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氧和二氧化碳慢性感知机制的免疫调节作用

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摘要：感知氧和二氧化碳浓度变化并做出适当响应是机体维持正常生理功能的重要环节。目前已知的氧与二氧化碳感知信号通路主要分为急性感知(acute sensing)和慢性感知(chronic sensing)两类。通过由中枢和外周化学感受器介导的急性感知信号通路，机体能够对氧或二氧化碳水平的突然变化做出快速响应，即时调整通气量；而当长时间处于氧或二氧化碳浓度异常环境时，机体则不仅需要通过急性感知系统调整通气量，还需要通过慢性感知通路调整组织、细胞的基因转录和代谢状态来适应异常的氧和二氧化碳浓度。慢性感知是由分布于各种细胞中的分子感受器介导的，该通路对细胞功能具有广泛而复杂的影响。该文将在扼要回顾氧和二氧化碳感知机制的基础上，着重阐述二者的慢性感知通路与机体免疫应答之间的关系。

关键词：氧感知机制；二氧化碳感知机制；低氧诱导因子；可溶性腺苷酸环化酶；免疫应答

The role of oxygen and carbon dioxide chronic sensing pathways in immune reglulation

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Abstract: Sensing and responding to changes in oxygen and carbon dioxide concentrations are a vital part for the maintenance of normal physiological functions. There are two different mechanisms in oxygen and carbon dioxide sensing, including acute sensing and chronic sensing. Through the acute sensing pathway mediated by central and peripheral chemoreceptors, the body could respond quickly to sudden changes in oxygen or carbon dioxide levels and adjust ventilation instantly. While, if being exposed to abnormal oxygen or carbon dioxide concentration for a long time, the body will not only need to adjust ventilation through the acute sensory mechanism, but also need to modulate the genes transcription and the metabolism of tissues and cells through the chronic sensing pathway to adapt to the abnormal environment. Chronic sensing pathway is mediated by molecular sensor expressed in various cells, which has extensive and complex effects on cellular

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pathways. In this review, we briefly summarized the mechanisms of oxygen and carbon dioxide sensing and focused on the relationships between the chronic sensing pathways of O_2/CO_2 and immune responses.

Key Words: oxygen sensing mechanism; carbon dioxide sensing mechanism; HIF-1α; soluble adenylyl cyclase; immune response

氧气和二氧化碳是参与生命活动的两种至关重要的气体分子，由二者水平异常引起的病理效应(如低氧血症、高碳酸血症)严重时可危及生命[1]。机体内氧气的消耗和二氧化碳的产生是相互关联的，因此在细胞和组织中二者的浓度存在密切的负相关关系[2]。在正常生理状态下，机体能够通过分布于中枢和外周的感知反馈系统维持血液中氧气和二氧化碳含量的稳定：在氧气浓度下降或者二氧化碳浓度升高时，机体能够及时的通过调整通气量使之恢复正常水平[3,4]。但在某些病理状态下，例如急性呼吸窘迫综合征、阻塞性睡眠呼吸暂停综合征[5]、慢性阻塞性肺疾病[6]、感染性肺炎等，氧气与二氧化碳的浓度维持机制被打破，二者可单独或同时出现异常，并可通过相应的细胞感受器触发一系列下游病理反应。概括而言，机体对氧气与二氧化碳的感知可以分为急性感知和慢性感知两类。其中，急性感知是指机体外周神经通过化学感受器探测氧与二氧化碳分压的变化，继而通过神经反馈调节换气节律；慢性感知是指机体通过分布于细胞表面或细胞内的受体分子探测氧与二氧化碳浓度的变化，继而调节细胞代谢和基因转录(图1)[1]。本文将着重回顾氧气与二氧化碳的慢性感知机制，并扼要阐述其与免疫应答的关系。

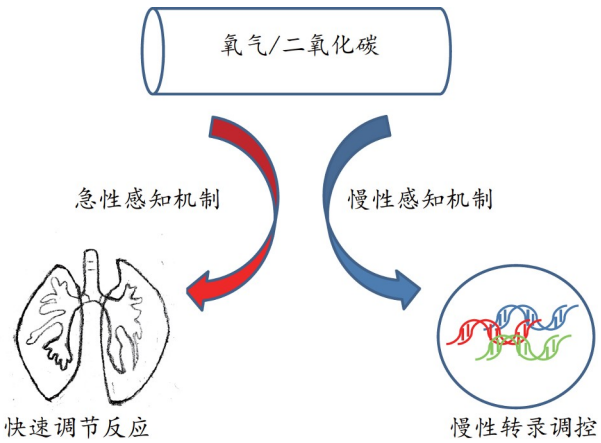

图1 氧和二氧化碳的急性与慢性感知[1]

