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昆虫对杀虫剂和转 *Bt* 基因植物的抗性进化机制研究进展

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摘 要： 为防治昆虫对农作物的危害，采取了喷施杀虫剂和种植转 *Bt* 基因抗虫植物等措施。然而，杀虫剂的大规模使用和转 *Bt* 基因抗虫植物的大面积连续种植使得一些靶标昆虫产生了抗性进化，这不仅影响防治效果，而且还影响整个农业生态系统服务功能。本文综述了昆虫对化学杀虫剂、微生物杀虫剂和转 *Bt* 基因植物产生抗性的分子机制。昆虫对化学杀虫剂的抗性进化机制主要是靶标位点敏感性下降和解毒酶系活性增强；对微生物杀虫剂的抗性进化机制主要是免疫系统激活和共生菌群变化；对转 *Bt* 基因植物的抗性进化机制主要是昆虫中肠结合受体基因突变或表达下调和中肠蛋白酶活性降低。为了减缓昆虫抗性进化和提高杀虫剂效率，未来建议减少使用化学杀虫剂，合理利用杀虫谱广和活性高的微生物杀虫剂以及抗虫植物等方法系统治理农业害虫。

关键词： 昆虫防治；化学杀虫剂；微生物杀虫剂；转 *Bt* 基因植物；抗性机制
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Research Progress in the Evolution Mechanisms for Insect Resistance to Insecticides and *Bt*-transgenic Plants

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Abstract: To reduce the damage to crop from insects, some agricultural practices have been used such as spraying insecticides and planting *Bt*-transgenic insect-resistant plants. However, since insecticides are continuously sprayed and *Bt*-transgenic insect-resistant plants are continuously cultivated at large scales, target insects tend to evolve the resistance to insecticides and insect-resistant plants. This insect-resistance evolution of target insects not only decrease the insect-control effectiveness of insecticides and transgenic plants but also affect the functional services in agricultural ecosystems. Here, we reviewed the molecular mechanisms of insect resistance to chemical and microbial insecticides and *Bt*-transgenic plants. Insects evolve resistance to chemical insecticides via decreasing the sensitivity of target sites and enhancing the activities of detoxifying enzymes in insects, resistance to microbial insecticides via activating immune systems and changing symbiotic flora in insects, and resistance to *Bt*-transgenic plants via downregulating midgut binding receptors and decreasing midgut protease activities in insects. To delay the resistance evolution of insects and increase the insect-control efficiency of insecticides, it is urgent to systematically control agricultural insects through reducing the use of chemical insecticides and to increasing the integrative use of broad-spectrum and high-activity microbial insecticides as well as insect-resistant plants.

Key words: insect control; chemical insecticides; microbial insecticides; *Bt*-transgenic plants; resistance mechanism

农业害虫严重影响农作物的产量和经济效益，导致全球作物产量每年损失约 20%-40%，造成高达 700 亿美元的经济损失[1]。为防治昆虫对农作物的危害，采取了喷施化学杀虫剂、微生物杀虫剂

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和种植转基因抗虫植物等措施。例如，环氧虫啶防治白背飞虱（*Sogatella furcifera*）[2]，虱螨脲防治草地贪夜蛾（*Spodoptera frugiperda*）[3]；球孢白僵菌（*Beauveria bassiana*）防治马铃薯块茎蛾（*Phthorimaea operculella*）[4]，斜纹夜蛾核型多角体病毒（SlitNPV）防治棉铃虫（*Helicoverpa armigera*）[5]；转 *Bt*（*Bacillus thuringiensis*）基因水稻防治二化螟（*Chilo suppressalis*）[6]，转 *Cry1Ab* 和 *Vip3Aa19* 基因玉米防治草地贪夜蛾[7]。然而，随着杀虫剂的大规模使用和转 *Bt* 基因植物的大面积连续多年种植，使得一些靶标昆虫产生了抗性进化[8-10]，这不仅影响昆虫防治效果，还影响农业生态系统服务功能。本文综述了昆虫对化学杀虫剂、微生物杀虫剂和转 *Bt* 基因植物产生抗性的分子机制，并简要介绍了延缓昆虫抗性进化的可行措施，旨在为安全、有效、绿色治理农业害虫提供科学依据。

1　昆虫对化学杀虫剂的抗性机制

随着化学杀虫剂的不合理使用，昆虫对化学杀虫剂的抗性进化受到了广泛关注。自 1908 年 Melander 首次发现梨园蚧（*Aspidiotus perniciosus*）对石硫合剂产生抗性以来，已经有 600 多种昆虫对一种或多种化学杀虫剂产生了抗性[11-13]。昆虫对化学杀虫剂的抗性进化机制主要有靶标位点抗性和代谢抗性。

1.1　靶标位点抗性

靶标位点不敏感性是昆虫对化学杀虫剂产生抗性进化的一个重要原因。昆虫体内重要的酶、离子通道、受体是化学杀虫剂常见的作用靶标，包括乙酰胆碱酯酶（AChE）、电压门控钠离子通道（VGSC）、γ- 氨基丁酸（GABA）受体、烟碱乙酰胆碱受体（nAChR）等。

