蛋白质翻译后修饰在哮喘发病机制中的研究进展

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摘　要：哮喘主要以气道炎症、气道重塑和气道高反应性为特征，其分子机制未明。蛋白质翻译后修饰是指以共价方式在氨基酸残基上加上或去除修饰基团，进而调节蛋白功能，主要包括磷酸化、乙酰化、泛素化、糖基化、脂质化、亚硝基化和蛋白水解等。该文总结了蛋白质翻译后修饰在哮喘发病机制中的研究进展，提出现存问题及展望。

关键词：哮喘；磷酸化；乙酰化；泛素化；糖基化
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Research advances of protein post-translational modifications in the pathogenesis of asthma

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Abstract: Asthma is mainly characterized by airway inflammation, airway remodeling and airway hyperresponsiveness, but the molecular mechanisms are not completely understood. Protein post-translational modifications, mainly including phosphorylation, acetylation, ubiquitination, glycosylation, lipidation, nitrosylation and proteolysis, are the covalent addition or removal of modification groups to amino acid residues, in order to regulate the function of protein. This article summarizes the research advances on protein post-translational modifications in the pathogenesis of asthma, as well as existing problems and prospects.

Key words: asthma; phosphorylation; acetylation; ubiquitination; glycosylation

支气管哮喘简称哮喘，是全球范围内发病率较高的慢性异质性气道疾病，全球约有 3.34 亿哮喘患者，且每年与之相关的死亡人数高达 1.8 亿[1]。其临床表现主要为反复发作的喘息、气急，伴或不伴胸闷或咳嗽等症状；气道病理改变表现为气道高反应性、可变的气流受限以及气道重塑。哮喘发病机制复杂，由遗传因素和环境因素共同作用所致，涉及神经系统、内分泌系统、免疫系统等多系统相关的多个基因转录、翻译及翻译后修饰等过程的改变。由于哮喘发病机制未明晰，目前尚未建立理想的治疗方法。

基因的转录和翻译，到最终蛋白质发挥作用的过程决定生物的表型和功能。这一复杂的过程中，蛋白质翻译后修饰（protein translational modifications，PTMs）是蛋白质生物合成的关键步骤，官能团的添加、

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折叠或去除均会导致蛋白质功能的急剧改变[2]，进而影响疾病的发生、发展。PTMs是指蛋白质在RNA翻译后进行的一系列共价修饰，磷酸化、乙酰化、泛素化和糖基化是较为常见的类型。本文总结了PTMs在哮喘发病机制中的研究进展，提出现存问题及展望。

1 磷酸化在哮喘发病机制中的作用

磷酸化是指在蛋白质或中间代谢产物上加磷酸基团的过程，主要发生在丝氨酸和苏氨酸上，激活或抑制各种酶或受体，从而调节不同的信号通路，控制细胞的新陈代谢、生长和分化、免疫反应和细胞凋亡等。哮喘发病机制中的蛋白磷酸化修饰包括与炎症因子信号转导和转录激活相关STAT6的磷酸化[3]、细胞有丝分裂相关paxillin蛋白的磷酸化[4]、细胞凋亡相关Caspase-9的磷酸化[5]、程序性坏死相关混合系激酶区域样蛋白MLKL的磷酸化[6]、效应蛋白激酶如肌球蛋白轻链激酶[7]和蛋白激酶C的底物MARCKS的磷酸化[8]等。目前已发现哮喘中磷酸化的蛋白涉及P38/MAPK通路[9-12]、PI3K/Akt通路[13-14]、NF-κB/IκB通路[15-16]、TGF-β/Smad通路[17]等。

