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·专论与综述·

BTB 蛋白结构与功能研究进展 *

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摘要：BTB（Broad-complex, Tramtrack, and Bric-a-brac）蛋白家族存在于痘病毒以及几乎所有真核生物中，该类蛋白为多结构域蛋白，最为显著的特征是含有高度保守且能介导蛋白与蛋白间相互作用的 BTB 结构域。BTB 蛋白具有多种功能，其功能特异性取决于 BTB 蛋白中其他结构域以及它的互作蛋白。BTB 蛋白广泛参与转录调节，染色质重组装，细胞骨架调控和泛素化降解等过程，与胚胎发育，器官形成，信号转导以及免疫调节等生理过程密切相关。除此之外，多种疾病如癌症，神经系统和骨骼肌系统疾病等的病理过程也与 BTB 蛋白相关。本文以蛋白结构为基础总结了该家族的共性规律并重点论述了 BTB 蛋白在转录调节以及泛素化降解过程中发挥的重要作用，以期为后续研究提供重要参考。

关键词：BTB 蛋白；蛋白互作；转录调节；泛素化降解；胚胎发育

中图分类号：Q593.4；Q71 **文献标识码**：A **文章编号**：1673-6273(2019)07-1367-07

Research Progress on the Structure and Function of BTB Protein Family*

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ABSTRACT: BTB (Broad-complex, Tramtrack, and Bric-a-brac) protein family, existing in poxvirus and almost all eukaryotes, is closely related to embryos development, organ formation, signal transduction, immune regulation and the pathological process of cancer, neurological or musculoskeletal diseases. The typical protein of this family contains multiple domains including evolutionarily conserved BTB domain that plays a role in protein-protein interaction. BTB proteins have diverse functions, ranging from transcription regulation, chromatin reassembly, cytoskeleton regulation to ubiquitin-degradation. Specificity of functions are determined by additional domains present in BTB family proteins, as well as by interaction partners. The article summarized the general rule of the family on the basis of protein structure and elaborated the significant function in the transcriptional regulation and ubiquitin-degradation in order to provide important reference for further study.

Key words: BTB domain; Protein-protein interaction; Transcriptional regulation; Ubiquitin-degradation; Embryos development

Chinese Library Classification(CLC): Q593.4; Q71 Document code: A

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前言

BTB/POZ 结构域最早发现于果蝇的三个蛋白 Broad-Complex、Tramtrack 和 Bric-a-brac，取这三个蛋白首字母得名“BTB”[1,2]，同时该结构域也出现于痘病毒锌指蛋白(Pox Virus and Zinc Finger, POZ)，所以也称为 POZ 结构域[3]。BTB/POZ(简称 BTB)结构域进化上高度保守，真核生物中几乎都有 BTB 蛋白分布[4]。研究表明，BTB 蛋白在转录调控、染色质重构、蛋白降解和细胞骨架调控中起重要作用，与哺乳动物生长发育密切相关，包括淋巴细胞发育，轴突导向，性腺形态发生等[4]。此外，癌细胞的增殖也与 BTB 蛋白密切相关，如人急性早幼粒细胞白血病，组织瘤等[5-7]。BTB 蛋白以其结构和功能的重要性日益受到广泛关注，然而目前对大部分 BTB 蛋白中 BTB 结构域参与生理过程的分子作用机理仍不清楚，本文重点论述了 BTB 蛋白及其与 CUL3 复合物的结构特征，试图归纳其参与转录调节，泛素化降解等生理过程的同一性，希望为后面进一步研究 BTB 蛋白的分子机理提供理论依据。

1 BTB/POZ 蛋白结构特征

BTB/POZ(以下简述为 BTB)结构域大约包含 115 个氨基酸残基，能介导蛋白之间相互作用形成寡聚体，包括同源、异源二聚体[8,9]。BTB 结构域空间结构高度保守，核心包含五个 α 螺旋(α1-α5)，四个 β 折叠股(β1-β4)和一个可变链区，其中 α1/2 和 α4/5 分别形成 α 螺旋发卡结构，三个 β 折叠股(β1-β3)形成