乙酰胆碱酯酶（AChE）是有机磷和氨基甲酸酯类杀虫剂的作用靶标。此类杀虫剂过度使用后，昆虫体内编码 AChE 的基因 *ace* 发生突变，影响与杀虫剂的结合，导致对杀虫剂的敏感性降低[14]。分子和遗传学研究表明与抗性相关的突变基本发生在 AChE 氨基酸残基上。例如甜菜夜蛾（*Spodoptera exigua*）敏感和抗性品系的 *ace1* 基因序列分析表明 443 位的苯丙氨酸（F）突变为酪氨酸（Y）（F443 Y），该突变改变了 AChE 的催化特性，大幅降低了 *AChE1* 对毒死蜱的敏感性[15]。此外，相对于单一点突变，AChE 突变组合能够使昆虫对杀虫剂产生更高水平的抗性[16]，Zhang 等[17] 向表达不同突变的褐飞虱（*Nilaparvata lugens*）重组 AChEs 突变体喷施 AChE 特异性抑制剂丝氨酸和两种杀虫剂（毒死蜱和克百威）发现，与 F331C 和 I332L 两个单突变相比，双突变 F331C/I332L 进一步降低褐飞虱 *AChE1* 对抑制剂和杀虫剂的敏感性。

电压门控钠离子通道（VGSC）是拟除虫菊酯类和有机氯类杀虫剂的作用靶点。昆虫对拟除虫菊酯产生抗性进化是由于 *VGSC* 基因突变引起的击倒抗性（knockdown resistance, kdr）。击倒抗性（*kdr*）突变首先在家蝇（*Musca domestica* L.）中被发现并定位到家蝇的钠离子通道位点，单核苷酸多态性导致亮氨酸取代了 1 014 位的苯丙氨酸，降低了其神经元对拟除虫菊酯的敏感性[18]。此后，在不同抗拟除虫菊酯昆虫种群中检测到多种 *kdr* 突变，例如烟草甲虫（*Lasioderma serricorne*）抗性品系中存在 T929I 和 F1534S 突变，导致其对拟除虫菊酯产生抗性[19]。Gao 等[20] 发现从我国不同地区采集的两个白纹伊蚊（*Aedes albopictus*）种群均对拟除虫菊酯产生抗性，并检测到其体内携带 *kdr* 突变基因 I1532T 和 F1534S。这些 *kdr* 突变的高频率和新突变等位基因的发现表明昆虫对杀虫剂的抗性进化迅速，需要持续监测抗性变化，严格规范化学杀虫剂的使用。

γ- 氨基丁酸（GABA）是昆虫中枢神经系统突触前末端释放的抑制性神经递质，与之结合的 GABA 受体被阻断，GABA 就无法正常传递，因此 GABA 受体是杀虫剂重要的靶标位点[21]。早在九十年代初期，Ffrench-Constant 等[22] 就从抗狄氏剂的黑腹果蝇中克隆得到首个 GABA 受体亚基基因 *Rdl*，并发现其抗性与 *Rdl* 上 302 位的丙氨酸突变为丝氨酸有关。除了作为狄氏剂的靶点之外，Rdl 亚基也是苯基吡唑类（如氟虫腈）、异噁唑啉类（如氟雷拉纳）以及间二酰胺类杀虫剂（如溴虫氟苯双酰胺）的靶点，昆虫对这些杀虫剂的抗性进化研究相继展开。Nakao[23] 证实了灰飞虱（*Laodelphax striatellus*）和白背飞虱 Rdl 亚基第二跨膜区的两个核苷酸替换导致 A2′N 突变，降低了对氟虫腈的敏感性。Zhang 等[24]

通过构建二化螟 Rdl 亚基突变体进行异源表达和电生理监测发现，Rdl 亚基第三跨膜区的 G3′M 突变导致对氟雷拉纳敏感性下降显著，甚至几乎失去对氟雷拉纳的响应。氟虫腈与氟雷拉纳在 Rdl 亚基上的结合位点相互独立，表明抗苯基吡唑类杀虫剂的昆虫不会对异噁唑啉类或间二酰胺类杀虫剂表现出交叉抗性。