2 乙酰化在哮喘发病机制中的作用

乙酰化是指通过乙酰基转移酶在分子中加入乙酰基的过程。目前已经发现了多种蛋白质可以发生乙酰化修饰，包括组蛋白、P53和微管蛋白等。根据蛋白质乙酰化位点的不同，乙酰化可以被分为3种类型：Nα-乙酰化、赖氨酸乙酰化和O-乙酰化[18]。乙酰化修饰对各种细胞信号传导、细胞核功能及相关通路调控有调节作用，可以改变关键的代谢酶类的功能。在哮喘患者中发现，外周血单个核细胞（PBMC）中过氧化还原蛋白6（Peroxiredoxin-6）赖氨酸乙酰化水平显著升高[19]，去乙酰化酶1（SIRT1）缺陷加重哮喘病情[20]。据哮喘动物模型研究报道，IL33存在乙酰化修饰[21-22]，哮喘易感基因ORMDL3启动子的乙酰基转移酶p300数量增加[23]，以及染色质组蛋白乙酰化修饰[24-27]等。在哮喘患者的治疗中，糖皮质激素将组蛋白去乙酰化酶2（HDAC2）募集到激活的炎症基因转录复合物，逆转激活炎症基因的组蛋白乙酰化，从而抑制哮喘中被激活的多种炎症基因[28]。此外，在哮喘治疗的动物模型研究中，具有抗炎作用龙胆苦苷（GPS）可以上调SIRT1的表达，而下调乙酰核因子κB（NF-κB）p65的表达[29]。

3 泛素化在哮喘发病机制中的作用

泛素化修饰通过E3泛素连接酶和去泛素化酶的协同作用，参与了包括蛋白酶体降解、转录调控、蛋白-蛋白相互作用的调控、内吞作用、自噬、DNA修复和细胞周期调控等多种生理过程[30]。其中，E3泛素连接酶如AMFR[31]、Cul5[32]、MID1[33]、Itch[34]、Fbw7[35]、Parkin[36]、Cbl-b[37]、TRIM21[38]和去泛素化酶USP38[39]在哮喘疾病发生、发展中起着重要作用。此外，泛素-蛋白酶体途径在细胞内蛋白质的选择性降解中起着核心作用[40]，参与哮喘的疾病进程[41]，可降解参与细胞功能的关键蛋白质，如炎症基因等，有望缓解治疗哮喘的炎症反应[42]。

4 糖基化在哮喘发病机制中的作用

糖基化是在糖基转移酶作用下将糖基转移至蛋白质，与蛋白质上的氨基酸残基形成糖苷键的过程。蛋白质经过糖基化作用，形成糖蛋白。糖基化不仅极大地提高了机体蛋白质组的多样性，而且对蛋白质的功能、稳定性和亚细胞定位等有着重要的影响[43]。免疫球蛋白同型和保守的Fc糖基化位点通常决定了抗体的下游活性，其中糖基化的复杂性和程度有助于其结合Fc受体和激活补体的能力[44-45]，包括母乳免疫球蛋白G（IgG）的糖基化状态[46-47]、牛奶蛋白的糖基化[48]、谷物类过敏源的糖基化[49]、晚期糖基化终产物受体（RAGE）[50-51]、高度糖基化的细胞黏附分子（黏蛋白）[52-53]以及其他靶向受体[54]等都与哮喘的发生、发展密切相关。此外，基于糖基化修饰减轻哮喘发作的药物如Omalizumab[55]、kaempferol-3-O-rhamnoside[56]为哮喘的治疗提供了新的思路。

5 脂质化在哮喘发病机制中的作用

脂质化是指蛋白质在核糖体合成后与疏水脂质分子进行共价结合的一种PTMs。脂质介质是肥大细胞和嗜碱性粒细胞所共有，参与哮喘的发生和发展[57]。白三烯（LTs）包括半胱氨酸白三烯（CysLTs）和白三烯B4（LTB4）是最有效的炎症性脂质介质，在哮喘和其他炎症性疾病的病理生理中起着核心作用[58]。白三烯通路抑制对哮喘极具治疗意义，其相关的花生四烯酸脂氧合酶通路在哮喘中起着关键作用[59-62]。作为关键的细胞膜脂类和信号分子的鞘脂在哮喘发展，尤其是肥大细胞鞘脂中发挥重要作用[63-65]，其中ORMDL3是哮喘的易感基因，其作用与调节鞘脂稳态相关[66-67]。必需脂肪酸衍生的免疫化解剂，即脂素、化解素、保护素和乳脂素，是一种抗炎化合物，利于缓解哮喘和过敏[68]。

