科学通报 2017 年 第 62 卷 第 8 期: 759 ~ 769
《中国科学》杂志社
SCIENCE CHINA PRESS
Science125个科学前沿问题系列解读(XXIV)
How do proteins find their partners?

蛋白质翻译后修饰在蛋白质-蛋白质相互作用中的调控作用

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2016-09-26 收稿, 2016-12-07 修回, 2016-12-08 接受, 2017-02-17 网络版发表

摘要 蛋白质-蛋白质相互作用是蛋白质发挥功能的主要机制之一, 在DNA损伤修复、自噬和代谢等过程中都扮演着非常重要的角色, 蛋白相互作用异常便会导致肿瘤等疾病的发生. 在蛋白质的赖氨酸、丝氨酸和苏氨酸等氨基酸残基上, 可发生甲基化、乙酰化、磷酸化和泛素化等200多种翻译后修饰, 这些修饰通常能改变蛋白质的电性、疏水性和空间结构等属性, 为与之结合的蛋白提供结合的锚定或产生位阻效应, 像一把开关在时空上精确调控蛋白质-蛋白质相互作用的发生以及动态变化. 结构研究表明, 蛋白质之间的相互作用通常由临近的几个氨基酸残基直接结合, 替换该区域的氨基酸残基, 通常能破坏结合, 使其失去部分功能或酶活性, 可以针对性地开发和设计抑制剂或激活剂, 用于肿瘤等疾病的治疗. 本文简要介绍了蛋白质翻译后修饰在蛋白质-蛋白质相互作用中的调控作用, 以及发挥的重要生理功能.

关键词 蛋白质-蛋白质相互作用, 翻译后修饰, 甲基化, 乙酰化, 磷酸化, 泛素化

蛋白质与蛋白质之间可通过共价结合, 也可通过蛋白质表面与另一蛋白质表面, 或蛋白质表面与另一蛋白质的肽残基接触而发生相互作用[1]. 蛋白质-蛋白质相互作用(protein-protein interaction, PPI)在机体正常运转过程中扮演着非常重要的角色, 参与调节各项生理功能. 在剪接体调节[2,3]、蛋白翻译、T细胞信号激活[4]、DNA损伤修复[5]、蛋白稳定性[6]、自噬[7,8]、代谢[9]、信号通路[10]、胚胎干细胞多能性维持[11]等生理过程中, 蛋白相互作用均发挥着十分重要的作用. 当蛋白相互作用异常, 便会导致肿瘤[12,13]、骨关节炎、神经退行性疾病[14]和糖尿病[15]等疾病的发生.

按照不同的标准, PPIs有多种类型[16,17]. 按相互作用发生在同一蛋白还是不同蛋白之间, 形成同源或异源多聚蛋白复合体, 如异染色质蛋白HP1的3个成员HP1α, HP1β和HP1γ, 能形成同源多聚体或异源多聚体[18]. 根据相互作用的蛋白对彼此的依赖性, 分为专性复合体(obligate complex)和非专性复合体(non-obligate complex), 前者指原聚体不形成复合体时, 其结构不稳定, 同时不具备功能, 如催化组蛋白H3K9甲基化的组蛋白甲基化转移酶G9a, GLP, SETDB1和Suv39h1形成一个巨大的蛋白复合物, 而把*Suv39h*或*G9a*敲掉后, 复合体内其他的几个组蛋白甲基转移酶也会变得不稳定[19]; 非专性复合体的成

引用格式: 侯天云, 陆小鹏, 朱卫国. 蛋白质翻译后修饰在蛋白质-蛋白质相互作用中的调控作用. 科学通报, 2017, 62: 759–769
Hou T Y, Lu X P, Zhu W G. Importance of protein post-translational modifications in finding partners (in Chinese). Chin Sci Bull, 2017, 62: 759–769, doi: 10.1360/N972016-00833

员即使不形成复合体, 彼此也能稳定存在并能独立发挥功能, 如胞内的信号通路复合体、抗原与抗体之间的相互作用、配体与受体及酶与其抑制剂之间的相互作用. 根据蛋白相互作用的时间长短, 分为瞬时和永久性相互作用. 永久性相互作用存在的时间很长, 以至于其主要以蛋白复合体的形式存在, 如组蛋白八聚体; 瞬时相互作用则不同, 彼此结合和分开很迅速; 瞬时相互作用又有强弱之分, 弱的瞬时相互作用总处于动态平衡, 即处于连续不断地结合与脱开的状态; 而强的瞬时相互作用需要一个分子来诱发其结合状态的改变.