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β 折叠片层结构，三维空间上，β1/α1/β2/β3/α2/α3/β4 区与 β5/α5/α6 区通过 α4 和可变链区相连(图 1A 和图 1B)[10]，其同源二聚体三维空间结构(PDB 3BIM)[11]显示，β1 和 β5' 形成反向平行的 β 折叠片，α1 插入 α1' 和 α2' 形成的 α 螺旋发卡结构(图 1C)，这是 BTB 结构域形成同源二聚体的结构基础。

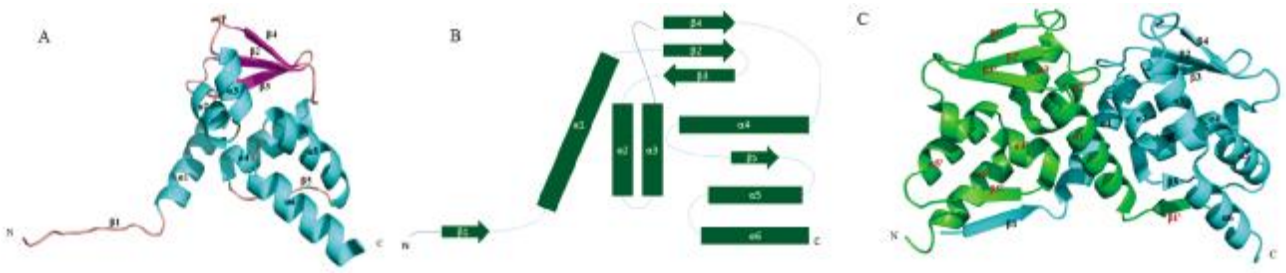

图 1 BTB 结构域及其同源二聚体三维结构示意图

Fig.1 Monomer and homodimer structure of Broad Complex, Tramtrack, and Bric-a-Brac (BTB) domain

Note: A. Structure of BTB domains (PDB 1BUO); B. Schematic representation of the topology of the dimer (PDB 3BIM). α-Helices are indicated by rectangles, and b-sheets by thick arrows.

BTB 蛋白中除 BTB 结构域外，还含有多种其他结构域(图 2)。BTB 结构域一般存在于 BTB 蛋白的 N 端，此类蛋白靠近 C 端大部分有一至多个 Kelch 重复 [12] 或各种不同的锌指结构(Zinc Finger Motif，ZF motif)，例如 C_2H_2 锌指等[10,13]。BTB 蛋白家族种间分布检验表明，脊椎动物中包含丰富的 BTB-ZF 和 BTB-Kelch 蛋白[14]，通过调节基因转录，参与泛素化降解，在细胞生理功能中发挥重要作用。除此之外，一少部分 BTB 蛋白含有其它功能结构域，比如与 DNA 结合相关的 AT 钩(AT-Hook)[13]，与表皮生长因子相关的 FYVE 指状结构域（FYVE zinc finger domain)[15]，与植物趋光性相关的 NPH3 结构域[16]，与蛋白互作相关的锚蛋白重复(ankyrin-repeat，ANK)结构域[17]以及 MATH (meprin and TRAF homology)结构域[18]等(表 1)，BTB 结构域还被预测与包含 T1 结构域的钾离子电压门控通道(voltage-gated potassium channels)相关[19]。

