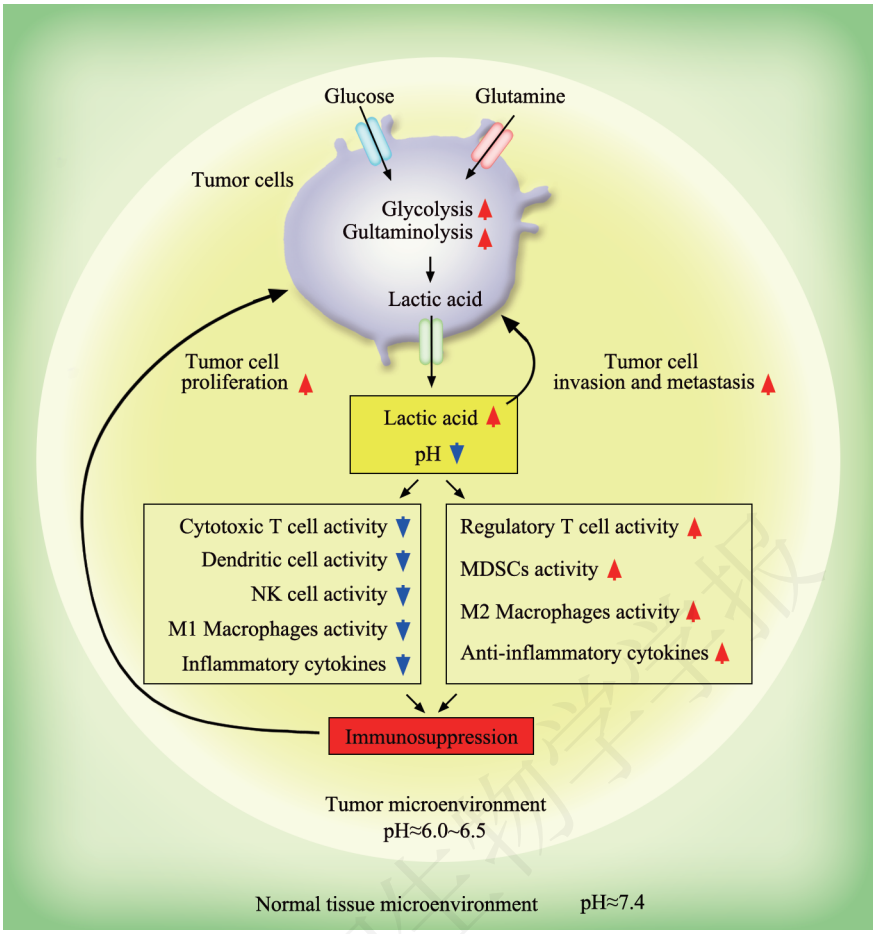
肿瘤代谢产物包括多种有机酸、乳酸、葡萄糖和氨基酸等, 首个被发现的致癌代谢物是2-羟基戊二酸(2-hydroxyglutaric acid, 2-HG), 有研究表明, 异柠檬酸脱氢酶(isocitrate dehydrogenase-1, *IDH-1*)和*IDH-2*基因的突变体在继发性弥漫性胶质瘤中表达显著升高, 导致其可以高效地将异柠檬酸转化为D-2-羟基戊二酸(D-2-HG)并在肿瘤微环境中累积, 抑制活化的T细胞迁移, 增殖和细胞因子分泌, 从而促进了肿瘤的发生[66]。

乳酸是最具代表性的肿瘤相关代谢物之一, 在肿瘤细胞生长过程中, 由于Warburg效应, 癌细胞分泌大量的乳酸到细胞外, 使微环境pH下降(图1)[67], 而当肿瘤微环境中的乳酸含量过高时, 不仅T细胞的增殖能力会被抑制, 而且乳酸还会阻止T细胞释放IL-2和IFN等细胞因子, 从而显著减弱杀伤性T细胞的杀伤效果[68]。乳酸在树突状细胞的分化过程也发挥着重要作用, 当乳酸升高时, 抑制树突状细胞分泌CD-1a, 并且树突状细胞会朝着肿瘤相关树突状细胞(tumor-associated dendritic cells, TADC)分化[69]。Potzl等[70]发现, 如果事先用乳酸处理NK细胞而降低其杀伤能力, 这就说明, 乳酸对NK细胞的杀伤功能也具有一定的调控作用。同样在巨噬细胞中, 也有研究表明乳酸可以通过激活ERK/STAT3信号通路诱导M2型巨噬细胞的产生, 从而促进肿瘤的发生发展[70](图1)。