1 细胞的氧浓度感知机制及其对机体免疫应答的影响

如前所述，机体能够通过急性和慢性感知通路感受体内氧浓度变化，急性感知可通过调节呼吸频率和深度从整体层面调节体内氧浓度；而慢性感知机制则可通过分布于细胞中的氧分子感受器来调节机体细胞的转录和代谢，帮助机体组织细胞适应氧浓度的变化。慢性感知机制主要通过调节基因转录得以实现，已发现的能被氧浓度调节的转录因子包括低氧诱导因子-1α(hypoxia-inducible factor-1α，HIF-1α)、活化B细胞的核因子κ轻链增强子(nuclear factor kappa-light-chain-enhancer of activated B cells，NF-κB)、转录激活因子4(activating transcription factor 4，ATF4)、肿瘤蛋白P53(tumour protein p53，P53)等(表1)[7,8]。这其中多数因子需要在特定细胞类型或特定细胞状态下发挥作用，而HIF通路的调节作用是广泛存在的，被认为是细胞氧浓度感知信号通路的总调节因子(master regulator)[7]。

1.1 低氧诱导因子家族的结构和功能特征

HIFs家族在多细胞动物中广泛存在，该分子家族已知成员包括HIF-1、HIF-2和HIF-3。活化的HIFs是由HIF-α和HIF-β亚基构成的异源二聚体，前者是氧敏感的亚基，在常氧条件下极不稳定；后者是组成性表达亚基。与广泛表达的HIF-1α相比，HIF-2α则主要表达于癌组织、肺、内皮组织和颈动脉体，促进侵袭性肿瘤病情恶化[9,10]。随着对HIF家族的研究逐渐深入，目前认为，低氧环境也可使HIF-3α表达增加，但此过程需要HIF-1α诱导[11]。 HIF-1α作为缺氧感受器被Semenza提出[12]，HIF-1α的转录和合成不受氧的影响，但是，在常氧状态下，HIF-1α合成后迅速降解，导致HIF-1α基本无法检被测到，其降解主要通过2个经典途径实现(图2)[13]。(1)HIF-1α需氧降解区域(oxygen-

表1 能够感知氧浓度变化的转录因子[7,8]

缩写	英文全名	中文全名
HIF*	hypoxia-inducible factor	低氧诱导因子
NF-κB*	nuclear factor kappa-light-chain-enhancer of activated B cells	活化B细胞的核因子κ轻链增强子
ATF4	activating transcription factor 4	转录激活因子4
FOXO3a*	forkhead box O3a*	叉形头转录因子O亚型3a
P53	tumour protein p53	肿瘤蛋白P53
CREB*	cyclic AMP response element binding protein*	环一磷酸腺苷反应元件结合蛋白
Myc	Myc avian myelocytomatosis viral oncogene homolog	Myc禽髓细胞瘤病毒癌基因同源物
AP-1	activating protein-1	激活蛋白1
NF-IL6/C/EBPβ	CCAAT/enhancer binding protein (C/EBP) beta	CCAAT/增强子结合蛋白β
EGR-1	early growth response-1	早期生长反应-1
GATA-2	GATA binding protein-2	GATA结合蛋白-2
Ets-1	V-Ets avian erythroblastosis virus E26 oncogene homolog-1	V-Ets禽成红细胞病病毒E26致癌基因同源物-1
Dec1/2	differentially expressed in chondrocytes 1/2	软骨细胞1/2中的表达差异
RTEF-1	related transcriptional enhancer factor-1	相关转录增强因子-1
Purα	purine-rich binding protein alpha	富含小嘌呤的结合蛋白α
STAT	signal transducer and activator of transcription	信号传感器和转录激活因子
GADD153	growth arrest and DNA damage-153	生长停滞和DNA损伤-153
SP1/SP3	SP/XKLF	特异性蛋白1/特异性蛋白3
MASH2	mammalian achaete-scute homologous protein-2	哺乳动物的同源蛋白-2