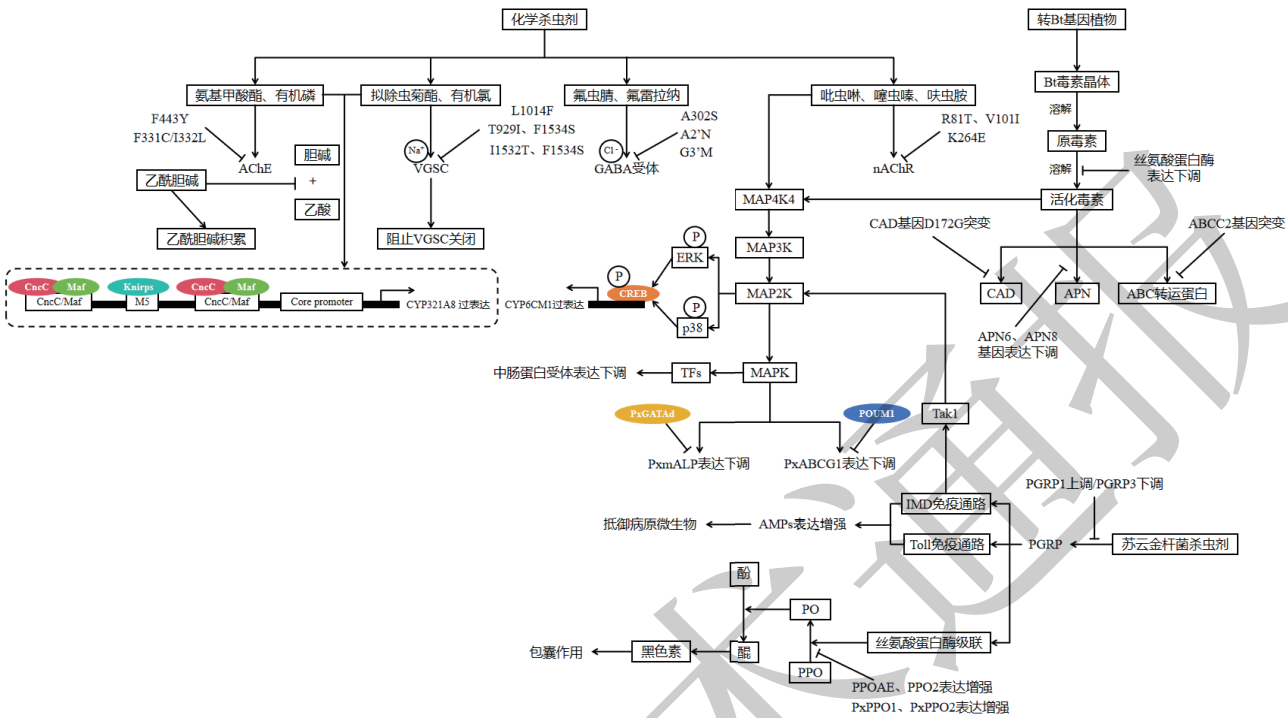
烟碱乙酰胆碱受体（nAChR）是新烟碱类杀虫剂的直接靶标。吡虫啉、噻虫嗪、呋虫胺等已用于多种农业害虫的防治，例如半翅目、鞘翅目、双翅目等昆虫。nAChR 突变是昆虫对新烟碱类杀虫剂产生抗性的关键机制。Xu 等[25]在抗吡虫啉桃蚜（*Myzus persicae*）种群的烟碱乙酰胆碱受体 β1 亚基中检测到了 R81T 和 V101I 突变，从抗性稳定种群中鉴定出四种类型桃蚜并发现，与未突变个体相比，R81T 杂合突变体、V101I 纯合突变体以及 R81T 和 V101I 双杂合突变体对吡虫啉、噻虫嗪和呋虫胺的抗性显著增强。Munkhbayar 等[26]对我国山东省棉蚜（*Aphis gossypii*）田间种群的突变检测也发现，nAChR β1 亚基的 R81T 和 K264E 突变与棉蚜对新烟碱类杀虫剂的抗性有关。除了 *nAChR* 突变引起昆虫抗性，*nAChR* 基因表达量减少也在昆虫对新烟碱类杀虫剂的抗性进化中发挥重要作用。例如 Yin 等[27]通过 RNAi 敲低烟粉虱（*Bemisia tabaci*）nAChR β1 亚基基因的表达发现，其对新烟碱类杀虫剂的敏感性显著降低。比较韭菜迟眼蕈蚊（*Bradysia odoriphaga*）吡虫啉抗性和敏感种群 *nAChR* 亚基基因的表达水平发现，高抗性种群 α1 和 β1 亚基的转录水平显著下调，同时没有检测到与抗性表型有关的 *nAChR* 多态性，表明 *nAChR* 基因表达下调在抗性进化中发挥作用[28]。

1.2 代谢抗性

代谢抗性是指昆虫体内与化学杀虫剂代谢相关的解毒酶系解毒能力增强。细胞色素 P450 单加氧酶（P450s）、谷胱甘肽 S- 转移酶（GSTs）和羧酸酯酶（CarEs）是昆虫体内主要的解毒代谢酶系。