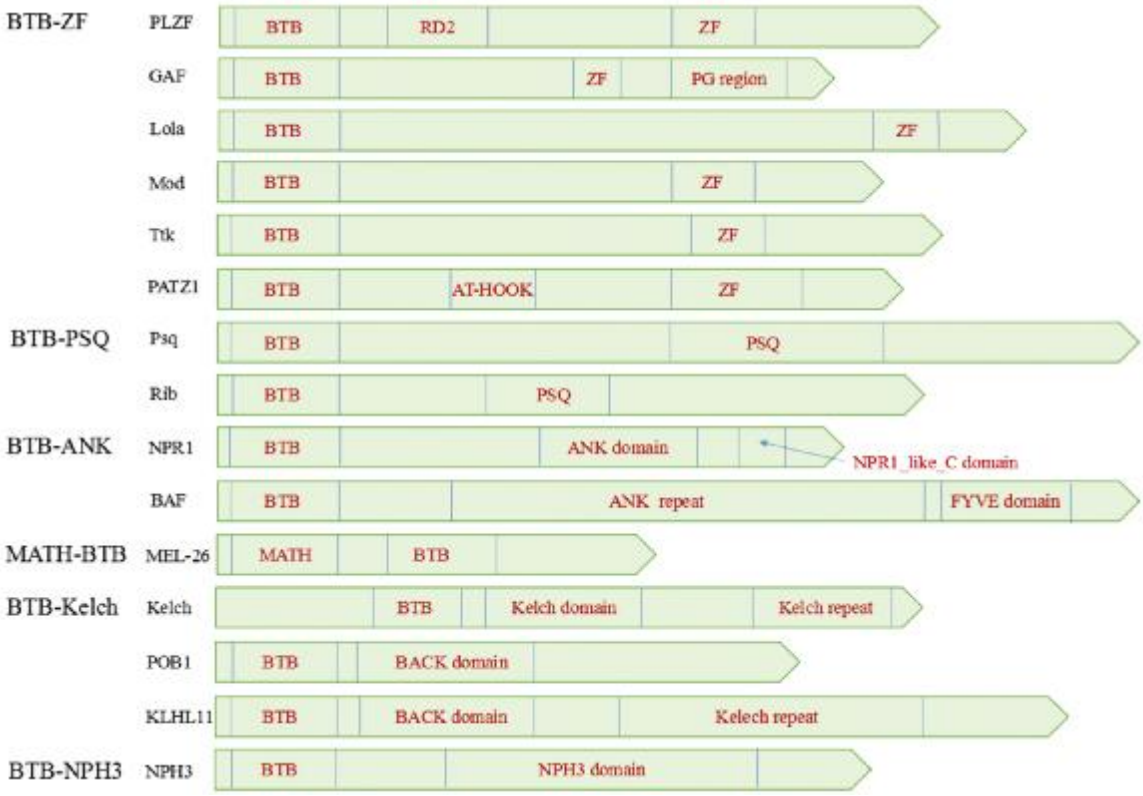

图 2 BTB 蛋白主要结构域组成示意图

Fig.2 A schematic diagram of the main domain organization of BTB proteins

Note: PLZF, human Promyelocytic Leukemia Zinc Finger, AAD03619; GAF, GAGA factor, Q08605; Lola, Longitudinals Lacking, NP_788312; Mod, Modifier of Midget 4, NP_788698; Ttk, Tramtrack, P17789; PATZ1, POZ/BTB and AT-Hook Containing Zinc Finger, NP_114439; Psq, Pipsqueak, NP_523686; Rib, Ribbon, AAL11905; Kelch, NP_724095; NPR1, Nonexpresser of PR genes 1, AT1G64280.1; BAF, BTB-ANK 2 and FYVE domain containing protein, CDW56200.1; MEL-26, AAC63596.1; POB1, S. Pombe Boi-like protein, OAP06681.1; POB1, S. Pombe Boi-like protein, OAP06681.1; KLHL11, Kelech Like protein 11, Q9NVR0.1; NPH3, Nonphototropic Hypocoty protein l, BAD86496.1.

表 1 BTB 蛋白主要结构及功能分类

Table 1 The mainly structural and functional classification of BTB proteins

Domain	Protein	Source	Function	Reference
ZF domain	PLZF	Homo sapiens	Asociated with transcriptional regulation, chromosomal breakpoints and translocation in acute promyelocytic leukemia (APL)	[20]
	GAF	Drosophila melanogaster	Combined with GA-rich DNA sequences and participates in multiple transcriptional regulation	[21]
	Lola	Drosophila melanogaster	Demonstrated to promote photoreceptor differentiation in the larval eye and ocelli	[22]
	Ttk	Drosophila melanogaster	Inhibits transcription through form multimers and interaction with GAF	[23]
PSQ domain	PATZ1	Homo sapiens	Participate in pathologically related transcriptional regulation	[13]
	Psq	Drosophila melanogaster	Involved in egg formation and embryonic development through transcriptional regulation	[24]
	Rib	Drosophila melanogaster	Associated with cell migration and early organ morphogenesis	[25]
ANK domain	BAF	Trichuris trichiura	Associated with epidermal growth factor	[15]
MATH domain	NPR1	Arabidopsis thaliana	Related to plant rhythms and immune regulation	[26]
	MEL-26	Caenorhabditis elegans	Associated with cell cycle through ubiquitin-degradation	[27]
Kelch domain	KLHL39	Channa punctata	Suppresses colon cancer metastasis by blocking KLHL 20-mediated ubiquitination	[28]
NPH3 domain	NPH3	Arabidopsis thaliana	Required for several auxinmediated growth processes, including phototropism, leaf positioning, and leaf expansion	[16]