蛋白质的翻译后修饰(post-translational modifications, PTMs)在PPIs调控中发挥了十分重要的作用, 同一蛋白的多个位点以及多种修饰之间协同或拮抗, 组成蛋白质相互作用精确调控的复杂网络. PTMs通常是在酶的催化作用下将相应的基团共价加到蛋白质的氨基酸残基上, 一些活性代谢产物也可在不用酶参与的情况下与蛋白上的亲核残基共价结合[20]. 常见的PTM有甲基化、乙酰化、磷酸化和泛素化等修饰, 可发生在赖氨酸(lysine, K)、精氨酸(arginine, R)、丝氨酸(serine, S)、苏氨酸(threonine, T)和酪氨酸(tyrosine, Y)等氨基酸残基上. 蛋白质的PTMs可通过改变蛋白质的电性、亲疏水性和空间结构等特性, 提供锚定被特定的结构域识别并结合, 在相应的时间将含该结构域的下游蛋白招募到相应位点发挥相应功能[21], 或发生位阻阻挡蛋白相互作用的发生; 此外, PTMs改变其在细胞内定位, 宏观或微观、直接或间接调节蛋白质-蛋白质相互作用, 如通过将蛋白定位在核内, 一般情况下, 细胞核内的蛋白便不能与线粒体和细胞膜上等亚细胞定位处的蛋白相互作用, 但在生长因子、氧化应激等刺激下, 核蛋白发生修饰被转运出核或浆蛋白发生修饰被转运入核, 原本不同亚细胞定位的蛋白得以发生相互作用.

1 甲基化修饰

甲基化修饰能改变修饰位点氨基酸残基的分子大小和疏水性, 结构生物学研究结果表明, 甲基化修饰极大地促进该区域形成稳定有序的三维结构, 决定其与其他蛋白发生特异性相互作用[22]. 组蛋白和非组蛋白的赖氨酸残基被甲基化修饰后, 能被一些特定的蛋白结构域中2~4个芳香族氨基酸残基形成的芳香族笼子识别并结合. 这类结构域包括: ADD (ATRX-DNMT3-DNMT3L)、锚蛋白重复序列、邻近溴代同源结构域(bromo-adjacent homology, BAH)、染色质域(chromodomain)、双染色质域(double chromodomain, DCD)、恶性脑瘤结构域(malignant brain tumor, MBT)、植物同源锌指结构域(plant homeodomain, PHD)、串联Tudor结构域(tandem Tudor domain, TTD)、Tudor结构域等.

组蛋白去甲基化酶KDM2A特异性识别甲基化修饰的H3K36并催化其发生去甲基化反应, 对其结构研究发现, H3K36me2与KDM2A结合时形成一个U形通道, 伴随着其G34和P38氨基酸残基的子链方向发生改变. 组蛋白H3上的G33-G34-V35-K36me2以及Y41这几个氨基酸残基与KDM2A直接接触, 其中, G34-V35形成的分子内氢键以及V35与KDM2A的K323的侧链基团和F234的苯环之间形成的疏水相互作用, 稳定H3K36me2多肽段在G34发生巨大的弯曲, 而P38促进H3K36me2肽段内第2个弯曲的形成, 即形成1个U形通道. 在此过程中, KDM2A的Q181-M191混合环片段从无序状态转变成有序状态, K323-F324重新定位, 不仅形成一个窄的通道以容纳和适应H3K36me2多肽段的G33–G34, 同时还形成一个皮瓣覆盖住底物肽段的中心区域. 而把KDM2A形成混合域环状的N186A和形成皮瓣的K323A/F324A突变后, KDM2A对H3K36me2的去甲基化酶催化活性降低了60%. KDM2A与H3K36me2的识别特征, 就决定了KDM2A识别底物位点的特异性, 而不会催化甲基化修饰的H3K4, H3K9, H3K27, H3K79和H4K20等位点[23].