P450s 由多个基因家族组成，与昆虫抗性相关的研究大多集中在 *CYP4*、*CYP6*、*CYP9* 和 *CYP12* 家族。*P450* 基因过表达是昆虫对杀虫剂产生抗性进化的主要原因[29]。研究烟粉虱对吡虫啉和噻虫嗪的抗性进化时发现，与敏感种群相比，P450 基因 *CYP4G68* 在抗性种群中过量表达，进一步相关性分析表明，*CYP4G68* 的表达与烟粉虱各品系的相关抗性水平呈显著正相关[30]。Wei 等[31]同样发现 *CYP6DB3* 基因与烟粉虱对吡虫啉和噻虫嗪的抗性进化密切相关，抑制 *CYP6DB3* 的表达提高了烟粉虱成虫对吡虫啉和噻虫嗪的敏感性。此外，进化出杀虫剂抗性的 *P450* 基因受到调控因子的调控或介导，顺式调控元件或反式作用因子在 *P450* 基因对杀虫剂的过表达中起关键作用[32]。例如，*CYP321A8* 在甜菜夜蛾对有机磷和拟除虫菊酯杀虫剂的抗性进化中发挥重要作用，并证实抗性品系中反式作用因子 CncC 和 Maf 的组成型过表达与 *CYP321A8* 启动子的顺式作用突变相结合，促进了核受体 Knirps 的结合，增强了 *CYP321A8* 的表达[33]。*CYP6CM1* 基因过表达导致烟粉虱对吡虫啉产生抗性，进一步发现过表达的转录因子 CREB 受到丝裂原活化蛋白激酶（MAPK）信号通路调控，MAPK 家族的 ERK 和 p38 激酶磷酸化激活 CREB，进而增强了下游 *CYP6CM1* 基因的表达（图 1）[34]。

谷胱甘肽 S- 转移酶（GSTs）催化还原型谷胱甘肽与亲电子外源化合物的结合反应，提高其可溶性并通过排泄达到解毒目的[35]。昆虫体内 GSTs 介导对杀虫剂的抗性进化主要是由 *GST* 基因过表达引起的。Tao 等[36]通过对中华按蚊（*Anopheles sinensis*）转录组的分析发现，*GSTd2* 和 *GSTe2* 基因在对拟除虫菊酯产生抗性的田间种群中显著上调，且沉默 *GSTd2* 和 *GSTe2* 能显著提高中华按蚊对溴氰菊酯的敏感性。Lu 等[37]比较了桔小实蝇（*Bactrocera dorsalis*）马拉硫磷抗性和敏感品系 GST 基因的表达差异，与敏感品系相比，*BdGSTe2*、*BdGSTe4* 和 *BdGSTe9* 在抗性品系中显著过表达，表明 GTSs 在昆虫抗性进化过程中起着重要作用。与调控因子介导 *P450* 基因过表达类似，GSTs 经过杀虫剂筛选和诱导之后活性增强，这与调控 GSTs 表达的基因有关[38]。研究发现，转录因子 AhR 可调节苹果蠹蛾（*Cydia pomonella*）参与高效氯氟氰菊酯抗性的 *GST* 基因的表达，并进一步影响其编码的酶的活性，*CpAhR* 表达上调提高了 GSTs 活性，从而使苹果蠹蛾对高效氯氟氰菊酯产生抗性进化[39]。



昆虫对化学杀虫剂产生抗性的机制主要是靶标位点突变和代谢抗性，突变的靶标位点有乙酰胆碱酯酶（AChE）、电压门控钠离子通道（VGSC）、γ-氨基丁酸（GABA）受体、烟碱乙酰胆碱受体（nAChR）等；CncC/Maf 反式作用因子和 MAPK/CREB 信号通路分别调控 P450 基因 *CYP321A8* 和 *CYP6CM1* 过表达帮助代谢解毒。昆虫对转 *Bt* 基因植物产生抗性的机制是钙黏蛋白（CAD）、氨肽酶 N（APN）、ABC 转运蛋白、碱性磷酸酶（ALP）以及丝氨酸蛋白酶等发生突变或表达下调。昆虫对苏云金杆菌杀虫剂的抗性机制主要有肽聚糖识别蛋白（PGRP）表达变化或 MAPK/TFs 信号通路调控中肠蛋白受体表达下调，Toll 和 IMD 免疫信号通路调控抗菌肽（AMPs）表达增强抵御入侵病原微生物，丝氨酸蛋白酶级联调控酚氧化酶（PO）介导形成黑色素消除入侵病原微生物

The evolution mechanisms of insects resistance to chemical insecticides are mainly through mutation and metabolic resistance of target sites with mutation sites in acetylcholinesterase（AChE）, voltage-gated sodium channel（VGSC）, gamma-aminobutyric acid（GABA）receptor, and nicotinic acetylcholine receptor（nAChR）, and with metabolic detoxification of CncC/Maf trans-acting factor and the MAPK/CREB signaling pathways through regulating the overexpression of the P450 genes *CYP321A8* and *CYP6CM1*, respectively. Insects resist to *Bt*-transgenic plants through downregulating midgut binding receptors and decreasing midgut protease activity in insects, with mutations or down-regulation of the expression of calreticulin（CAD）, aminopeptidase N（APN）, ABC transporter proteins, alkaline phosphatase（ALP）, and down-regulation of the expression of serine proteases. Insects resist to microbial insecticides through activating immune system and changing symbiotic flora in insects, with the expression changes of peptidoglycan recognition protein（PGRP）or down-regulation of midgut protein receptor expression by the MAPK/TFs signaling pathways, the expression enhance of antimicrobial peptides（AMPs）against pathogenic microorganisms by Toll and IMD immune signaling pathways, and the melanin formation mediated by serine protease cascades regulating phenoloxidase（PO）