*表示能感知氧气和二氧化碳浓度变化的转录因子

dependent degradation domain，ODD)的第402和/或564位脯氨酸残基被脯氨酸羟化酶(the prolyl hydroxylase domain，PHD)羟基化。羟基化本质上是氧化反应，脯氨酸羟化酶需要氧气作为底物，缺乏氧气脯氨酸羟化酶就无法发挥作用。羟基化的HIF-1α可被希佩尔-林道蛋白(von Hippel-Lindau protein，pVHL)识别，使得pVHL介导的E3泛素连接酶复合体与羟基化的HIF-1α结合，导致HIF-1α的泛素化和蛋白酶体的降解[14]。(2)通过HIF-1抑制因子(factor inhibiting HIF-1，FIH-1)使第803位天冬酰胺残基羟基化，抑制cAMP反应元件结合蛋白(cyclic-AMP response binding protein，CBP)与腺病毒E1A相关的300 kDa蛋白(adenovirus E1A-associated 300 kDa protein，p300)的结合，从而抑制HIF通路[15]。由于PHDs发挥作用需要氧气作为底物，因此在低氧条件下，PHDs无法发挥羟基化作用，使得HIF-1α不被降解且能够入核与HIF-1β结合形成二聚体复合物，促进下游靶基因的表达[16]。HIF-1α能够导致很多靶基因的上调，例如促红细胞生成素(erythropoietin，EPO)、血管生长因子(vascular endothelial growth factor，VEGF)以及对心脏有保护作用的抗氧化酶。HIF-1α的作用有利有弊，例如，在缺氧条件下，它会使VEGF的生成增加，引发血管生成，增加氧的利用率，缓解组织和器官的缺氧程度，避免细胞死亡[17]。但与此同时，VEGF也可增加血管的通透性，使免疫细胞更易迁移到组织中，加重炎症程度[18]。

1.2 HIF-1α与免疫应答的关系

生理或病理性原因均可导致组织微环境缺氧。生理性缺氧经常出现在细胞增殖快，代谢需求高的组织部位，例如细胞增殖活跃的免疫器官或组织[19]。由病理因素导致的组织缺氧可见于肿瘤[20]以及炎症部位[21]。当血液富氧环境中的循环免疫细胞被招募到缺氧组织环境之中时，HIF能够帮助这些免疫细胞快速适应缺氧微环境[22]。HIF在暴露于缺氧环境的天然免疫细胞和适应性免疫细胞中发挥重要的调节作用。在树突状细胞中，HIF-1α可调节其存活、迁移、抗原呈递、干扰素合成和分化[23,24]。在T细胞中，HIF-1α不仅可调节其存活和分化，还可调节其抗肿瘤能力[13]。同样，HIF-

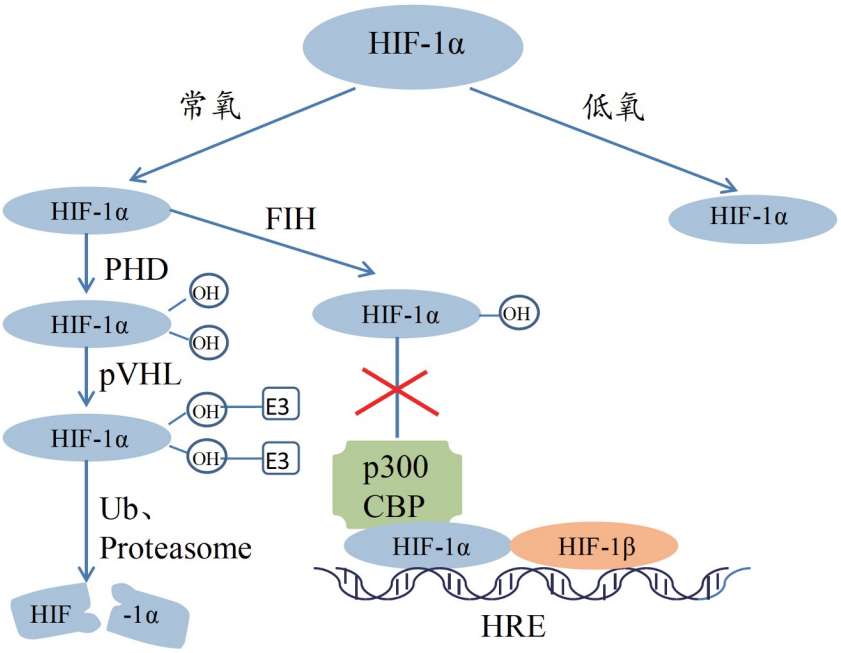

图2 HIF-1α在常氧条件下的调控方式[13]