吲哚胺2,3-双加氧酶1(indole-amine-2,3-dioxygenase-1, IDO1)的底物色氨酸以及产物犬尿氨酸也是近年研究较为广泛的肿瘤代谢物之一[71]。临床证据发现, 在多种人类癌症中IDO1的表达显著上调, 可能是由于IDO1与CTLA-4的相互调节作用, 在调节性T细胞中, CTLA-4的表达会促进IDO1的表达, 同时IDO1的表达又促进了CTLA-4的表达, 两者的相互促进导致了免疫逃逸[72]。还有研究表明, IDO1在调节性T细胞中能上调PD-1的表达, 从而进一步增强免疫逃逸[73]。

5 肠道代谢物和神经代谢物对免疫细胞的影响

代谢系统和免疫细胞之间的相互作用在多种炎性疾病中起关键作用, 而胆酸作为胆汁的关键组分之一, 是脂类代谢中重要的调节物, 除此之外, 胆酸还发挥着激素调节作用, 可以通过激活多种受体发挥复杂的生理和病理功能。Guo等[74]发现, 胆汁酸可以通过抑制NLRP3炎症小体从而改善炎症性疾病, 包括脂多糖诱导的全身性炎症、明矾诱导的腹膜炎症和II型糖尿病相关的炎症, 揭示了脂代谢通路蛋白参与炎症性疾病发生发展的新机制。胆汁酸通过TGR5-cAMP-PKA来抑制NLRP3炎性体激活, 胆汁酸受体TGR5激活PKA激酶进而直接磷酸化NLRP3 291位点的丝氨酸, 进而导致NLRP3的泛素化。此外, 体内结果也表明, 胆汁酸和TGR5活化阻



▲: 升高; ▼: 降低。
▲: rising ; ▼: reducing.

图1 乳酸在调节免疫细胞功能和促进免疫抑制中的作用

Fig.1 The role of lactic acid in regulating immune cell function and promoting immunosuppression

断了NLRP3炎性体依赖性炎症[74]。

来自日本的研究人员Yoshimoto等[75]使用化学致癌物诱导的肝细胞癌(hepatocellular carcinoma, HCC)小鼠模型研究了衰老相关分泌表型(senescence-associated secretory phenotype, SASP)对肥胖相关癌症的影响。高脂喂食的肥胖小鼠与正常喂食的健康小鼠在未接受化学致癌物质诱导时, 肿瘤发生几率差异不显著, 但受化学致癌物质诱导, 所有的肥胖小鼠体内都形成了肝癌, 且肝脏星状细胞(hepatic stellate cell, HSC)中检测到较高水平的SASP荧光, 而只有5%的健康小鼠体内形成了癌症。这些研究结果表明, 微生物菌群通过发出某些信号改变微环境, 促进了癌症发生, HSC则是这些信号的重要传感器。膳食或遗传性肥胖增强HCC形成并增加HSC中衰老标志物(包括细胞周期抑制剂和SASP细胞因子)的表达与SASP促进肥胖相关HCC的特定作用相一致, 编码SASP上游调节因子的IL-1的缺失导致肥胖小鼠中SASP细胞因子水平降低和HCC生长受损, 但不影响衰老相关的细胞周期停滞。这种致瘤作用依赖于肥胖诱导的革兰氏阳性肠道微生物的积累和脱氧胆酸(deoxycholic acid, DCA)产生增加, 脱氧胆酸是一种二级胆汁酸和细菌代谢产物, 同时也是SASP的触发因子, 与肝脏肿瘤的发生有关。相比之下, DCA刺激HSC的衰老并且促进抗生素治疗的肥胖小鼠HCC的发展, 表明DCA的肠肝循环通过诱导SASP, 促进肥胖相关的肿瘤发生。此外, 在非酒精性脂肪性肝病患者的HCC肿瘤附近检测到HSC衰老和SASP存在的证据, 提示了这一途径可能导致人类与肥胖相关的肝癌发生[75]。