组蛋白去甲基化酶JMJD2A与其底物甲基化的H3K9和H3K36形成氢键和范德华力, 来实现对组蛋白上特定位点的识别和催化组蛋白发生去甲基化. JMJD2A的双Tudor结构域, 形成一个如双手十指叉握似的特殊结构, 特异性地与发生甲基化修饰的H3K4或H4K20结合, 对其晶体结构研究发现, 双Tudor结构域中的3个芳香族氨基酸残基形成一个笼子结构, 其中第1个Tudor模体(motif)中的相应氨基酸的侧链相互作用决定了结合的特异性[24]. 虽然H3K4me3和H4K20me3都与JMJD2A的第2个tudor结构域内3个芳香族氨基酸残基组成的笼子结合, 但二者的朝向相反且与JMJD2A的tudor结构域内不同的氨基酸残基结合; 尽管JMJD2A的Asp残基与底物肽段的Arg残基间形成库仑力和氢键, JMJD2A的Asp945

与H3K4me3的Arg2相互作用，却不和H4K20me3肽段接触；与之相反，JMJD2A的Asp939与H4K20me3的Arg19形成1个盐桥，却不参与其与H3K4me3之间的相互作用；JMJD2A的Asp939与H4K20me3的Arg19形成的盐桥极大地促进二者之间的相互作用，当把Arg19突变为Ala后，JMJD2A与H4K20me3的亲和力下降了约55倍[25].

组蛋白赖氨酸甲基转移酶NSD2通过其PWWP结构域，识别H3K36me2，促进NSD2被招募到核小体，进一步催化H3K36me2，促进细胞增殖[26]. 在G_1期和早S期，错配识别蛋白hMutSα (hMSH2-hMSH6)通过hMSH6的PWWP结构域，直接识别三甲基化的H3K36，被招募到错配位点，防止染色质的错配被引入DNA复制过程中，进而维持微卫星稳定性(microsatellite instability, MSI). 对其结构研究发现，hMutSα的PWWP结构域中的Y103，W106和F133 3个芳香环氨基酸残基围住H3K36me3，其中W106和F133的旋转异构体构象调整空间构象，使其结合H3K36me3[27]. 此外，DNA甲基转移酶Dnmt3a通过其PWWP结构域，特异性识别H3K36me3，介导相应位点的DNA甲基化[28]. ING2的PHD结构域对三甲基化修饰的H3K4有很强的亲和性，在DNA损伤刺激下，细胞增殖调控基因的启动子区域高H4K4me3修饰，将ING2招募至该启动子区域，稳定具有转录抑制作用的hSin3a-HDAC1组蛋白去乙酰化酶复合物在该启动子区域的存在，抑制这些基因的表达[29]. HP1通过其chromo结构域，特异性地与甲基化修饰的H3K9结合，维持基因沉默和异染色质紧密状态[30,31]. DNA损伤时，NBS1的BRCT2结构域直接与H3K36me2结合，被招募至DNA双链损伤位点[32].

53BP1的两个串联Tudor模体的界面处的氨基酸残基折叠形成一个很深的口袋，与甲基化修饰的H3K79结合，被招募至DNA双链损伤位点，发挥DNA双链损伤感受器的功能，介导下游DNA损伤检查和修复应答[33]. DNA甲基转移酶Dnmt3a的ADD结构域能特异性地与组蛋白H3结合，H3 N端的一些氨基酸残基修饰能影响Dnmt3a与H3的结合亲和力，H3K4乙酰化、二甲基化和三甲基化修饰及H3T3, S10和T11磷酸化能阻止二者的结合. K4未甲基化修饰的H3与Dnmt3a的ADD结构域有很强的亲和性，破坏ADD结构域与催化结构域CD之间的结合，释放ADD-CD结合对Dnmt3a与DNA结合的阻碍作用和对其催化DNA甲基化修饰的抑制作用，促进Dnmt3a催化与之结合的DNA甲基化；而H3K4me3阻碍与Dnmt3a的ADD结构域之间的结合，ADD与CD结合阻碍CD与DNA结合，使Dnmt3a处于自我抑制状态[34,35].