6　亚硝基化在哮喘发病机制中的作用

一氧化氮（NO）是有机体内一种重要的气体信号小分子，通过介导S-亚硝基化修饰、酪氨酸硝基化修饰等翻译后修饰，影响蛋白质的生物活性、稳定性、亚细胞定位以及蛋白质间相互作用，从而导致蛋白质结构和功能的改变，继而影响细胞的多种病理和生理过程。其中，蛋白质巯基亚硝基化修饰是NO与蛋白质半胱氨酸残基中的自由巯基（-SH）共价结合形成亚硝基硫醇（SNOs）的过程。研究发现，严重哮喘患者气道s-亚硝基硫醇耗竭[69]，并伴有S-亚硝基谷胱甘肽还原酶（GSNOR）活性显著增加，以及气道高反应性增加[70]。此外，β2-肾上腺素能受体（β2AR）的S-亚硝基化修饰是哮喘患者脱敏以及支气管松弛的重要因素[71-72]。由于GSNOR通过S-亚硝基谷胱甘肽（GSNO）的分解代谢在体内调节SNOs和NO，在哮喘的抗炎和平滑肌松弛活性等发挥重要作用，GSNOR抑制剂已成为治疗急性哮喘的潜在药物[73]。

7　蛋白水解在哮喘发病机制中的作用

蛋白酶对蛋白质的降解性水解作用，可去除未组装的蛋白质亚单位和错误折叠的蛋白质，并可将给定的蛋白质减少到小肽或氨基酸水平以维持蛋白质浓度稳态。蛋白酶家族主要包括丝氨酸蛋白酶、半胱氨酸蛋白酶、天冬氨酸蛋白酶和金属蛋白酶。丝氨酸蛋白酶在哮喘发病机制、促进炎症和气道重塑中起着重要作用[74]。此外，尘螨中丝氨酸蛋白酶变应原与哮喘的发生、发展紧密相关[75]。丝氨酸蛋白酶抑制剂甲磺酸nafamostat和甲磺酸gabexate在哮喘小鼠模型中减弱过敏原诱导的气道炎症和嗜酸性粒细胞增多，具有治疗意义[76]。半胱氨酸蛋白酶变应原引起气道上皮细胞的组织损伤，激活2型固有淋巴细胞介导的气道炎症[77]。尘螨中半胱氨酸蛋白酶变应原影响哮喘疾病的发生、发展[78-79]。金属蛋白酶33（ADAM33），作为Th2细胞因子和生长因子的激活剂发挥着重要的生物学作用，与儿童和成人哮喘有关[80-82]。金属蛋白酶ADAM8在哮喘患者中表达增加[83]，与白细胞从血管募集到气道部位诱导气道炎症相关[84]。

8　结语与展望

PTMs在生命体内普遍发生，且一个蛋白质会有多种PTMs位点，从而极大地丰富了蛋白质的种类和功能。随着特异性蛋白质修饰位点检测、纯化方法和质谱技术的不断进步，近年来蛋白质组中PTMs调控位点的鉴定和定量研究呈指数增长趋势。这些研究大多证明，PTMs广泛参与到包括哮喘在内的多种疾病的发生、发展过程中。所以研究PTMs对揭示哮喘的发生、发展机制以及探寻治疗靶点具有重要的意义。

然而，包括巴豆酰化、棕榈酰化、琥珀酰化、二羟基异丁酰化、乳酸化、氨基酰化及组蛋白甲基化等新型的PTMs在哮喘的研究中尚未见文献报道。而且，我们应该注意到PTMs多数情况下并不是单一起作用，而是多种修饰联合发挥作用，如糖皮质激素将配体结合磷酸化修饰的糖皮质激素受体（GR），并将HDAC2募集到激活的炎症基因转录复合物，逆转激活炎症基因的组蛋白乙酰化，进而缓解哮喘的病程[85]。可见，单纯一种PTMs的研究难以阐明哮喘的生理病理机制。但是目前针对多种类型的PTMs以拮抗或组合的方式在哮喘中发挥作用的研究极少。所以，未来的研究除揭示哮喘疾病中新的PTMs外，对不同蛋白质修饰类型、修饰位点时空特征、功能关系、调控机制和蛋白质相互作用等影响哮喘发生、发展的研究是其主要方向。

此外，由于PTMs的普遍性、多样性和复杂性等，对其在哮喘疾病整体水平上认识还比较困难，所以对已经发现了的PTMs在哮喘中的作用机理以及生物学意义还有待进一步研究，最终为探索哮喘的发生、发展机制以及提供靶向治疗等提供新思路。

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