肠道微生物被称为人类的“第二基因组”, 其结构、组成和状态与宿主健康息息相关。这些微小的生命体之所以会产生如此大的影响, 其中一个重

要的原因是: 它们会分泌次级代谢产物进入血液循环。有研究发现, 肠道微生物中的一个特定细菌——生孢梭菌(*Clostridium sporogenes*)会将色氨酸分解并分泌次级代谢产物吲哚丙酸(indolepropionic acid, IPA)进而导致中性粒细胞、单核细胞和记忆T细胞大量活化以及炎症性肠病的发生[76]。

胆碱能抗炎通路(cholinergic anti-inflammatory pathway, CAP)是近年发现的存在于神经系统与免疫系统之间发挥炎症调节作用的重要通路。当机体遭受免疫刺激时, 人体感受器通过中枢神经系统激活迷走神经, 引起乙酰胆碱递质的释放, 乙酰胆碱与免疫细胞上乙酰胆碱受体(nicotinic acetylcholine receptors, nAchRs)结合, 参与细胞增殖活化及炎症反应的调节。这条“胆碱能抗炎通路”能高效地抑制多种促炎因子的生成和释放, 最终抑制炎症反应, 为临床研究各种抗炎手段提供了思路。一系列动物实验发现, 使用胆碱能受体激动剂或直接刺激迷走神经, 炎性因子如TNF-α、细胞间黏附分子-1(intercellular cell adhesion molecule-1, ICAM-1)、IL-1和IL-6的表达明显降低, 对败血症、结肠炎、风湿性关节炎和肥胖症等疾病模型有治疗作用[77-78]。值得一提的是, 胆碱能受体根据其对天然生物碱的药理反应分为毒蕈碱型乙酰胆碱受体(muscarinic acetylcholine receptor, mAChR)和烟碱型乙酰胆碱受体(nicotinic acetylcholine receptor nAChR), mAChR属于G-蛋白偶联受体家族, nAChR属于配体门控的离子通道受体家族。人类的nAChR存在16种不同亚单位(α1~10、β1~4、γ、δ), 其中α7nAChR表达于多种免疫细胞如单核细胞、巨噬细胞、树突状细胞、T淋巴细胞和B淋巴细胞, 它由5个相同的亚基构成, 活化可引起钙离子内流。例如在单核−巨噬细胞中, 体外实验证明, LPS刺激巨噬细胞可上调α7nAchR的表达[79]。烟碱能抑制LPS刺激巨噬细胞炎性因子分泌, 降低TNF-α、IL-6和HMGB1等[80]。Middlebrook等[81]在短期和长期烟碱处理大鼠T淋巴细胞后, 发现烟碱抑制单核淋巴细胞对刀豆蛋白(concanavalin A, ConA)的增殖反应, 加入nAChR的拮抗剂后可以阻断该现象, 表明nAChR参与了T细胞增殖[81]。

6 结语与展望

目前免疫细胞代谢组学是相关领域的研究热点, 越来越多的研究表明, 调节不同的代谢途径将决定免疫细胞的命运。本文讨论了不同代谢通路和代谢中间物对免疫细胞增殖、分化和迁移及分泌细胞因子、趋化因子、炎症因子过程的影响。免疫细胞自身通常缺乏营养物质的储备, 为满足上述过程中其对能量和代谢中间物的需求, 免疫细胞必须依赖微环境中的物质和能量。所以, 局部微环境中各种代谢中间物的水平对免疫细胞的命运发挥了至关重要的作用。无论是巨噬细胞、树突状细胞等固有免疫细胞还是T细胞等适应性免疫细胞, 都在身体各组织中不断地感应外部刺激、启动特异性免疫应答或免疫耐受反应。以树突状细胞为例, 即使是同一亚型的树突状细胞, 在不同组织中其基因表达和表面标志物具有很大的异质性, 反映了其独特的抗原提呈和与效应淋巴细胞结合的能力。