氧化应激时，甲基转移酶SET7/9与β-catenin结合增加，催化其K180位点发生甲基化修饰，甲基化修饰的β-catenin被GSK-3β识别并介导其降解[6]. NuRD复合物中MTA2的SANT结构域，能与H3K27me3直接结合，通过与核小体结合，将组蛋白甲基转移酶EZH2招募至沉默基因如*TSC2*，进一步催化*TSC2*启动子区域组蛋白H3K27me3，抑制*TSC2*表达，进而抑制自噬的发生[7]. DNA损伤刺激时，SET7/9与SIRT1结合增加并催化其N端区域发生赖氨酸甲基化修饰，甲基化修饰的SIRT1与P53脱开，使得P53乙酰化修饰水平升高，促进其下游基因*p21*等表达[36].

含Tudor结构域的蛋白不仅能识别和结合甲基化修饰的赖氨酸模体(motif)，还能与甲基化修饰的精氨酸motif结合[37]. 人体中至少有36种蛋白含有Tudor结构域，其中至少约10种能与含甲基化的赖氨酸motif的蛋白结合，至少8种能结合含甲基化修饰的精氨酸motif的蛋白. 对这些含Tudor结构域的蛋白研究发现，Tudor结构域中与甲基化修饰的精氨酸motif结合的芳香族氨基酸组成的笼子比与甲基化修饰的赖氨酸motif结合的笼子要窄一些，这更利于其与处于同一平面的精氨酸的甲基-胍基结合.

2 乙酰化修饰

乙酰化修饰通常发生在蛋白结构域，如α-螺旋和β-折叠片，且发生乙酰化修饰的蛋白通常比较保守，如代谢相关酶、核糖体和分子伴侣等[38]. 和甲基化修饰一样，乙酰化修饰也能改变修饰位点氨基酸残基的分子大小和疏水性，除此之外，乙酰化修饰还能减弱该氨基酸残基的正电性，促进该区域形成稳定有序的三维结构，决定其与其他蛋白发生特异性相互作用，抑制非特异性相互作用的发生.

在有丝分裂过程中，BET家族蛋白BRD2能与乙酰化修饰的染色质结合，促进基因的转录激活. BRD2与组蛋白结合的晶体结构表明，BRD2的N端溴结构域BD1与乙酰化修饰的H4K12结合，而低乙酰化修饰的H4K8侧链与BRD2-BD1二聚体界面的凹处结合. 具体而言，H4K12ac主链上的N原子分别与

BRD2-BD1上Asn-156和Asp-160的侧链形成一个分叉的静电相互作用；BRD2-BD1的Pro-98, Phe-99, Val-103, Leu-108, Lys-110, Cys-152和Ile-162形成一个疏水口袋，H4K12ac的侧链处于疏水口袋的深处，使其羧基上羟基基团与BRD2-BD1的Asn-156的Nδ2静电相互作用，以及通过一个水分子与Tyr-113的侧链间接作用. 水分子与H4K12ac侧链的一侧形成一系列氢键，H4K12ac侧链的Nζ与一个水分子静电结合，而另一个水分子像一座桥将H4K12ac侧链的Nζ与BRD2-BD1的Pro-98的羰基连接起来；此外Phe-99, Val-103和Ile-162的疏水性残基将H4K12ac的CH_3-基团包裹住. H4K12ac肽段上Gly-13主链上的氮原子和羰基上的氧原子与Asp-160的Oδ1形成氢键，同时，Gly-13的羰基上的氧原子与Asp-161的氨基形成一个主链氢键；而H4K12ac肽段上的Gly-14不与BRD2结合；而H4K12ac肽段上位于裂缝末端的Ala-15主链上的N和O原子，分别与Thr-159的羰基和Thr-168的羰基形成2个氢键. H4K12ac肽段上与BRD2-BD1浅口袋结合的Lys-8和Leu-10与BRD2-BD1有多种结合，Leu-10的羰基与BRD2-BD1上Lys-157的Nζ产生静电相互作用，而Lys-8通过带正电荷的侧链与BRD2-BD1形成很多疏水相互作用，如Lys-8的Nζ与位于α螺旋的Tyr-153, Ile-154和Asn-156的羰基结合[39].