1α也能调节B细胞的存活[25]。除此之外，HIF-1α也可通过代谢途径调节免疫细胞，例如其可以通过转录上调糖酵解相关基因的表达从而增加糖酵解的速率，糖酵解速率的增加反过来又可促进巨噬细胞、树突状细胞、T细胞和B细胞等免疫细胞的激活[26]。与此同时，激活的免疫应答也能通过细胞因子或者代谢产物信号通路调节HIF-1α的表达水平或转录活性[22]。例如，被炎症信号(细胞因子、细菌产物)激活的NF-κB可促进HIF-1α的转录活性；免疫代谢物S-2-羟基戊二酸(S-2-hydroxyglutarate，S-2-HG)、气体介质(NO、H_2S)也可增强HIF-1α的转录活性。此外，HIF-1α与NF-κB信号通路存在交互作用，HIF-1α能够促进肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)和白介素-6(interleukin-6，IL-6)等炎症因子的产生(图3A)[27]，而白介素-1β(interleukin-1beta，IL-1β)等炎症因子也可以促进HIF-1α的表达[28]，在参与炎症应答的同时，HIF-1α还能够增强巨噬细胞和中性粒细胞的功能，提高其抵御细菌感染的能力(图3B)[27]。不仅如此，HIF-1α也可促进非免疫细胞的炎性反应。例如，HIF-1α与脂肪细胞中炎症标志物(TNF-α、IL-6等)的升高呈正相关[29]；敲低急性期缺血性脑卒中小鼠小胶质细胞中的HIF-1α，可减少TNF-α的产生，促进神经元的存活[30]。

在病毒感染和抗感染免疫应答发生过程中，HIF-1α也被发现扮演重要角色。甲型流感病毒H5N1亚型感染猕猴后能够迅速上调肺组织中HIF-1α的表达水平[31]。Uematsu等[32]发现，敲除*Mint3*/*Apba3*基因能够显著减轻由H1N1感染导致的炎症应答，并改善小鼠肺炎症状。由于*Mint3*/*Apba3*敲除能够抑制HIF-1α的激活[32,33]。因而这些发现间接提示了HIF-1α在流感病毒感染过程中具有促进炎症应答的作用。此外，体外实验证明HIF-1α在流感病毒诱导炎症反应过程中发挥关键的调控作

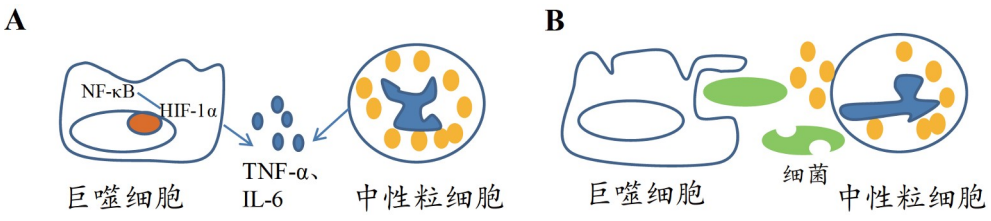

图3 HIF-1α能够促进炎症因子产生并提高巨噬细胞和中性粒细胞的功能[27]

用，抑制HIF-1α可显著降低TNF-α和IL-6的表达[34]。此外，HIF-1α缺陷的肺上皮细胞通过减少糖酵解和增强自噬，促进了甲型流感病毒H1N1亚型的复制[35]。这表明HIF-1α在甲型流感病毒感染中的病毒复制、细胞因子反应和肺部炎症中起重要作用。而且，在新型冠状病毒导致的新型冠状病毒肺炎(corona virus disease 2019，COVID-19)中，由病毒感染导致的HIF-1α在肺内累积可导致趋化因子释放并致使单核细胞、树突状细胞和中性粒细胞在肺部快速浸润。这种浸润会导致气管甚至毛细血管的阻塞，这种阻塞会进一步加重缺氧，迫使细胞进入厌氧糖酵解途径，促进病毒复制[36]。除病毒感染外，脂多糖(lipopolysaccharide，LPS)在缺氧条件下也可诱导出更高水平的TNF和IL-6，而将*HIF-1α*基因敲除后，LPS刺激后产生的TNF和IL-6减少[37,38]。