有氧糖酵解、线粒体氧化磷酸化和脂肪酸β氧化在调节固有和适应性免疫应答方面具有关键作用。通常有氧糖酵解途径是炎性和快速增殖的免疫细胞的主要代谢方式; 而许多非炎性和非快速增殖的免疫细胞, 例如M2型巨噬细胞、Treg细胞和记忆性T细胞, 则表现出对脂肪酸β氧化途径的依赖性。为什么细胞在选择有氧糖酵解途径与脂肪酸β氧化途径之间会延伸出相反的免疫反应和调节功能? 一些观点认为, 产生炎性和快速增殖的免疫细胞选择有氧糖酵解途径是因为需要大量的代谢中间物用于生物合成和分泌; 而M2型巨噬细胞或Treg细胞等耐受性细胞多生活于营养物质相对缺乏的组织微环境中, 因此ATP生成效率至关重要。另外一些观点认为, 产生炎性和快速增殖的免疫细胞增殖期间需要脂肪酸合成形成的脂质来构建细胞膜, 而记忆性免疫细胞等生长缓慢, 生物合成需求相对较少, 因此以分解代谢为主。改变能量代谢谱能否能够在一定程度上实现对同类免疫细胞活性和功能的调节? 因此积极探索在局部微环境中免疫细胞的代谢水平和代谢谱, 不仅有助于深刻解读免疫细胞应答“自我”和“非我”物质的深层机制, 同时也能够为免疫系统疾病、代谢系统疾病和恶性肿瘤等寻求可能的更为有效的分子靶标。

参考文献 (References)

1 Murray PJ, Rathmell J, Pearce E. SnapShot: Immunometabolism. Cell Metab 2015; 22(1): 190.

2 Ghesquiere B, Wong BW, Kuchnio A, Carmeliet P. Metabolism of stromal and immune cells in health and disease. Nature 2014;

