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专论与综述

球孢白僵菌响应氧化胁迫的分子机制研究进展

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摘 要：球孢白僵菌作为模式丝状真菌，以分生孢子、菌丝体、虫菌体等多种形态存在，在真菌孢子发育、寄主与宿主互作的研究中具有重要意义。同时，球孢白僵菌又是一类广泛应用的真菌杀虫剂，对森林防护和农业生产具有实际应用价值。球孢白僵菌的相关基因被敲除后，突变体响应氧化胁迫，孢子发育和毒力会发生改变。本文综述了近年来球孢白僵菌在响应氧化胁迫方面的研究进展，为丝状真菌氧化胁迫信号途径的研究提供参考。

关键词：球孢白僵菌；氧化胁迫；活性氧

Molecular mechanisms of *Beauveria bassiana* in response to oxidative stress: a review

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Abstract: Entomopathogenic *Beauveria bassiana* shows a variety of morphological patterns such as aerial conidia, mycelia and single-cell form known as hyphal bodies. As a typical filamentous fungal species, *B*. *bassiana* plays important roles in conidial development and host-pathogen interactions. It is also widely applied for biological control of pests and thus is of great value in forest protection and agricultural production. Once related genes in the species are knocked out, the mutants show responses to oxidative stress associated with conidial development and virulence. This study summarizes the molecular genetics of *B*. *bassiana* involved in oxidative stress in recent years, which is expected to serve as a reference for the study of oxidative stress signaling pathway in filamentous fungi.

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虫生真菌寄生在昆虫成体或幼体上，如蛹虫草(*Cordyceps militaris*)、白僵菌(*Beauveria* spp.)、绿僵菌(*Metarhizium anisopliae*)、冬虫夏草(*Ophiocordyceps sinensis*)、蝉花(*Isaria cicadae* Miquel)等，所产生的次生代谢产物可开发出农药和生物医药[1]。其中，白僵菌属的球孢白僵菌(*Beauveria bassiana*)具有寄主范围广、致病力强、易发生流行、对人畜安全性高等特点，是国内外研究最多和应用最广的虫生真菌，也成为人们获取酶和代谢产物的新资源[2]。然而，球孢白僵菌自身对环境的依赖性比较强，环境的波动会影响球孢白僵菌的生存能力，引起形态的转变和毒力的改变。例如，氧化胁迫引起球孢白僵菌分生孢子分化为微菌核样结构来抵抗外界环境胁迫[3]。当外施含 Cu^{2+}的化学物质时，球孢白僵菌的发育受到抑制[4]。环境中活性氧(reactive oxygen species，ROS)含量的增加可导致球孢白僵菌分生孢子质量的下降，削弱其对昆虫的毒力[5]。内源性 ROS 在球孢白僵菌响应环境胁迫和侵染宿主过程中也会发生改变[6-7]。这些结果暗示，抗氧化酶等相关因子在球孢白僵菌的生长分化、氧化胁迫和致病过程中扮演着重要角色。下面就近年来关于球孢白僵菌响应氧化胁迫的相关研究进行综述。

1 活性氧的产生

活性氧(ROS)在真菌遭受生物或非生物胁迫中扮演着重要角色，主要包括超氧阴离子($O_2\cdot^-$)、过氧化氢(H_2O_2)、羟基自由基($\cdot OH$)等成分。真菌分生孢子遇到热、紫外线、高湿等非生物胁迫时，其细胞壁形成棒状层和黑色素层，增加抗氧化酶、海藻糖和热击蛋白等含量，进入休眠状态，抵抗外界环境胁迫[8-9]。当分生孢子附着在宿主体壁上进行 β-氧化分解虫体体壁脂肪酸时，脂酰基辅酶 A 氧化酶将电子供给氧分子，产生 $O_2\cdot^-$和 H_2O_2[10]，细胞膨大进行极性伸长，形成附着胞和侵染钉，并且释放水解酶破坏宿主体壁[11]。一旦真菌穿透昆虫表皮的角质层时，昆虫的酚氧化酶级联反应被激活，将酚类底物氧化成不同的色素，同时产生 ROS 和有毒中间体，引起氧化胁迫[12]。球孢白僵菌分泌漆酶来分解昆虫免疫反应产生的 ROS，并干扰宿主酚氧化酶的激活[13]。当真菌进入昆虫体腔时，昆虫的蛋白水解级联反应引起血淋巴出现凝结和黑化，并增加 ROS 的积累来抑制真菌入侵[14]。在宿主体内，球孢白僵菌转变为虫菌体形态来躲避宿主的攻击，进而发育为菌丝体吸取宿主的营养物质，同时产生次生代谢产物如白僵菌素，导致宿主死亡。在死亡的僵虫体内，球孢白僵菌通过增加卵孢素合成与宿主体内微生物进行营养竞争[15]。当真菌的菌丝体穿出僵虫体壁后，继续以分生孢子形式进行下一轮增殖。