AF9蛋白的YEATS结构域介导其特异性识别组蛋白H3K9乙酰化修饰，也能较弱地识别H3K27和H3K18乙酰化；对其结构研究发现，YEATS结构域的F62和W81形成的一个芳香笼把发生乙酰化修饰的H3K9夹在中间，进而达到对其特异性识别的作用[40]. 同时，AF9又能与组蛋白甲基转移酶DOT1L结合，使组蛋白乙酰化修饰与DOT1L介导的H3K79甲基化协同发挥转录调控功能[41]. 在转录过程中，与Pol Ⅱ结合的BRD4通过其bromodomain结构域，与高乙酰化修饰的组蛋白结合，促进转录延伸[42].

在血清饥饿和氧化应激时，浆中的FOXO1与组蛋白去乙酰化酶SIRT2脱开，FOXO1的赖氨酸乙酰化修饰水平升高，乙酰化修饰的FOXO1与ATG7结合，诱发自噬[43]. 赖氨酸乙酰化修饰调节FOXO1的胞内定位，组蛋白去乙酰化酶SIRT6催化FOXO1去乙酰化，使其出核，抑制糖异生相关基因表达[9]. 紫外(ultraviolet, UV)放射线诱导DNA损伤时，PCNA被乙酰化修饰，乙酰化修饰的PCNA与MTH2形成的复合体被破坏，与MTH2脱离开的PCNA稳定性大大降低，DNA合成减少，细胞周期停滞[44]. 组蛋白乙酰化酶p300和PCAF催化AKT PH结构域的K14和K20位点发生乙酰化修饰，抑制其与PIP3结合、定位到细胞膜被磷酸化激活，而组蛋白去乙酰化酶SIRT1能催化AKT该位点发生去乙酰化，促进其定位到细胞膜和激活、调控心肌肥大和肿瘤发生[45].

3 磷酸化修饰

真核细胞至少有1/3的蛋白会发生磷酸化修饰，磷酸化修饰是磷酸化修饰位点及其附近区域结构灵活改变所必需的. 底物蛋白与激酶结合，二者之间需形成氢键，而底物肽键骨架内部形成氢键与否并不重要.

磷酸化修饰促进4E-BP2折叠成具有稳定三维结构的蛋白，抑制其与eIF4E结合和解除其对翻译起始的抑制作用. 以前的研究表明，4E-BP2不具有稳定的三维结构，它通过一个经典的YXXXXLΦ (从Y54起始) motif与eIF4E结合. 对其结构解析发现，4E-BP2的T37和T46发生磷酸化修饰后，二者的磷酸基团分别与G39和G48的氨基质子形成氢键，稳定β-转角结构，诱导4E-BP2的P18–R62这段氨基酸残基折叠成4股稳定的β-折叠片，将螺旋状的YXXXXLΦ motif遮挡住，使其看起来似乎是一个部分被掩埋住的β-折叠片，破坏其被eIF4E识别和结合[46].

DNA双链损伤时，ATM与KDM2A结合显著增加，催化KDM2A T632磷酸化，磷酸化修饰的KDM2A与染色质的亲和力大大降低，使得DNA双链损伤位点附近的H3K36me2显著升高，将包含NBS1的MRE11复合物招募至DNA双链损伤位点，促进损伤修复. 丝/苏氨酸激酶AKT催化FOXO1的T24, S256和S319发生磷酸化，导致FOXO1与14-3-3蛋白结合，改变了FOXO1的核定位信号的结构，促进其被转运到细胞浆[47~51]. 发生磷酸化修饰的FOXO1在细胞浆中被泛素E3连接酶SKP2, COP1, MDM2和CHIP等识别和结合下，通过泛素-蛋白酶体途径降解[52~57]. 谷氨酰胺饥饿处理时，ERK1/2磷酸化XBP1u，磷酸化修饰的XBP1u出核并与未发生乙酰化修饰的FOXO1结合，介导其通过20S蛋白酶体途径降解[8].