511(7508): 167-76.
3 Zeng H, Chi HB. Metabolic control of regulatory T cell development and function. Trends Immunol 2015; 36(1): 3-12.
4 Norata GD, Caligiuri G, Chavakis T, Matarese G, Netea MG, Nicoletti A, *et al*. The cellular and molecular basis of translational immunometabolism. Immunity 2015; 43(3): 421-34.
5 Buttgereit F, Burmester GR, Brand MD. Bioenergetics of immune functions: fundamental and therapeutic aspects. Immunol 2000; 21(4): 192-9.
6 Fox CJ, Hammerman PS, Thompson CB. Fuel feeds function: Energy metabolism and the T-cell response. Nat. Rev. Immunol 2005; 5(11): 844-52.
7 Hume DA, Radik JL, Ferber E, Weidemann MJ. Aerobic glycolysis and lymphocyte transformation. Biochem J 1978; 174(3): 703-9.
8 Straub RH, Cutolo M, Buttgereit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. J Intern Med 2010; 267(6): 543-60.
9 Tollefsbol TO, Cohen HJ. Culture kinetics of glycolytic enzyme induction, glucose utilization, and thymidine incorporation of extended-exposure phytohemagglutinin-stimulated human lymphocytes. J Cell Physiol 1985; 122(1): 98-104.
10 Palmer CS, Ostrowski M, Balderson B, Christian N, Crowe SM. Glucose metabolism regulates T cell activation, differentiation, and functions. Front Immunol 2015; 6: 1.
11 Newsholme P, Curi R, Gordon S, Newsholme EA. Metabolism of glucose, glutamine, long-chain fatty acids and ketone bodies by murine macrophages. Biochem J 1986; 239(1): 121-5.
12 Curi TC, De Melo MP, De Azevedo RB, Zorn TM, Curi R. Glutamine utilization by rat neutrophils: presence of phosphate-dependent glutaminase. Am J Physiol 1997; 273(4): C1124-9.
13 Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? J Nutr 2001; 131(9): 2515S-22S,23S-4S.
14 Frauwirth KA, Thompson CB. Regulation of T lymphocyte metabolism. J Immunol 2004; 172(8): 4661-5.
15 Calder PC. Fuel utilization by cells of the immune system. Proc. Nutr Soc 1995; 54(1): 65-82.
16 Lv L, Li D, Zhao D, Lin RT, Chu YJ, Zhang H, *et al*. Acetylation targets the M2 isoform of pyruvate kinase for degradation through chaperone-mediated autophagy and promotes tumor growth. Mol Cell 2011; 42(6): 719-30.
17 Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic instruction of immunity. Cell 2017; 169(4): 570-86.
18 Sbarra AJ, Karnovsky ML. The biochemical basis of phagocytosis. I. Metabolic changes during the ingestion of particles by polymorphonuclear leukocytes. J Biol Chem 1959; 234(6): 1355-62.
19 Fossati G, Moulding DA, Spiller DG, Moots RJ, White MR, Edwards SW. The mitochondrial network of human neutrophils: role in chemotaxis, phagocytosis, respiratory burst activation, and commitment to apoptosis. J Immunol 2003; 170(4): 1964-72.
20 Borregaard N, Herlin T. Energy metabolism of human neutrophils during phagocytosis. J Clin Invest 1982; 70(3): 550-7.
21 Kirchner T, Moller S, Klinger M, Solbach W, Laskay T, Behnen M. The impact of various reactive oxygen species on the formation of neutrophil extracellular traps. Mediators Inflamm 2012; 2012(1): 849136.
22 Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, *et al*. Neutrophil extracellular traps kill bacteria. Science 2004; 303(5663): 1532-5.
23 Cramer T, Yamanishi Y, Clausen BE, Forster I, Pawlinski R, Mackman N, *et al*. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell 2003; 112(5): 645-57.
24 Peachman KK, Lyles DS, Bass DA. Mitochondria in eosinophils: functional role in apoptosis but not respiration. Proc Natl Acad Sci USA 2001; 98(4): 1717-22.
25 Peyssonnaux C, Datta V, Cramer T, Doedens A, Theodorakis EA, Gallo RL, *et al*. HIF-1alpha expression regulates the bactericidal capacity of phagocytes. J Clin Invest 2005; 115(7): 1806-15.
26 Kempner W. The nature of leukemic blood cells as determined by their metabolism. J Clin Invest 1939; 18(3): 291-300.
27 Venge P, Moberg L, Bjornsson E, Bergstrom M, Langstrom B, Hakansson L. Mechanisms of basal and cytokine-induced uptake of glucose in normal human eosinophils: relation to apoptosis. Respir Med 2003; 97(10): 1109-19.
28 Newsholme P, Gordon S, Newsholme EA. Rates of utilization and fates of glucose, glutamine, pyruvate, fatty acids and ketone bodies by mouse macrophages. Biochem J 1987; 242(3): 631-6.
29 Gallucci S, Matzinger P. Danger signals: SOS to the immune system. Curr Opin Immunol 2001; 13(1): 114-9.
30 Bours MJ, Swennen EL, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther 2006; 112(2): 358-404.
31 Oronsky BT, Oronsky N, Fanger GR, Parker CW, Caroen SZ, Lybeck M, *et al*. Follow the ATP: tumor energy production: a perspective. Anticancer Agents Med Chem 2014; 14(9): 1187-98.
32 Faas MM, Saez T, de Vos P. Extracellular ATP and adenosine: The Yin and Yang in immune responses? Mol Aspects Med 2017; 55(1): 9-19.
33 Lazarowski ER. Vesicular and conductive mechanisms of nucleotide release. Purinerg Signal 2012; 8(3): 359-73.
34 Dean GE, Fishkes H, Nelson PJ, Rudnick G. The hydrogen ion-pumping adenosine triphosphatase of platelet dense granule membrane. Differences from F1F0- and phosphoenzyme-type ATPases. J Biol Chem 1984; 259(15): 9569-74.
35 Tokunaga A, Tsukimoto M, Harada H, Moriyama Y, Kojima S. Involvement of SLC17A9-dependent vesicular exocytosis in the mechanism of ATP release during T cell activation. J Biol Chem 2010; 285(23): 17406-16.
36 Lohman AW, Billaud M, Isakson BE. Mechanisms of ATP release and signalling in the blood vessel wall. Cardiovasc Res 2012; 95(3): 269-80.
37 Anderson P, Rohlich P, Slorach SA, Uvnas B. Morphology and storage properties of rat mast cell granules isolated by different methods. Acta physiologica Scandinavica 1974; 91(2): 145-53.
38 Corthay A. How do regulatory T cells work? Scand J Immunol 2009; 70(4): 326-36.
39 Schenk U, Frascoli M, Proietti M, Geffers R, Traggiai E, Buer J, *et al*. ATP inhibits the generation and function of regulatory T cells through the activation of purinergic P2X receptors. Sci Signal 2011; 4(162): ra12.
40 Jacob F, Perez Novo C, Bachert C, Van Crombruggen K. Purinergic signaling in inflammatory cells: P2 receptor expression,