2 活性氧在环境胁迫中发挥重要作用

活性氧(ROS)作为一种信号分子，在真菌侵入宿主过程中能启动下游信号分子，对抗环境胁迫，以达到自身存活和增殖的目的[16]。例如球孢白僵菌分泌的核糖核酸酶毒素通过调节昆虫 ROS 响应，抑制昆虫抗菌肽的产生，减弱昆虫角质层对抗菌丝穿入的抗性[17]，而球孢白僵菌自身抗菌肽 BbAFP1 能结合植物病原真菌细胞壁的几丁质和葡聚糖，富集到植物病原菌表面，引发 ROS 暴发，导致其细胞膜的破裂，抑制植物病原真菌的发育[18]。相反地，球孢白僵菌和绿僵菌等真菌杀虫剂通过增加植物 ROS 的

含量，启动植物防御基因的表达，加强植物防御系统对病虫害的抗性并促进植物生长[19]。人们还可以利用 ROS 影响球孢白僵菌代谢的特性，外源添加一定浓度的 H_2O_2，诱导 3-磷酸甘油醛脱氢酶(glyceraldehyde-3-phosphate dehydrogenase，GAPDH)活性，提高芳香族除草剂中间体(R)-2-(4-羟基苯氧基)丙酸[(R)-2-(4-hydroxyphenoxy) propionic acid，HPOPA]的含量[20]。外施一定浓度的 H_2O_2 还可以增强球孢白僵菌的脂质代谢和糖代谢，增加菌丝的产量和真菌的毒力[21]。因此，球孢白僵菌对外界的感应能力、ROS 的产生方式及 ROS 平衡的维持将成为宿主和寄主之间对抗的重要因素。

3 膜蛋白感应氧化胁迫反应

3.1 完整膜蛋白

真核生物体内有 2 种类型的膜蛋白，即完整的膜蛋白和脂质锚定蛋白[22]。完整的膜蛋白包含一个或几个跨膜区域，构成疏水的 α-螺旋结构，将蛋白嵌入流动的脂质双分子层中。球孢白僵菌 G 蛋白耦连受体(G protein-coupled receptor，GPCR)具有 7 个 α-螺旋跨膜结构域，诱导热击蛋白基因和抗氧化酶等基因的表达，响应渗透和 H_2O_2 胁迫反应[23]。构巢曲霉(*Aspergillus nidulansa*) WSC 蛋白存在一个富含半胱氨酸的结构域(也称 WSC 结构域)、一个富含丝氨酸/苏氨酸的区域、一个跨膜区域和一个高度带电的羧基末端细胞质区域[24]。在球孢白僵菌中，具有跨膜结构域的 Wsc1A 和 Wsc1E 的基因被敲除后，突变菌株对细胞壁抑制剂、氧化胁迫、高渗及金属离子的敏感性增强，同时，丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)级联途径中 Hog1 的磷酸化水平被剥夺[25-26]。另一个跨线粒体膜蛋白 Ohmm 位于 Hog1 MAPK 级联途径下游，基因突变干扰了线粒体膜电位平衡，积累了高水平 ROS[27]。在内膜系统中，跨液泡膜的转运蛋白 ATPase (V-ATPase)对细胞内钙离子浓度的维持、环境 pH 的稳定、无性增殖和毒力等方面都发挥重要作用，敲除突变体对氧化胁迫敏感，胞内的甘油和海藻糖含量下降[28]。