磷酸化修饰的酪氨酸p-Y motif能被二型Src同源结构域SH2识别和结合，SH2结构域由中间两条反向平行的β折叠片和位于两侧翼的α螺旋组成，SH2结构域还能与细胞膜上的脂类物质结合，而且部分含SH2

结构域的蛋白，如T细胞ZAP70蛋白, SH2结构域与细胞膜上的磷脂酰肌醇PI45P2和PIP3结合后，能极大地提高SH2结构域与p-Y的亲和力，进而调控T细胞中ZAP70信号通路[4].

一些蛋白激酶常能与含固定motif的蛋白结合，如AKT的底物常含有RXRXXS/T[58]. 含该motif的蛋白有组蛋白甲基转移酶EZH2[59]、组蛋白乙酰基转移酶P300[60]、促凋亡蛋白BAD[61]、E3泛素连接酶MDM2[62]、一氧化氮合成酶eNO[63]和IKKα[64]等. 其他一些蛋白激酶如CK2, Erk, PKA, Pim, Pak, MAP3K, AMPK和IKK家族激酶等的底物都有比较固定的motif[65~70].

4 泛素化修饰

蛋白质可发生单泛素化修饰，也可发生多聚泛素化修饰；泛素链可通过不同赖氨酸位点连接到底物，通过K48和K63连接是最常见的方式，蛋白质发生泛素化修饰后，能被含泛素相互作用motif (ubiquitin-interacting motif, UIM)的蛋白识别和结合. RPA80有两个串联的UIMs，分别标为UIM1和UIM2，二者分别与泛素基团的近端和远端结合. UIM1和UIM2之间由一个连续的长α螺旋相连，这个长的α螺旋确保了UIMs特异性地与Lys-63相连的泛素结合. 泛素链的Leu 8, Ile 44和Val 70的侧链，以及Arg 42, His 68和Gln 49的脂肪族侧链形成一个疏水小片，其中Ile 44处于中心位置，UIM1和UIM2都能识别泛素链上的这个疏水片状结构，UIM1的Phe 85, Leu 87, Ala 88和Met 91的侧链以及Gln 84侧链的脂肪族部分形成一个疏水界面，与近端泛素的疏水小片结合；进一步发现, UIM1中Glu 81的Oε原子和Ser 92的Oγ原子分别与近端泛素中Leu 73和Gly 47的氨基N原子形成氢键. 和UIM1类似, UIM2的Leu 109, Leu 110, Ala 113和Ile 114的侧链以及Lys 112和Glu 116侧链上脂肪族部分，与远端泛素的疏水小片结合，且UIM2中Glu 106的Oε原子和S117的Oγ原子分别与远端泛素的Leu 73和Gly 47的氨基N原子形成氢键；此外, UIM2中Leu118的侧链和Lys 105侧链的脂肪族部分分别与远端泛素的Gly47和Leu73结合. 但UIM1和UIM2都不和与Lys-63相连的异肽键结合[71].

通过K48连接多聚泛素化到底物蛋白赖氨酸残基时，介导其通过26S蛋白酶体途径降解；而K63多聚泛素化常与酶活性和蛋白定位及招募等相关. 组蛋白乙酰转移酶P300/CBP, PCAF和GCN5，去乙酰化酶HDAC1，HDAC2和SIRT6等都能通过泛素-蛋白酶体途径降解[72,73].