图 1　昆虫对杀虫剂和转 *Bt* 基因植物的抗性机制

Fig.1　Mechanisms of insect resistance to insecticides and *Bt*-transgenic plants

羧酸酯酶（CarEs）是昆虫体内重要的代谢解毒酶之一，能催化水解杀虫剂中的酯键，或与杀虫剂螯合使其无法作用于靶标位点。羧酸酯酶介导的昆虫代谢抗性机制主要是 *CarE* 基因过表达以及编码的氨基酸序列突变[40-41]。桃蚜有机磷抗性品系和敏感品系的 CarEs 数量和活性存在差异，进一步研究表明抗性品系中 *CarE* 基因 *E4* 和 *FE4* 发生扩增导致 *CarEs* 表达量增加，从而产生对有机磷类杀虫剂的抗性[42]。Lu 等[43]分析褐飞虱敏感品系和抗毒死蜱品系中 *CarE* 基因的表达模式发现，*CarE3*、*CarE17* 和 *CarE19* 在抗性品系中过表达，通过 RNAi 敲低任一 *CarE* 基因均显著提高抗性褐飞虱对毒死蜱的敏感性。*CarE* 基因突变导致的抗性在一些昆虫中也有报道。例如在抗有机磷杀虫剂棉蚜品系中，CarEs 的 4 种非同义突变组合增加了有机磷水解酶的活性，结构变化的 *CarE* 基因可能以失去其活性为代价赋予有机磷水解酶活性[44]。Bai 等[45]研究发现抗性棉铃虫 *CarE* 基因 *CarE001G* 在富含甘氨酸区域发生缺失突变是导致其对 β-氯氰菊酯产生抗性进化的原因（表 1）。

表 1 昆虫对化学杀虫剂的抗性机制

Table 1 Resistance mechanisms of insects to chemical insecticides

抗性机制 Resistance mechanism	靶标位点 / 代谢类型 Target sites/Metabolic types	参考文献 References
靶标位点抗性 Target site resistance	乙酰胆碱酯酶 Acetylcholinesterase	[15-17]
	电压门控钠离子通道 Voltage-gated sodium channel	[18-20]
	γ- 氨基丁酸受体 γ-aminobutyric acid receptor	[22-24]
	烟碱乙酰胆碱受体 Nicotine acetylcholine receptor	[25, 28]
代谢抗性 Metabolic resistance	细胞色素 P450 单加氧酶 Cytochrome p450 monooxygenase	[29-30, 32-33]
	谷胱甘肽 S- 转移酶 Glutathione S-transferase	[36, 39]
	羧酸酯酶 Carboxylesterases	[40-42, 44]

2 昆虫对微生物杀虫剂的抗性机制

微生物杀虫剂利用微生物及其代谢产生的各种生物活性成分防治害虫。已发现的昆虫病原体种类包括细菌、真菌、病毒、线虫、原生动物等，这些病原体都可开发作为微生物杀虫剂[46-48]。与微生物杀虫剂相互作用的过程中，昆虫进化出了多种多样的抵抗策略阻止微生物入侵。其中，免疫防御反应是昆虫对微生物杀虫剂产生抗性的重要因素[49-50]。当微生物杀虫剂攻击昆虫时，模式识别受体（PRRs）被激活识别病原体,进而激活 Toll 和免疫缺陷（IMD）信号通路，调控抗菌肽（AMPs）表达以应对病原体侵染。肽聚糖识别蛋白（PGRPs）在免疫应答的信号识别和传递中发挥了关键作用（图 1）。Liu 等[51]检测到 *PGRP1* 高表达和 *PGRP3* 低表达共同影响抗性小菜蛾（*Plutella xylostella*）的免疫调节，导致对苏云金杆菌产生抗性。抗菌肽（AMPs）是昆虫体内经诱导产生的具有广谱抗菌活性的小分子多肽。埃及伊蚊（*Aedes aegypti*）受到真菌类杀虫剂侵染后，体内多种 *AMP* 基因表达显著增强，且 RNAi 沉默表明多种 AMPs 协同抵御真菌[52]。在果蝇（*Drosophilidae*）[53] 和黄粉虫（*Tenebrio molitor*）[54] 中也观察到了类似的结果，AMPs 以协同作用抑制细菌生长。抗菌肽不仅在抗细菌和真菌方面得到表征，而且在抗病毒免疫中也起着重要作用。感染核型多角体病毒（NPV）的舞毒蛾（*Lymantria dispar*）幼虫 *AMP* 基因表达显著增强，AMPs 有效抵御了病毒侵染[55]。此外，昆虫免疫系统也会通过 MAPK 信号通路调节昆虫中肠蛋白受体表达，从而产生对苏云金杆菌的抗性。IMD 免疫通路中的转化生长因子 β 激活激酶 1（Tak1）属于 MAP3K 家族成员[56]，可将信号传递到下游效应子 MAPK，进而激活相关转录因子（TFs）调控昆虫中肠蛋白受体差异表达（图 1）[57]。