3.2 锚定蛋白

一类脂质锚定蛋白通过磷脂或脂肪酸的共价键锚定在膜上，以小 GTP 酶蛋白家族为典型代表。球孢白僵菌的 RasGTPase 调控发育和毒力，响应多种胁迫反应[29]。例如 GTPase (Ras3)定位在脂膜内侧，通过羧基末端“CAAX”序列与脂肪酸共价结合在细胞膜内侧面，调控抗氧化酶基因的表达及 Hog1 MAPK 级联途径上游因子 Hog1 的磷酸化水平[30]。另一类脂质锚定蛋白通过其羧基末端的糖基化磷酯酰肌醇(glycosylphosphatidylinositol，GPI)结构锚定于真核细胞膜表面。球孢白僵菌 GPI 锚定蛋白基因 *Bbecm33* 被敲除后，突变菌株的生长存在缺陷，同时伴随着胞内甘露糖和海藻糖含量的下降，对氧化剂甲奈醌和 H_2O_2 及细胞壁合成的抑制剂更加敏感，对高渗物质 NaCl 和 Ca^{2+} 也表现出一定敏感性[31]。

以上研究结果暗示球孢白僵菌膜蛋白通过 MAPK 级联途径传递信号，影响真菌发育，响应氧化和渗透胁迫反应。

4 抗氧化酶维持活性氧动态平衡

活性氧在球孢白僵菌受到环境胁迫及其和宿主互作过程中均会发生改变，因此，其动态平衡在球孢白僵菌对环境的适应过程中显得尤为重要，而抗氧化酶起到关键作用。

4.1 超氧化物歧化酶

超氧化物歧化酶(superoxide dismutase，SOD)催化超氧化物阴离子自由基歧化生成

H_2O_2与O_2。球孢白僵菌中有5类超氧化物歧化酶，主要为胞质Cu/ZnSOD (Sod1)和MnSOD (Sod2)、线粒体MnSOD (Sod3)和FeSOD (Sod4)及细胞壁锚定Cu/ZnSOD (Sod5)，它们催化$O_2\cdot^-$形成H_2O_2，在孢子发育和胁迫反应中发挥作用[32]。化学杀菌剂对球孢白僵菌的孢子萌发和孢子形成过程影响较大，同时伴随着SOD活性的增加和H_2O_2水平的升高[4]。超表达*Bbsod2*增加菌株对$O_2\cdot^-$的耐受性，提高分生孢子的萌发率[33]。当将*Bbsod2*和*Bbsod3*敲除后，分生孢子形成延迟、产量减少，对H_2O_2胁迫的敏感性增加[34]。另外3种突变株*ΔBbsod1*、*ΔBbsod4*和*ΔBbsod5*对氧化和紫外胁迫敏感，但它们在抗氧化胁迫中的功能不尽相同，*ΔBbsod1*突变体积累较高水平的ROS，*ΔBbsod5*突变体的SOD酶活性改变不明显，而*ΔBbsod4*突变体的SOD酶活性不但未降低反而增强，但过氧化氢酶(catalase，CAT)的活性却显著降低[32]。在绿僵菌中，SOD1−3主要负责抗氧化活性，*Δsod1*对$O_2\cdot^-$更加敏感,*Δsod2*和*Δsod3*这2个突变体对H_2O_2更敏感[35]。这些研究结果说明，虫生真菌中SOD在抗氧化胁迫和分生孢子发育方面担负着主要功能，在功能上存在交叉和互补，而且与其他抗氧化酶又存在协调关系。

4.2 过氧化氢酶

过氧化氢酶(CAT)催化H_2O_2水解生成H_2O和O_2。CAT参与球孢白僵菌的胁迫反应和毒力。虽然CAT (BBA_06186)在球孢白僵菌感染大蜡螟的24−72 h过程中表达量低，在毒力方面表现不明显[36]，但*catA*、*catP*和*catD*突变株的毒力下降了33%−47%，而且*catA*和*catD*敲除突变株对高温和紫外胁迫敏感[37]。多种CAT同工酶的存在，暗示着它们之间存在功能上的互补作用，但不排除在球孢白僵菌发育的不同阶段或不同的胁迫环境中所起的作用不同。绿僵菌*MakatG1*兼有CAT和过氧化物酶2种酶活性，在虫生真菌穿过宿主角质层致病性过程中起关键作用，突变菌株对H_2O_2、甲奈醌和紫外胁迫的敏感性增加[38]。H_2O_2在不同生物互作中起信号识别作用，其含量多少主要通过CAT来维持，也证实CAT与毒力相关。