functional effects, and modulation of inflammatory responses. Purinerg Signal 2013; 9(3): 285-306.
41 Killeen ME, Ferris L, Kupetsky EA, Falo L, Jr., Mathers AR. Signaling through purinergic receptors for ATP induces human cutaneous innate and adaptive Th17 responses: implications in the pathogenesis of psoriasis. J Immunol 2013; 190(8): 4324-36.
42 Ecker J, Liebisch G, Englmaier M, Grandl M, Robenek H, Schmitz G. Induction of fatty acid synthesis is a key requirement for phagocytic differentiation of human monocytes. Proc Natl Acad Sci USA 2010; 107(17): 7817-22.
43 Freigang S, Ampenberger F, Weiss A, Kanneganti TD, Iwakura Y, Hersberger M, *et al*. Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1 alpha and sterile vascular inflammation in atherosclerosis. Nat Immunol 2013; 14: (10)1045.
44 Ecker J, Liebisch G, Englmaier M, Grandl M, Robenek H, Schmitz G. Induction of fatty acid and phospholipid synthesis is a key requirement for phagocytic differentiation of human monocytes. Proc Natl Acad Sci USA 2010; 107(17): 7817-22.
45 MacIver NJ, Michalek RD, Rathmell JC. Metabolic regulation of T lymphocytes. Annu Rev Immunol 2013; 31(1): 259-83.
46 Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu BL, Bell LN, *et al*. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat Commun 2015; 6: 6692.
47 Im SS, Yousef L, Blaschitz C, Liu JZ, Edwards RA, Young SG, *et al*. Linking lipid metabolism to the innate immune response in macrophages through sterol regulatory element binding protein-1a. Cell Metab 2011; 13(5): 540-9.
48 Everts B, Amiel E, Huang SCC, Smith AM, Chang CH, Lam WY, *et al*. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKK epsilon supports the anabolic demands of dendritic cell activation. Nat Immunol 2014; 15(4): 323.
49 Bietz A, Zhu HY, Xue MM, Xu CQ. Cholesterol metabolism in T cells. Front Immunol 2017; doi: 10.3389/fimmu.2017.01664.
50 Wang F, Beck-Garcia K, Zorzin C, Schamel WWA, Davis MM. Inhibition of T cell receptor signaling by cholesterol sulfate, a naturally occurring derivative of membrane cholesterol. Nat Immunol 2016; 17(7): 844.
51 Takeda A, Umemoto E, Miyasaka M. Lysophosphatidic acid as a regulator of lymphocyte trafficking in the lymph nodes. Transl Cancer Res 2015; 4(5): 537-43.
52 Chan LC, Peters W, Xu Y, Chun J, Farese RV, Cases S. LPA(3) receptor mediates chemotaxis of immature murine dendritic cells to unsaturated lysophosphatidic acid (LPA). J Leukoc Biol 2007; 82(1): 1193-200.
53 Robertson EC, Tisdall FF. Diet and nutrition: Nutrition and resistance to disease. Can Med Assoc J 1939; 40(1): 282-4.
54 Belokrytov GA MI, Sorochinskaia EI. Amino acids as immunogenesis stimulants. Doklady Akademii nauk SSSR 1986; 286(2): 471-3.
55 Yaqoob P, Calder PC. Glutamine requirement of proliferating T lymphocytes. Nutrition 1997; 13(7/8): 646-51.
56 Coeffier M, Miralles-Barrachina O, Le Pessot F, Lalaude O, Daveau M, Lavoinne A, *et al*. Influence of glutamine on cytokine production by human gut *in vitro.* Cytokine 2001; 13(3): 148-54.
57 Barbul A. Arginine: biochemistry, physiology, and therapeutic implications. Jpen-Parenter Enter 1986; 10(2): 227-38.
58 Visek WJ. Arginine needs, physiological-state and usual diets: a reevaluation. J Nutr 1986; 116(1): 36-46.
59 Rath M, Muller I, Kropf P, Closs EI, Munder M. Metabolism via arginase or nitric oxide synthase: Two competing arginine pathways in macrophages. Front Immunol 2014; 5(1): 532.
60 Law GK BR, Adjiri-Awere A, Pencharz PB, Ball RO. Adequate oral threonine is critical for mucin production and gut function in neonatal piglets. Am J Physiol Gastrointest Liver Physiol 2007; 292(5): G1293-301.
61 Tang H, Pang S. Proline catabolism modulates innate immunity in *Caenorhabditis elegans*. Cell Rep 2016; 17(11): 2837-44.
62 Calder PC. Feeding the immune system. Proc Nutr Soc 2013; 72(3): 299-309.
63 Ananieva EA, Powell JD, Hutson SM. Leucine metabolism in T cell activation: mTOR signaling and beyond. Adv Nutr 2016; 7(4): 798S-805S.
64 Bonvini A, Coqueiro AY, Tirapegui J, Calder PC, Rogero MM. Immunomodulatory role of branched-chain amino acids. Nutr Rev 2018; 76(1): 840-56.
65 Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927; 8(6): 519-30.
66 Zhang L, Sorensen MD, Kristensen BW, Reifenberger G, McIntyre TM, Lin F. D-2-hydroxyglutarate is an intercellular mediator in IDH-mutant giomas inhibiting complement and T cells. Clin Cancer Res 2018; 24(21): 5381-91.
67 Goetze K, Walenta S, Ksiazkiewicz M, Kunz-Schughart LA, Mueller-Klieser W. Lactate enhances motility of tumor cells and inhibits monocyte migration and cytokine release. Int J Oncol 2011; 39(2): 453-63.
68 Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, *et al*. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007; 109(9): 3812-9.
69 Mu X, Shi W, Xu Y, Xu C, Zhao T, Geng B, *et al*. Tumor-derived lactate induces M2 macrophage polarization via the activation of the ERK/STAT3 signaling pathway in breast cancer. Cell Cycle 2018; 17(4): 428-38.
70 Potzl J, Roser D, Bankel L, Homberg N, Geishauser A, Brenner CD, *et al*. Reversal of tumor acidosis by systemic buffering reactivates NK cells to express IFN-gamma and induces NK cell-dependent lymphoma control without other immunotherapies. Int J Cancer 2017; 140(9): 2125-33.
71 Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, *et al*. LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab 2016; 24(5): 657-71.
72 Zhai L, Ladomersky E, Lenzen A, Nguyen B, Patel R, Lauing KL, *et al*. IDO1 in cancer: a Gemini of immune checkpoints. Cell Mol Immunol 2018; 15(5): 447-57.
73 Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R, *et al*. Modulation of tryptophan catabolism by regulatory T cells. Nat Immunol 2003; 4(12): 1206-12.
74 Guo CS, Xie SJ, Chi ZX, Zhang JH, Liu YY, Zhang L, *et al*. Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome. Immunity 2016; 45(4): 944.
75 Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, *et al*. Obesity-induced gut microbial metabolite promotes liver