2 BTB 蛋白调节基因转录

2.1 BTB-ZF 蛋白

BTB-ZF 蛋白首先发现于果蝇，随后在其他真核生物中也有发现，包括小鼠、斑马鱼和人等，序列分析结果表明，果蝇、小鼠、斑马鱼和人源的 BTB 蛋白中约有 25 %含有锌指结构[14]。大部分锌指结构有 20-30 个氨基酸残基，其中两个半胱氨酸残基和两个组氨酸残基能螯合锌离子，这是锌指结构与 DNA 结合的结构基础[29]。ZF 基序与其他基序相比其保守性较低，暗示 BTB-ZF 基因编码的一系列 DNA 结合蛋白能与不同 DNA 序列特异性结合，同时，这些具有 DNA 识别特异性的 BTB-ZF 蛋白能通过 N 端的 BTB 结构域形成同源或异源二聚体。BTB-ZF 蛋白还有一个 N 端延伸区，该区包含一个 β 折叠股（β1）和一个 α 螺旋（α1）[10]，此外，Skp 家族蛋白另有一包含两个 α 螺旋（α7 和 α8）的 C 端延伸区[14]；PATZ1（POZ/BTB and AT-Hook Containing Zinc Finger 1）蛋白在 BTB 和 ZF 结构域之间存在一个 AT-HOOK 基序，该基序通过一小沟槽结合 DNA，通常与其他 DNA 结合蛋白共同调节转录和染色质重组装[13]。BTB-ZF 蛋白有高度保守的带电荷天冬氨酸残基和赖氨酸 / 精氨酸残基[10]，突变这两个位置的氨基酸会破坏 BTB 结构域与抑制因子的相互作用，包括核抑制子（Nuclear Co-repressor，NCoR）、视黄酸和甲状腺激素受体抑制子，也会阻碍其与组蛋白去乙酰化酶的相互作用[30,31]。BTB-ZF 蛋白不仅与转录调节抑制相关，也能与转录激活因子相互作用（如 p300）[32]或者通过抑制染色质重新组装来促进基因转录[33,34]。BTB-ZF 蛋白通过调节基因转录参与多种生理过程，如纵向神经束缺失蛋白（Longitudinals Lacking, Lola）、Midget4 蛋白修饰因子（Modifier of Midget4, Mod）、人早幼粒细胞白血病锌指蛋白（Human Promyelocytic Leukemia Zinc finger, PLZF）和 BTB 结构蛋白 7（BTB Domain Containing Protein 7, BTBD7）等。Lola 蛋白参与调节性腺和神经系统发育[35,36]。Mod 蛋白不与 DNA 直接相互作用，通过与其他含 BTB 或不含 BTB 的蛋白形成多聚体，进而与 DNA 结合，该蛋白可以改变染色质结构促进减数分裂染色体分离以及花斑型位置效应，通过促进染色质重组装抑制基因表达以及诱导细胞凋亡，在发育和组织分化中起作用[37]。人源 PLZF 作为抑癌因子参与基因转录调节，染色质断点、异位修复[38,39]，与急性早幼粒细胞白血病密切相关[20,29]。在器官形态发生和病变的过程中，BTBD7 与纤连蛋白表达相关，具有调控肿瘤血管塑性以及肿瘤细胞上皮间质转化的功能[40]。

2.2 BTB-PSQ 蛋白

PSQ 基序在真菌，昆虫和脊椎动物中均有存在，首次发现于果蝇 PSQ 蛋白（Pipsqueak, PSQ），该蛋白包含四个 PSQ 基序和一个 BTB 结构域 [41]。PSQ 基序形成螺旋 - 转角 - 螺旋（Helix-turn-helix, HTH）结构，通过该结构识别并结合 DNA 来调节基因转录[24]。目前发现的 BTB-Psq 蛋白仅存在于昆虫中，共 9 种，在果蝇生长发育过程中，BTB-Psq 蛋白在卵子形成和胚胎发育过程中发挥重要作用，参与极细胞形成，背腹轴形成等过程[22]。酪氨酸激酶相关蛋白（Ribbon, Rib）是 PSQ 蛋白中的一种，包含一个 N 端 BTB 结构域和一个 C 端 PSQ 基序，昆虫生长发育过程中，该蛋白主要参与调节细胞迁移以及早期器官和神经系统的形成[22,25]。