免疫系统涉及的酚氧化酶原级联反应也是昆虫抗性形成的重要因素。酚氧化酶（PO）是参与昆虫免疫防御的一种关键酶，可导致入侵微生物周围形成黑色素，发挥包囊作用清除微生物。微生物杀虫剂被昆虫 PRRs 识别后，激活一系列丝氨酸蛋白酶级联，进而水解酚氧化酶原（PPO）形成活化的 PO，活化的 PO 氧化酚形成醌，醌类化合物进一步聚合成黑色素（图 1）[58]。Duffield 等[59]观察到暴露于球孢白僵菌的粉纹夜蛾（*Trichoplusia ni*）幼虫体内具有更高的 PO 活性，同时两个重要的酚氧化酶原级联基因 *PPOAE* 和 *PPO2* 表达显著增加。Li 等[60]研究发现抗苏云金杆菌小菜蛾中的酚氧化酶原 *PxPPO1* 和 *PxPPO2* 在卵、第 4 龄、头部和血淋巴中的表达量高于敏感品系，PO 活性分析显示，用苏云金杆菌处理的抗性品系比敏感品系表现出更高的 PO 活性。

除了激活的免疫反应，昆虫体内共生菌群变化也对昆虫抗微生物杀虫剂有重要影响，这与共生菌多样性和丰度有关[61-63]。Chen 等[64]检测表明抗 *Bt* 杀虫剂的二化螟肠道微生物多样性显著高于敏感品系，高多样性和丰度的肠道微生物抑制了二化螟对 *Bt* 杀虫剂的吸收。同样的，甜菜夜蛾肠道共生菌多样性和丰度越高，对 *Bt* 杀虫剂的抗性就越高[65]。Wang 等[66]发现与用抗生素处理后的幼虫相比，梨小食心虫（*Grapholita molesta*）角质层共生细菌群的存在引起其对球孢白僵菌的抗性，其中优势细菌泛

菌属（*Pantoea* sp.）抑制了球孢白僵菌的感染。此外，昆虫共生菌群还能产生抗菌物质作为屏障防止病原微生物定殖[67-68]。Zhou 等[69]发现葱蝇（*Delia antiqua*）幼虫共生细菌群产生的有机酸代谢物抑制球孢白僵菌的萌发和生长，导致对球孢白僵菌的抗性。顶切叶蚁（*Acromyrmex subterraneus*）角质层共生丝状放线菌分泌的抗真菌化合物引起其对金龟子绿僵菌（*Metarhizium anisopliae*）的抗性，去除细菌生物膜实验降低抗真菌化合物浓度后，顶切叶蚁对金龟子绿僵菌的敏感性显著增加[70]（表 2）。

表 2　昆虫对微生物杀虫剂的抗性机制

Table 2　Resistance mechanisms of insects to microbial insecticides

抗性机制 Resistance mechanism	主要因素 Major factors	参考文献 References
免疫反应增强	激活模式识别受体，进而激活 Toll 和 IMD 信号通路调控抗菌肽表达	[51-52, 55, 57]
Enhances immune response	Activate pattern recognition receptors, thereby activating Toll and IMD signaling pathways to regulate antimicrobial peptide expression	
	酚氧化酶原级联形成黑色素，发挥包囊作用清除微生物	[58-60]
	Prophenoloxidase cascade forms melanins that act as an encapsulation to remove microorganisms	
共生菌群抑制微生物侵染	存在高多样性和丰度的共生菌群或优势菌	[64, 66]
Symbiotic flora inhibits microbial infestation	Symbiotic flora or dominant bacteria having high diversity and abundance	
共生菌群产生抗菌物质	抗菌物质发挥作用抵御微生物	[69-70]
Symbiotic flora produces antimicrobial substances	Antimicrobial substances resist against microorganisms	

3　昆虫对抗虫转 *Bt* 基因植物的抗性机制

随着抗虫转 *Bt* 基因植物的大面积连续种植，昆虫对转 *Bt* 基因植物产生了抗性进化。*Bt* 毒素的杀虫过程中涉及多种受体蛋白，包括钙黏蛋白（CAD）、氨肽酶 N（APN）、碱性磷酸酶（ALP）、ATP 结合盒转运蛋白（ATP-binding cassette transporter proteins，ABC 转运蛋白）等。中肠受体蛋白突变或表达下调是昆虫对 *Bt* 毒素产生抗性的主要原因[71-72]。Xiao 等[73]报道了与昆虫 *Bt* 抗性相关的 CAD 点突变，由于 CAD 等位基因 *HaCad* 发生 D172G 突变，导致 CAD 错误定位无法发挥其受体蛋白的作用，使得棉铃虫对 *Cry1Ac* 毒素产生抗性。Sun 等[74]通过 RNAi 敲低二化螟 *APN* 基因 *APN6* 和 *APN8* 发现，*APN* 基因表达下调显著降低二化螟对转 *Cry1Ac/Cry1Ab* 融合基因和 *Cry1Ca* 基因水稻的敏感性。Flagel 等[75]检测到草地贪夜蛾抗性品系的两个 *ABCC2* 突变等位基因导致蛋白质截短，使翻译后的蛋白质不能发挥毒素受体的功能，减少了与 *Cry1Fa* 和 *Cry1A.105* 毒素的结合。此外，昆虫中肠受体蛋白还受到 MAPK 信号通路介导的转录因子（TFs）调控表达（图 1）。响应并受控于激活的 MAPK 级联的转录因子 POUM1 在抗 *Cry1Ac* 毒素小菜蛾中表达降低，导致 *PxABCG1* 基因表达下调，减少了 *Bt* 毒素与 ABC 转运蛋白的结合，从而产生 *Bt* 抗性[76]。Guo 等[77]发现 MAPK 信号通路介导的转录因子 PxGATAd 调控是导致小菜蛾 *Cry1Ac* 抗性和敏感品系 *PxmALP* 差异表达的原因。转录因子 PxGATAd 受到 MAPK 信号通路负调控，激活的 MAPK 级联抑制 PxGATAd 的表达，导致 *PxmALP* 表达下调，从而增强了对 *Cry1Ac* 的抗性。