cancer through senescence secretome. Nature 2013; 499(7456): 97-101.

76 Dodd D, Spitzer MH, Van Treuren W, Merrill BD, Hryckowian AJ, Higginbottom SK, *et al*. A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites. Nature 2017; 551(7682): 648-52.

77 Borovikova LV, Ivanova S, Zhang MH, Yang H, Botchkina GI, Watkins LR, *et al*. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000; 405(6785): 458-62.

78 Pavlov VA, Ochani M, Yang LH, Gallowitsch-Puerta M, Ochani K, Lin XC, *et al*. Selective alpha 7-nicotinic acetylcholine receptor agonist GTS-21 improves survival in murine endotoxemia and severe sepsis. Crit Care Med 2007; 35(4): 1139-44.

79 Khan MA, Farkhondeh M, Crombie J, Jacobson L, Kaneki M, Martyn JA. Lipopolysaccharide upregulates alpha7 acetylcholine receptors: stimulation with GTS-21 mitigates growth arrest of macrophages and improves survival in burned mice. Shock 2012; 38(2): 213-9.

80 Wang H, Liao H, Ochani M, Justiniani M, Lin X, Yang L, *et al*. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. Nat Med 2004; 10(11): 1216-21.

81 Middlebrook AJ, Martina C, Chang Y, Lukas RJ, DeLuca D. Effects of nicotine exposure on T cell development in fetal thymus organ culture: arrest of T cell maturation. J Immunol 2002; 169(6): 2915-24.