泛素化修饰除了调控蛋白质通过蛋白酶体途径降解外，还调控出核转运、线粒体转位、稳定性和转录活性[74]. IGF-1刺激时，泛素E3连接酶TRAF6直接催化AKT发生K63多聚泛素化修饰，促进其定位到细胞膜与PDK1结合并被磷酸化修饰激活[75]，去泛素化酶CYLD能抑制该过程[76]. 而在EGF刺激时，由SKP2-SCF催化AKT发生泛素化修饰和细胞膜定位，调节乳腺癌糖吸收、糖酵解和肿瘤发生[77]. 肺癌中，并非是SKP2，而是TRAF4泛素化激活AKT，抑制糖代谢[78].

DNA损伤时，RNF8催化H2A和H2B的C端发生K63泛素化修饰，泛素化修饰被RAP80/UIMC1的UIM结构域识别，将RAP80及与之结合的BRCA1招募至损伤位点[79]. C端K63泛素化修饰的H2A招募RNF168，进一步催化H2A N端的K13/K15发生K63泛素化修饰，促进53BP1和BRCA1停留在损伤位点进行彻底修复[80~82]；当自噬缺陷时，P62在核内积累增加，抑制RNF168催化组蛋白H2A发生泛素化修饰，导致BRCA1，RAP80和Rad51等DNA双链损伤应答蛋白不能被招募至DNA双链损伤位点，抑制DNA损伤修复[83]. RNF8和RNF168催化KDM2A发生K48多聚泛素化，通过蛋白酶体途径降解，降低其与B3BP1对H4K20me2的竞争性结合[84]. UV处理时，CUL4-DDB-ROC1介导H3和H4泛素化，招募损伤修复蛋白XPC到损伤位点，进行DNA损伤修复[85].

5 其他修饰

除了甲基化、乙酰化、磷酸化和泛素化外，其他修饰在蛋白质-蛋白质相互作用的调控中也发挥了很重要的作用. 赖氨酸琥珀酰化、丙二酰化和戊二酸单酰化修饰三者的结构比较类似，而与其他的赖氨酸酰基化修饰的结构不同. 真核细胞中约90%以上的琥珀酰化位点都由组蛋白去乙酰化酶SIRT5调控，骨架上的氢键对于SIRT5与其底物之间的结合发挥最重要的作用；SIRT5含有两个高度保守的氨基酸(Y102和R105)，介导其与带负电的酰基化修饰基团结合，显著地增强了它的去琥珀酰化和去丙二酰化活性[86].

类泛素化SUMO化修饰能促进SIRT6与c-MYC的结合，促进SIRT6在c-MYC靶基因启动子区域富集；此外, SUMO化修饰调节SIRT6的底物特异性, SUMO

化修饰的SIRT6特异性地去除c-MYC靶基因启动子区域H3K56乙酰化，而对H3K9乙酰化无影响[13]. 半胱氨酸棕榈酸酰基化为T细胞激活配体的膜定位所必需[87]，除了调节蛋白与膜结构的亲和性外，半胱氨酸棕榈酸酰基化抑制AMPA受体GluR1/2与细胞骨架相关蛋白4.1N的结合，参与蛋白分选的动态调节[88].

人类免疫系统中，所有的免疫球蛋白和大多数补体成分均被糖基化，T细胞和抗原呈递细胞接触面糖蛋白发生糖基化修饰，帮助朝向正确的贴合面、防止降解以及限制潜伏期蛋白之间非特异性相互作用的发生[89]. 糖基化修饰为Stat5与其转录共激活子CBP结合和激活靶基因表达所必需[90]. 组蛋白H2BS112位点乙酰氨基葡萄糖基化与催化H2BK120位点发生泛素化修饰的泛素连接酶结合将其招募至染色质，催化H2BK120单泛素化修饰促进转录激活[91].

异戊二烯化在蛋白相互作用中也扮演了很重要的作用，如它为K-Ras与微管蛋白之间的特异性结合所必需，调节K-Ras的胞内运输[92,93]. 人凝血因子Ⅷ T1680硫酸化修饰为凝血因子Ⅷ与血管假性血友病因子Vwf结合所必需[94]. 中性粒细胞表面的P选择素糖蛋白配体PSGL-1酪氨酸硫酸化调节P选择素与PSGL-1的结合[95].