2 细胞的二氧化碳浓度感知机制及其对机体免疫应答的影响

与氧的细胞感知机制研究进展不同，在二氧化碳浓度感知信号通路上迄今为止尚未发现占据支配地位的主调控因子(master regulator)[1,39]，但有一些转录因子(表2)[8,40]已被证实参与由二氧化碳浓度变化引起的信号转导，例如NF-κB、热激转录因子1(heat shock transcription factor 1，HSF1)、叉形头转录因子O亚型3a(forkhead box O3a，Foxo3a)和环一磷酸腺苷反应元件结合蛋白(cyclic AMP response element binding protein，CREB)。NF-κB参与炎症、免疫、细胞生存、凋亡和细胞周期等相关基因的调控，体内pCO_2升高可伴随着NF-κB信号通路发生改变，但二者之间的因果关系仍然未知[41,42]。此外，另有一些因子被发现能够间接感知体内二氧化碳浓度的变化，例如可溶性腺苷酸环化酶(soluble adenylyl cyclase，sAC)可被HCO_3^-激活。由于体内的CO_2、H^+和HCO_3^-浓度可在碳酸酐酶作用下达到瞬间平衡状态，因此sAC通常也被认为是重要的CO_2浓度和pH值感受器[43]。

2.1 sAC在二氧化碳慢性感知中的作用

近年来，sAC被认为可通过感知HCO_3^-浓度的改变间接感知体内pCO_2的改变。sAC在20世纪70时代被发现[44]，最初被认为只存在于哺乳动物精细胞中，后被证实在多种组织中均有表达[45,46]。腺苷酸环化酶(adenylyl cyclases，ACs)是将ATP转化为cAMP的一类酶家族，哺乳动物细胞中存在两套独立调节cAMP的信号转导系统：跨膜型腺苷酸环化酶(transmembrane adenylate cyclase，tmAC)和sAC。二者的细胞定位和调控方式均有不同。首先，tmAC只局限于细胞膜，而sAC可分布于整个细胞，包括线粒体、中心粒、有丝分裂纺锤体、中间体和细胞核等特定的亚细胞器中[47]。其次，tmAC具有跨膜结构域，可与G蛋白偶联受体(G-protein coupled receptor，GPCR)结合，在细胞质中完成ATP向cAMP的转化，sAC则不与GPCR结合，而是在碳酸酐酶的介导下，被水合CO_2解离出的HCO_3^-或通过Na^+/HCO_3^-离子转运体进入到细胞内的HCO_3^-激活，即机体环境中HCO_3^-升高时，在Ca^{2+}的协同作用下，sAC活性增强，使ATP转化为cAMP(图4)[48]。sAC可不依赖于钙调素直接被Ca^{2+}和HCO_3^-激活，Ca^{2+}降低了底物和ATP之间的Km，而HCO_3^-则降低了底物抑制效应，增加了最大反应速率[49,50]。ACs均含有C1和C2催化结构域，二者在交界处形成了一个无催化活性的“口袋”结构，可

表2 能够感知二氧化碳浓度变化的转录因子[8,40]

缩写	英文全名	中文全名
Phox2b	paired-like homeobox 2b	配对同源异型盒蛋白2B
NF-κB*	nuclear factor kappa-light-chain-enhancer of activated B cells	活化B细胞的核因子κ轻链增强子
FOXO3a*	forkhead box O3a*	叉形头转录因子O亚型3a
CREB*	cyclic AMP response element binding protein*	环一磷酸腺苷反应元件结合蛋白
HIF*	hypoxia-inducible factor	低氧诱导因子
sAC	souble adenylyl cyclase	可溶性腺苷酸环化酶
HSF-1	heat shock transcription factor 1	热休克因子1

*表示能感知氧气和二氧化碳浓度变化的转录因子

使激活剂与之结合，激活ACs。图4为sAC的调控机制[44]。

2.2 sAC信号通路对机体免疫应答的影响

与氧气类似，二氧化碳也可影响机体感染与免疫应答。已有研究证实，将细胞或小鼠暴露于二氧化碳含量高于5%的气体环境中，可造成细胞分泌的巨噬细胞炎症蛋白(macrophage inflammatory protein，MIP)-1、MIP-2、 IL-8和IL-6等促炎因子增加，也诱导了更为严重的小鼠肺部炎症[51]。此外，二氧化碳诱导小鼠肺部炎症与吸入高二氧化碳时间相关，在用LPS诱导小鼠前分别用5%的二氧化碳预处理小鼠10 min和60 min，结果显示，预先吸入10 min高浓度二氧化碳可降低小鼠肺部损伤[52]。最近，有研究指出，CO_2在小鼠肺部免疫应答方面的影响，对小鼠鼻腔注入灰尘提取物或脂多糖并立即将其分别置于含有430 ppm(正常值)，1 000 ppm(建筑物推荐上限值)，5 000 ppm(极限值)的CO_2环境下，发现在CO_2浓度在1 000 ppm时，先天免疫会被抑制，而当CO_2浓度升高至5 000 ppm时，免疫反应增强[53]。在此前已有研究证明，短暂吸入低浓度的CO_2对临床疾病的治疗是安全有效的基础上[54-56]，最近的研究证明，对原代血管内皮细胞每3 h进行11 min的10% CO_2孵育，可有效降低因COVID-19导致的IL-6的升高，使其有可能成为治疗COVID-19的一种治疗措施[57]。