3 BTB 蛋白参与泛素化降解

泛素化降解广泛存在于真核生物中，是主要的蛋白选择性降解系统，在细胞代谢，细胞周期转换和细胞分化过程中发挥重要作用，泛素系统功能异常可导致多种疾病，如 Parkin 综合

征和癌症等[42,43]。泛素化降解途径是一个三级酶联反应，第一步，在 ATP 存在的情况下，化学惰性的泛素分子羧基碳与 E1 激活酶具有催化活性的半胱氨酸形成硫酯键，第二步，激活状态的泛素被转移到 E2 泛素结合酶的活性半胱氨酸位点，第三步，E3 泛素连接酶特异性地识别底物蛋白和 E2 泛素结合酶，并在泛素羧基碳和底物赖氨酸ε- 氨基间形成异肽键，将泛素连接到底物蛋白上，进而使底物被 26S 蛋白酶识别并降解[44,45]。E3 泛素连接酶分为两个主要类别：HECT（Homologous to the E6-AP Carboxyl Terminus）型和 RING（Really Interesting New Gene）型，单分子 HECT 型能与泛素形成硫酯中间化合物并将泛素转移到底物蛋白，而 RING 型则起到分子脚手架的作用，与底物蛋白结合的同时锚定 E2 泛素结合酶，进而将泛素转移到底物蛋白[44]。

Cullin（CUL）蛋白家族是 RING 型 E3 泛素连接酶中的典型代表，目前发现的具有催化活性的有 CUL1，CUL2，CUL3，CUL4a，CUL4b 和 CUL5[45]，其中 CUL3 能特异识别 BTB 蛋白，形成 cullin-RING 连接酶复合物（Cullin-RING Ligase complexes，CRLs），从而使底物蛋白泛素化降解（图 3）。CUL3 参与底物泛素化时，其 N 端与 BTB 蛋白结合，BTB 蛋白作为底物的配体蛋白，起到招募底物的作用（BTB 蛋白也可作为底物被泛素化降解），C 端与锌指蛋白 ROC（Regulator of Cullins）1 和 ROC2（又分别叫做 Rbx1/Hrt1，Rbx2）互作形成 RING- 锌指结构，该结构能螯合 Zn^{2+}，包含三个 β 折叠股，一个 α 螺旋和两个柔性环，柔性环靠一簇半胱氨酸残基和两个组氨酸残基稳定[44]。RING 型 E3 泛素连接酶通过 RING- 锌指结构来招募和变构激活结合泛素的 E2 酶并将泛素转移到底物。