4.3 硫醇/二硫化物氧化还原酶系

硫醇/二硫化物氧化还原酶系在维持靶蛋白还原性方面起重要作用，包括谷氧还蛋白(glutaredoxins，Grx)和谷胱甘肽还原酶(glutathione reductase，GR/Glr)组成的谷氧还蛋白-谷胱甘肽氧化还原酶系，由thioredoxins (Trx)和thioredoxin reductases (Trr)等组成的硫氧还蛋白氧化还原酶系[39]，以及谷胱苷肽-S-转移酶(Glutathione-S-transferase，GST)等。这些蛋白具有相似的功能，均通过还原含硫靶蛋白间二硫键维持氧化还原状态的平衡。球孢白僵菌中Grx1-5和Glr在功能上相似，因为突变其中一个基因会导致其他基因的表达水平升高；但两类酶功能存在差异，*Δgrx3*突变株对甲奈醌和H_2O_2敏感，而*Δglr*对硫醇的氧化剂二酰胺敏感性更高，不同的*Δgrx*或*Δglr*突变体的SOD和CAT活性变化也存在差异[40]。来自酿酒酵母(*Saccharomyces cerevisiae*)的Grxs (ScGrx1和ScGrx2)在氧化应激方面具有部分重叠的功能，与GST类的Gtt1/Gtt2有共同协作关系[41]。这一结果说明，Grx通过还原蛋白之间的二硫键或蛋白和谷胱甘肽形成的混合二硫键调节蛋白的氧化还原状态，与GST具有类似的功能，但球孢白僵菌GST是否与酵母的GST具有类似功能并不清楚。球孢白僵菌Trr1与酵母中同工酶在维持胞内还原状态方面同样发挥重要作用，敲除突变体的分生孢子在萌发、对热和紫外的胁迫反应及毒力方面均发生改变，同时突变体的Trx活性增加，但过氧化物酶(peroxidases， POD)和 SOD 活性却降低[42]。这些研究结果说明，球孢白僵菌中硫化物氧化还原酶系保守性比较强，在功能上存在互补作用，在胁迫、发育和毒力方面均具有重要的作用。

除了抗氧化酶作用外，非酶促抗氧化成分脯氨酸、海藻糖、甜菜碱、糖醇类等在丝状真菌的胁迫反应中也发挥着同等重要的作用。例如，在低氧供应的条件下，球孢白僵菌通过增加胞内甘露醇的含量响应氧化胁迫反应[43]。

5 转录因子调控氧化胁迫反应

5.1 转录辅激活因子

转录辅激活因子通过增强转录因子与靶基因的结合调控基因表达。转录辅激活因子 MBF1 具有保守的功能性 C 末端和多分化的 N 末端，通过与 TATA-结合蛋白(TATA-binding protein，TBP)的桥连形成复合物，能与靶基因启动子上游的保守序列 TATA-box 特异结合调控几丁质酶和蛋白酶等基因转录，在真核细胞发育和胁迫反应中起重要作用[44-47]。球孢白僵菌 *Bbmbf1* 基因被突变后，菌株对紫外线、氧化胁迫、高渗和热胁迫的敏感性增加[48]，推测 BbMBF1 可能与胁迫反应中的抗氧化因子有关，这种作用可以被氧化胁迫进行动态调控，当其与 BbAP-1 相互作用时调控多种氧化相关基因表达[49]。