除了 *Bt* 毒素与受体蛋白结合能力差异介导的抗性外，昆虫中肠蛋白酶活性降低引起的抗性也在研究中被报道[78]。*Bt* 毒素进入昆虫体内后需要经过中肠蛋白酶水解成活化的毒素才能发挥作用，*Bt* 毒素在活化过程中受到阻碍将影响毒素的生物活性，从而导致昆虫对 *Bt* 毒素产生抗性。Gong 等[79]发现小菜蛾抗性品系中的胰蛋白酶样丝氨酸蛋白酶基因 *PxTryp_SPc1* 表达下调显著降低了胰蛋白酶活性，使得抗性品系活化 *Bt* 原毒素的能力低于敏感品系，导致对 *Bt* 毒素产生抗性。Zhang 等[80]发现棉铃虫抗性品系内源性丝氨酸蛋白酶抑制剂基因的相对表达均显著高于易感品系，该基因表达增强使得胰蛋白酶和胰凝乳蛋白酶活性降低，阻碍了 *Cry1Ac* 原毒素

表 3　昆虫抗性机制和减缓抗性进化的措施

Table 3　Resistance mechanisms of insects and measures to delay resistance evolution of insects

类型 Type	抗性机制 Resistance mechanism	关键因素 Key factor	昆虫 Insect	减缓措施 Mitigation measure	参考文献 References
化学杀虫剂 Chemical insecticides	乙酰胆碱酯酶突变 Acetylcholinesterase mutation	乙酰胆碱酯酶 Acetylcholinesterase	甜菜夜蛾 *Spodoptera exigua*、马铃薯甲虫 *Leptinotarsa decemlineata*、褐飞虱 *Nilaparvata lugens*	轮换使用杀虫剂 Rotated use of insecticides	[15, 17, 84]
	电压门控钠离子通道突变 Voltage-gated sodium channel mutation	电压门控钠离子通道 Voltage-gated sodium channel	绿盲蝽 *Apolygus lucorum*、烟草甲虫 *Lasioderma serricorne*	减少杀虫剂使用、合理使用增效剂 Reducing the use of insecticides, and reasonable use of synergists	[19, 85]
	γ- 氨基丁酸受体突变 γ-aminobutyric acid receptor mutation	γ- 氨基丁酸受体 γ-aminobutyric acid receptor	灰飞虱 *Laodelphax striatellus*、白背飞虱 *Sogatella furcifera*、褐飞虱 *Nilaparvata lugens*	轮换使用杀虫剂 Rotated use of insecticides	[23, 86]
	烟碱乙酰胆碱受体突变 Nicotine acetylcholine receptor mutation	烟碱乙酰胆碱受体 Nicotine acetylcholine receptor	桃蚜 *Myzus persicae*、西花蓟马 *Frankliniella occidentalis*	轮换使用杀虫剂 Rotated use of insecticides	[25, 87]
	P450 解毒酶过表达 P450 detoxification enzyme overexpression	P450 解毒酶 P450 detoxification enzyme	烟粉虱 *Bemisia tabaci*、棉铃虫 *Helicoverpa armigera*	混合使用杀虫剂、合理使用增效剂 Mixed use of insecticides, and reasonable use of synergists	[30, 88]
	谷胱甘肽 S- 转移酶过表达 Glutathione S-transferase overexpression	谷胱甘肽 S- 转移酶 Glutathione S-transferase	小菜蛾 *Plutella xylostella*、褐飞虱 *Nilaparvata lugens*、斜纹夜蛾 *Spodoptera litura*	轮换使用杀虫剂、合理使用增效剂、减少杀虫剂使用 Rotated use of insecticides, reasonable use of synergists, and reducing the use of insecticides	[89–91]
	羧酸酯酶表达上调 Upregulation of carboxylesterase expression	羧酸酯酶 Carboxylesterases	桃蚜 *Myzus persicae*、棉蚜 *Aphis gossypii*	轮换使用杀虫剂 Rotated use of insecticides	[42, 44]
微生物杀虫剂 Microbial insecticides	免疫反应增强 Enhance immune response	肽聚糖识别蛋白 Peptidoglycan recognition proteins、抗菌肽 Antimicrobial peptide	小菜蛾 *Plutella xylostella*、舞毒蛾 *Lymantria dispar*	轮换使用杀虫剂、基因工程改造病毒基因组 Rotated use of insecticides,and genetic modification of virus genomes	[51, 55]
	共生菌群抑制微生物侵染 Symbiotic flora inhibits microbial infestation	泛菌属 Pantoea sp.	梨小食心虫 *Grapholita molesta*	微生物杀虫剂联合使用 Combined use of microbial insecticides	[66]
	共生菌群产生抗菌物质 Symbiotic flora produces antimicrobial substances	有机酸代谢物 Organic acid metabolites	葱蝇 *Delia antiqua*	轮换使用杀虫剂 Rotated use of insecticides	[69]
转 *Bt* 基因植物 *Bt* transgenic plants	中肠蛋白酶活性降低 Decreased midgut protease activity	胰蛋白酶 Trypsin、胰凝乳蛋白酶 Chymotrypsin	小菜蛾 *Plutella xylostella*、棉铃虫 *Helicoverpa armigera*	双价或多价转基因植物抗虫、RNAi 技术与 *Bt* 毒素协同抗虫 Bivalent or multivalent transgenic plants with insect resistance,RNAi technology and *Bt* toxin synergistically	[79–80]
	中肠受体蛋白基因突变或表达下调 Midgut receptor protein gene mutation or downregulation expression	氨肽酶 N Aminopeptidase N、ABC 转运蛋白 ATP-binding cassette transporter	二化螟 *Chilo suppressalis*、草地贪夜蛾 *Spodoptera frugiperda*	双价或多价转基因植物抗虫、“高剂量 / 庇护所”策略 Bivalent or multivalent transgenic plants with insect resistance, “High-dose/shelter” strategy	[74–75]