AC是GPCR下游的关键信号分子，通过调节cAMP的合成调控多种细胞功能，从而参与机体的多种病理生理过程。哺乳动物细胞表达了9个tmAC亚型AC1~9和1个sAC，也称为AC10[58]。以往研究已经表明，腺苷环化酶-cAMP-PKA信号通路具有重要免疫调节作用[59]。截至到目前，虽然已有较多研究证明激活后的sAC能够上调cAMP[60,61]，但是关于sAC直接调节免疫反应的报道极少，其对机体免疫应答的直接调节作用尚不明晰。鉴于cAMP-PKA信号通路在免疫调节中的重要作用[62,63]，我们推测sAC对免疫系统可能具有一定的调节作用，后续我们还会开展相关的实验研究。

3 氧与二氧化碳慢性感知信号通路的交互作用

虽然以往研究已经对氧与二氧化碳的细胞感知机制进行比较深入的探索，但是两条感知通路之间是否存在交互调节目前仍然缺乏确切的机制证据。已有一些研究提示，二者之间存在联系，例如PKA与HIF-1α之间存在相互激活的关系。而PKA的活性可由pCO_2升高导致，提示这两条感知通路之间可能存在交互调节[64,65]。此外，饲养于高二氧化碳环境的小鼠，HIF-1α被抑制，其血清中EPO水平显著降低[2]；而将小鼠饲养于高氧和高二氧化碳的条件下三周，小鼠脑组织中HIF-1α、HIF-

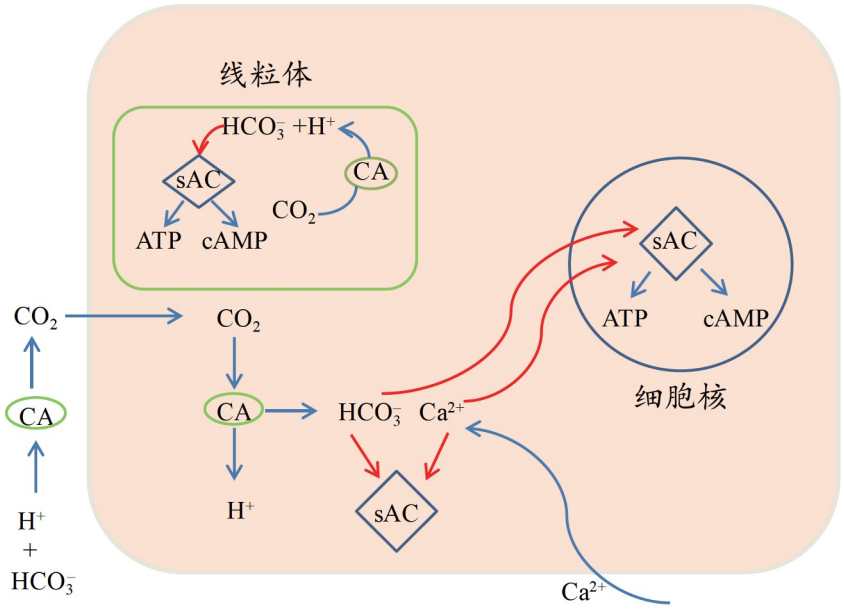

图4 sAC的调控机制

2α的累积及EPO的表达均显著增高[66]。这些研究结果进一步说明，二氧化碳感知通路可对氧感知通路造成影响，但现象背后的分子机制仍有待阐明。

4 总结与展望

氧和高二氧化碳浓度异常是在呼吸系统疾病发生发展过程中经常出现的病理改变，且这种异常往往与疾病预后相关[67-72]。鉴于氧和二氧化碳慢性感知通路与免疫系统的密切关系，我们认为二者浓度变化可能在肺部病毒感染病程中发挥重要作用，深入阐明该问题有望为促进重症感染性肺炎的临床诊治研究提供新的依据和切入点。

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