5.2 发育调控因子

发育调控转录因子主要是锌指蛋白类，包括 C2H2、C4 和 C6 型等，能够通过锌指结构域结合在靶基因启动子上响应氧化胁迫，调控菌株生长和分生孢子的发育过程。C2H2 类型 BbMsn2 负调控卵胞素合成，球孢白僵菌敲除突变株生长减缓，对荧光增白剂、H_2O_2 和刚果红的敏感性增强[50-51]；另一个调控卵胞素合成的锌指蛋白基因 *Bbsmr1* 被敲除后，突变体能够抗氧化胁迫，而在 *ΔBbsmr1* 中超量表达分生孢子梗发育启动的调控因子基因 *BbbrlA* 时，超表达菌株能够回复突变菌株在产孢量和对氧化胁迫反应方面的表型[52]。Zn(II)2Cys6 型锌指蛋白(C6 型)是真菌中特有的转录因子，在分生孢子成熟过程中，BbCmr1 作为次生代谢产物合成基因簇成员，能够通过 BbWetA 调控分生孢子成熟[53-54]。当敲除 *Bbcmr1* 和 *BbwetA* 时，突变体的分生孢子对氧化胁迫和渗透胁迫敏感，分生孢子萌发率下降[54-55]。BbSmr1、BbCmr1 和 BbWetA 在氧化胁迫、次生代谢产物产生和发育方面的异同暗示着不同信号的途径存在交叉，共同构成复杂的网络关系。另外，丝状真菌 Velvet 转录因子家族调控次生代谢产物，球孢白僵菌中的同源蛋白 VosA 和 VeA 参与氧化和渗透等胁迫反应，在孢子成熟和菌丝发育方面同样发挥着重要的调控作用[56-57]。

5.3 毒力调控因子

附着胞是虫生真菌侵染宿主的重要器官，附着胞的减少显著降低了真菌的杀虫毒力；在膜蛋白 Mr-OPY2 和 MAPK 激酶调控下，转录因子 AFTF1 控制附着胞的正常形成，使绿僵菌由腐生向寄生方式转变[58]。在附着孢形成过程中，抗氧化物质参与其中，如绿僵菌 *ΔMakatG1* 突变株抗氧化酶活性降低，穿出蝗虫翅膀的能力和附着胞形成速率显著下降[38]。转录因子调控氧化胁迫反应与抗氧化酶基因的表达调控有关。球孢白僵菌 p53 样转录因子敲除菌株下调抗氧化酶基因 *cat2* 和 *cat5* 的表达，减弱对氧化胁迫的抗性[59]。稻瘟菌(*Magnaporthe oryzae*)的极性生长调节转录因子 TPC 通过控制 NADPH 氧化酶复合物来控制肌动蛋白运动，进而控制附着孢极性定位[60]。最近研究发现，球孢白僵菌的碱性亮氨酸拉链转录因子 BbStf1 负调控 SOD 等抗氧化酶活性，突变菌株孢壁增厚、毒

力增强[61]。虽然氧化耐受性是预测白僵菌毒力的重要决定因素，但调控毒力的转录因子是否可以直接结合在氧化相关基因的启动子上调控毒力和胁迫反应，在虫生真菌中却少有报道。

另外，钙离子介导的信号途径也参与了球孢白僵菌的氧化应激反应。钙调磷酸酶受 Ca^{2+} 或钙调蛋白(calmodulin，CaM)调节的丝/苏氨酸蛋白磷酸酶是一种异二聚体蛋白，包括催化亚基 A (CNA)和调节亚基 B (CNB)，参与球孢白僵菌的氧化胁迫[62]。CN 通过去磷酸化调控转录因子 Crz1 的活性，当 *crz1* 基因被敲除后，突变体中甘露醇和海藻糖的含量降低，整个菌株中 SOD 和 CAT 活性也下降，对金属离子、氧化剂及细胞壁抑制剂等的敏感性增强[63]。

6 总结与展望

球孢白僵菌中多种因子参与氧化胁迫信号途径，响应外界环境，影响毒力和生长发育。这些因子涉及对外界刺激的反应、细胞内信号传递和基因转录调控等过程，但这些因子通过 ROS 形成的复杂信号网络目前还不清楚。ROS 与次生代谢产物之间以及球孢白僵菌与宿主互作过程中的具体信号路径均值得进一步探究。球孢白僵菌中基因的敲除和超量表达技术及转录组、代谢组、蛋白组分析为 ROS 调控机制的研究提供帮助，特别是植物和动物中 ROS 所执行的复杂功能为虫生真菌的研究提供了很好的借鉴。对虫生真菌中 ROS 功能的研究有助于筛选高抗氧化胁迫菌种，使虫生真菌适应更广的生活环境并增强其杀虫效果，同时也为虫生真菌次生代谢产物的开发提供思路。

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