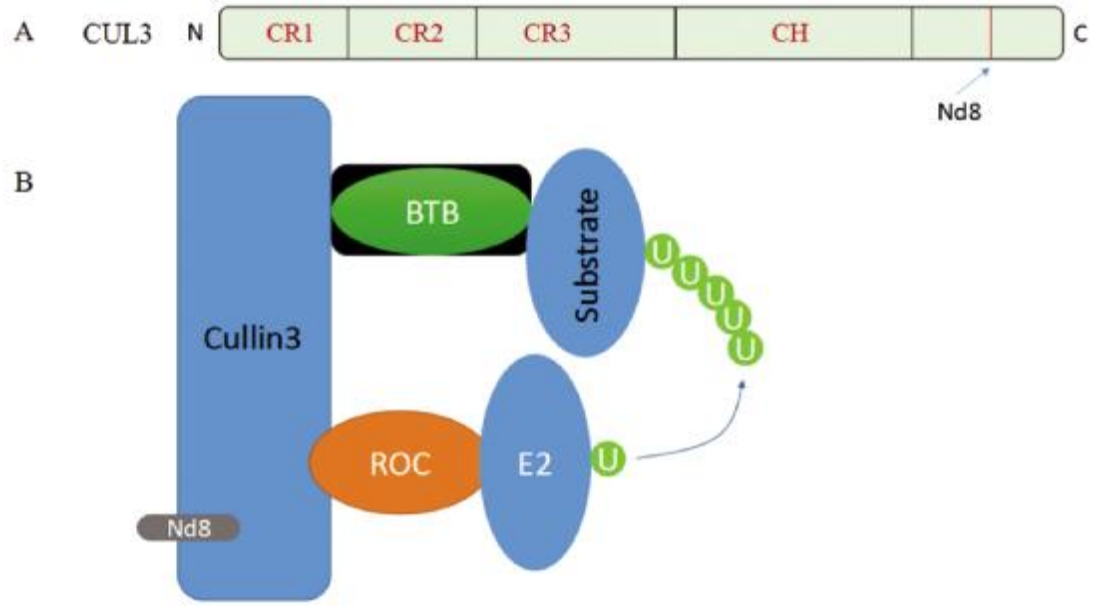

图 3 Cullin3 蛋白结构域组成及 Cullin-RING 泛素连接酶复合物示意图

Fig.3 Cullin protein domain organization and Assembly of Cullin-RING ubiquitin ligases (CRLs)

Note: A. CR: Cullin Repeat motif; CH: Cullin Homology domain; B. Nd8: NEDD8, ubiquitin-like modifier; BTB: BTB protein; U: Ubiquitin; ROC: Regulater of Cullins.

CUL3 与 BTB 蛋白互作依赖于 BTB 蛋白的“3-box”基序，几乎所有 BTB 配体蛋白中均有该基序[46]，3-box 基序位于 BTB 和 BACK 结构域之间，由 α7 和 α8 构成，并且与 BTB 结构域的 α5 和 α6 结合形成 3-box 结构(图 4A 和图 4B)。KLHL11 蛋白中的 BTB-BACK 结构域和 CUL3 复合物结构[47]以及 KEAP1 蛋白中的 BTB-3-box 结构域与 CUL3 N 端复合物结构（PDB 5NLB 尚未发表）均显示，CUL3 N 端特异延伸序列插入 3-box 结构的疏水凹槽，这是 CUL3 与 BTB 蛋白互作的结构基础（图 4A）。此外，KLHL11 蛋白中的 BTB-BACK 结构域能形成同源二聚体（PDB 3I3N，尚未发表），其同源二聚体的形成依赖于 BTB 结构域（图 4B）。BTB-BACK 同源二聚体两单体间的互作界面与 BTB-BACK 和 CUL3A 间的互作界面不在同一位置且空间上不排斥，由此可以推测，BTB 蛋白参与泛素化降解与 BTB 结构域的同源二聚化不相关。

3.1 BTB-ANK 蛋白

ANK 序列是一个相对保守的蛋白重复序列，首次发现于酵母的 Swi6p，Cdc10p 蛋白和果蝇 Notch 蛋白[48]，该序列广泛存在于原核以及真核生物蛋白中，人源 Ankyrin R 蛋白晶体结构（PDB 1N11）显示，该蛋白中的 ANK 结构域包括 12 个重复的 ANK 基序，每个基序由 33 个氨基酸残基组成，包含两个 α 螺旋和一个环状结构[49]。ANK 结构域主要参与调节蛋白与蛋白间相互作用，进而参与转录调节，细胞骨架形成和细胞周期调控，与细胞生长、分化以及细胞毒性密切相关[50]。植物病程基因相关非表达子（Nonexpresser of PR genes 1，NPR1）是 BTB-ANK 蛋白中的典型代表，该蛋白 N 端包含 BTB 结构域，C 端包含功能活性区，ANK 结构域位于二者之间。NPR1 在细胞内以寡聚状态存在与细胞质基质，当植物受到外界病原菌感染时，植物体内氧化还原状态发生变化，NPR1 从寡聚状态解聚为单体入核，与转录因子 TGA 相互作用调节病程免疫相关基因转录。免疫过程中，植物体内水杨酸浓度能调节 NPR1 及其同源蛋白 NPR3/NPR4 进行泛素化降解[51,52]。