的激活，降低了棉铃虫对 *Bt* 毒素的敏感性。

4　结论与展望

昆虫对杀虫剂和抗虫转 *Bt* 基因植物产生抗性是昆虫适应性进化的结果。昆虫对化学杀虫剂主要存在靶标位点抗性和代谢抗性两种抗性机制，靶标位点抗性是指杀虫剂结合位点发生突变，导致靶标敏感性下降；代谢抗性则是由于昆虫体内解毒酶系的过表达。对微生物杀虫剂产生抗性主要是昆虫的免疫系统和共生菌群发生了改变。当昆虫暴露于微生物杀虫剂后，其免疫系统会迅速做出应激和解毒反应，通过 Toll 和 IMD 免疫信号途径和丝氨酸蛋白酶转导级联，调控多种抗性基因差异表达、产生抗微生物效应物或增加 PO 活性参与昆虫抗性。昆虫对 *Bt* 毒素的抗性机制主要有两个方面，一方面是 *Bt* 毒素作用的中肠受体蛋白突变或表达下调引起的抗性，另一方面是中肠蛋白酶活性降低导致 *Bt* 原毒素活化受到阻碍引起的抗性。MAPK 信号通路介导的昆虫抗性调控网络在这三种抗性进化机制中发挥重要作用（图 1）。对比三种抗性机制，昆虫对微生物杀虫剂的抗性可以在短时间内被免疫系统诱导产生，而对化学杀虫剂和转 *Bt* 基因植物产生抗性的主要原因则需要更长时间的进化，基因发生突变使得相关蛋白的表达发生变化。

昆虫的抗性进化影响了农业害虫的防治效果。为减缓昆虫对杀虫剂和转 *Bt* 基因植物的抗性进化，可以采取以下延缓昆虫产生抗性的措施（表 3）：（1）减少杀虫剂使用频率，降低昆虫抗性水平；（2）轮换或混合使用不同作用机制的杀虫剂，减轻对靶标昆虫的持续选择压力；（3）合理使用增效剂，抑制杀虫剂对昆虫的解毒；（4）微生物杀虫剂联合使用，提高杀虫效率；（5）利用基因工程改造病毒基因组，提高侵染毒力；（6）双价或多价转基因植物抗虫；（7）在种植 *Bt* 作物区域实施“高剂量 / 庇护所”策略；（8）RNAi 技术与 *Bt* 毒素协同抗虫。然而，延缓昆虫抗性进化的措施在实际应用过程中也存在着一些问题有待解决。例如，微生物杀虫剂具有特异性强、无污染的特点，但易受到环境因素的影响，其活性难以保持稳定[81]。由于多种抗虫基因存在交互抗性现象，利用双价或多价转基因植物减缓昆虫抗性进化还有待深入研究。此外，RNAi 和 *Bt* 毒素协同抗虫也受到一些因素制约，例如如何克服 dsRNA 在昆虫中肠降解导致 RNAi 效率降低[82]，如何避免 dsRNA 靶向非靶标基因导致非特异性基因沉默的脱靶效应[83]。因此，需要综合考虑昆虫抗性的发展、使用杀虫剂的环境条件等因素，采取有效、安全、绿色的治理措施。未来建议减少使用化学杀虫剂，合理利用杀虫谱广和活性高的微生物杀虫剂以及抗虫植物等方法系统治理农业害虫。

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