6 展望

蛋白相互作用在机体稳定结构维持和生命活动调节中扮演了十分重要的角色，体内巨大基数的蛋白质种类和数量，为蛋白与蛋白之间相互作用提供了无限多种组合方式，只有对蛋白质相互作用进行精确调控才能让机体正常运转和维持稳态. 蛋白相互作用的方式和调控机制错综复杂，仅用酵母双杂交和免疫共沉淀等传统的生化研究手段，是一项巨大的挑战，需依托质谱与生物信息学手段结合的高通量方法对蛋白质组学进行系统和深入研究，如基于稳定同位素标记细胞的光交联策略(a photo-cross-linking strategy with stable isotope labeling in cell culture, SILAC)的定量质谱分析等方法[96]. 在此基础上，结合生化研究技术和结构生物学方法，即“以线到面到网络，再回归到面到线”的策略，搞清楚蛋白质-蛋白质相互作用网络的精确调控机制.

翻译后修饰尤其是在蛋白与蛋白结合界面或邻近的氨基酸残基上的修饰，在蛋白相互作用的时空精确调节中的重要性不言而喻. 深入研究蛋白质的翻译后修饰在蛋白相互作用网络的调控机制和作用，以及不同修饰之间的协同调控，是研究蛋白质-蛋白质相互作用的重要方向. 目前已有一些通过针对蛋白翻译后修饰来调控蛋白相互作用的药物问世，如组蛋白去乙酰化酶抑制剂、激酶抑制剂和溴结构域抑制剂，用于治疗心血管疾病和癌症等疾病[97]. 在不远的将来，以蛋白质翻译后修饰为突破口，更多更高效的靶向药将会被开发出治疗更多的疾病.

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Summary for “蛋白质翻译后修饰在蛋白质-蛋白质相互作用中的调控作用”

Importance of protein post-translational modifications in finding partners

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Cellular processes are tightly regulated by functional protein networks, which are composed of numerous protein-protein interactions (PPIs). Proteins interact with their binding partners through distinct mechanisms, while defects of these machineries have been consequently implicated in the development of various diseases, such as cancer, neurodegeneration and immunological disorders. Interactions between proteins contribute to a complicated network involving many signaling pathways, and these interactions are either permanent or transient depending on the circumstances. Stable interactions assemble relatively stable complexes, which are mainly responsible for cellular functions under unstressed conditions, such as the proteasome complex, nuclear pore complex and histone octamer. On the other hand, transient proteins interactions allow cells to respond to both intracellular signals and extracellular stimuli timely and efficiently. To understand how PPIs are precisely regulated, it is critical to know how proteins and their binding partners interact in precise orientations. It is now well accepted that post-translational modifications (PTMs) of certain amino acid residues can be recognized and bound by specific motifs. PTMs such as methylation, acetylation, phosphorylation or ubiquitination on certain protein amino acid residues located on or around the interaction surfaces may interfere the electrical property, hydrophobicity, structure of proteins and provide anchors or obstacles for intermolecular binding. This is of great importance in regulating both permanent and transient interactions, which are indispensable for the coordination of temporal and spatial adaption. Abnormal PTMs can result in aberrant protein interaction network, cause systematic dysfunctions and ultimately lead to diseases such as cancer. Therefore, inhibitors design based on PTMs regulated PPIs may have good therapeutic prospects for cancer treatment. Recent studies have begun to show that, with the right tools, certain classes of PTMs regulated PPI can yield to the efforts to develop inhibitors to disrupt the interactions between proteins and their partners, and the first PTMs regulated PPI inhibitors have reached clinical development. In this review, we described the research leading to these breakthroughs, briefly summarize the vital roles played by several common PTMs in PPIs regulation and highlight the existence of mechanisms and structural basis, and explore their roles in deciding whether the PPIs are specific or not. Besides, we also explore and discuss emerging effective research strategies for PTMs in PPIs regulation.

protein-protein interaction, post-translational modification, methylation, acetylation, phorsphorylation, ubiquitination

doi: 10.1360/N972016-00833