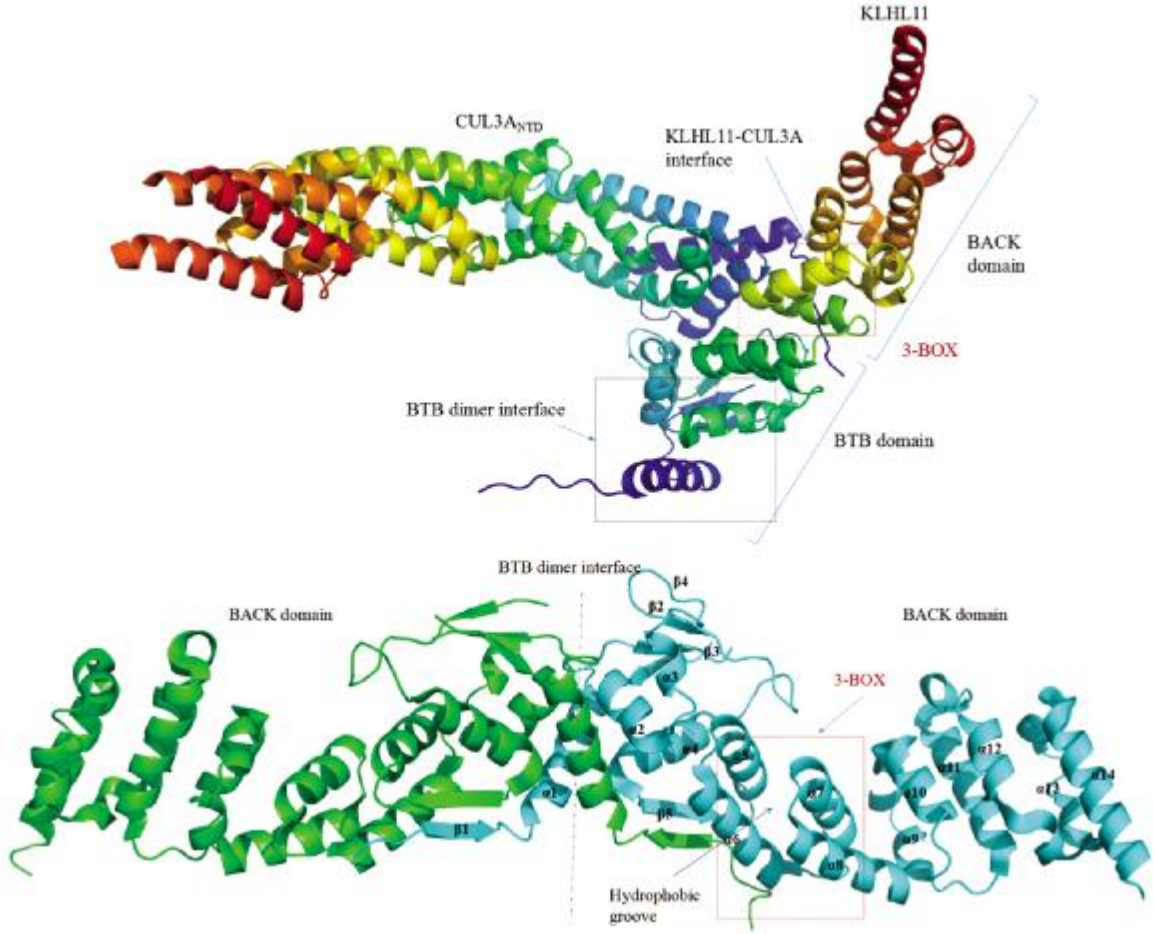

图 4 KLHL11-CUL3A 结构及 BTB-BACK 同源二聚体结构示意图

Fig.4 Structure of KLHL11-Cul3 complex and BTB-BACK homodimer

Note: A. Structure of KLHL11-Cul3 complex (PDB 4AP2); B. Structure of BTB-BACK homodimer (PDB 3I3N).

3.2 MATH-BTB 蛋白

MATH 结构域主要存在于真核蛋白,MATH 基序约 120 个氨基酸残基,与 Meprin-A 和 Meprin-B 蛋白的 C 端结构域以及 TRAF 蛋白的 TRAF-C 结构域同源而得名[18,53]。MATH 结构域主要介导蛋白与蛋白间的相互作用,TRAF 和 Meprin 都需要装配亚基来行使功能,TRAF 蛋白形成三聚体依赖其 TRAF-C 的卷曲螺旋基序,而 MATH 结构域则能与 TNF 受体和死亡受体形成复合物[54]。此外,Meprin-A 和 Meprin-B 还能通过 MATH 结构域与 MAM 结构域的 N 端互作,使异源二聚体二聚化形成四聚体[55,56]。减数分裂抑制因子 MEL-26 蛋白是 MATH-BTB 的典型代表,该蛋白包含 N 端 MATH 结构域和 C 端 BTB 结构域,MEL-26 作为配体蛋白与 CUL3 相互作用,参与纺锤体蛋白 MEI-1 的快速降解,调控细胞骨架和细胞周期转变[27]。

3.3 BTB-Kelch 蛋白

BTB-Kelch 蛋白包含 N 端的 BTB 结构域和 C 端的 Kelch-repeat 结构域(BTB and C-terminal Kelch,BACK),属于 Kelch-repeat 蛋白超家族,Kelch-repeat 结构域由 4-7 个重复的 Kelch 基序组成,具有明显的结构特征,在病毒、真菌、植物和动物中均有发现[12]。Kelch 基序由为 44-56 个氨基酸残基组成,起源早且进化上分支众多,该基序上四个氨基酸残基高度保守,其中包括两个甘氨酸残基,一个酪氨酸残基和一个色氨酸残基[57]。玫瑰茄寄生菌半乳糖氧化酶晶体结构(PDB 1GOF)显示,Kelch 基序可组装成 β- 螺旋桨结构。Kelch 基序是蛋白与蛋白间相互作用的基础,因此 BTB-Kelch 蛋白能通 Kelch 结构域与许多底物特异性结合[57]。KLHL 蛋白家族包含 N 端 BTB 结构域和 C 端 Kelch 重复基序,该家族蛋白与细胞周期转变和生理调节密切相关[58]。作为 CUL3 的配体蛋白,KLHL 蛋白能与CUL3 相互作用参与泛素化降解,如 KLHL6 能促进 B 细胞从Ⅰ型转变为Ⅱ型,诱导 B 细胞成熟[59],KLHL3 在无赖氨酸激酶(with-no-lysine kinase,WNK)信号通路中调控肾脏和平滑肌细胞电解质平衡[60]。

3.4 BTB-NPH3 蛋白

NPH3 结构域发现于植物下胚轴非向光蛋白 3(Nonphototropic Hypocotyl,NPH3),该蛋白和根向光蛋白 2(Root Phototropism 2,RPT2)同属于类 NPH3/RPT2 蛋白家族(NPH3/RPT2-Like family,NRL),目前已知的类 NPH3/RPT2 蛋白成员共 30 余种,都含有 N 端 BTB 结构域和 C 端 NPH3 结构域,部分成员在 NPH3 结构域后含有卷曲螺旋结构域[61]。NPH3 和 RPT2 蛋白可以和植物向光蛋白(Phototropin,phot)1 和 2 相互作用,与植物生长素调节的生长进程相关,包括植物趋光性,叶片定位和叶片伸展[62]。NPH3 能与 CUL3 在昆虫细胞中共表达形成 CRL3 复合物,用蓝光激活后,phot1 会被被该 CRL3 复合物泛素化降解[63]。Phot1 会诱导 NPH3 从细胞膜上解离下来,而phot2 会调控 NPH3 的在细胞膜上重新定位,从而增

加植物对蓝光的敏感性[64]。除此之外，NRL31 也是 CUL3 的配体蛋白，与植物免疫调控相关[65]。

4 小结与展望

BTB 结构域在氨基酸序列上和三维空间结构上高度保守，检索PDB 数据库分析发现，来自不同蛋白的 BTB 结构域差异仅存在于连接各个 α 螺旋和β 折叠股的柔性序列和可变链区。BTB 结构域是重要的蛋白相互作用结构域，最早在转录调控中发现于 BTB-ZF 蛋白，因此曾有人将 BTB 蛋白归于类锌指蛋白家族，但越来越多的 BTB 蛋白显示，BTB 结构域常与除锌指结构以外的其他结构域一起出现，这些蛋白主要通过泛素化降解等途径在细胞分化和生长发育等过程中起作用。本文综述了 BTB 蛋白近年来的研究进展并总结其共性规律，希望为后续 BTB 蛋白广泛且深入的研究提供理论依据，以期为生长发育，肿瘤发生相关的疾病研究提供借鉴和参考。此外，合成生物学近年来发展迅速，BTB 结构域三维结构已知，具有高度保守和介导蛋白互作的特性，易于满足蛋白设计过程中元件标准化，去耦合和模块化原则，因此 BTB 结构域有作为蛋白基本元件的潜在价值，有望利用 BTB 结构域和其他功能域设计出结构新颖的蛋白，进而在生理调节和疾病治疗中发挥作用。

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