



近二十年我国杀虫剂毒理学研究进展 (II) ——昆虫对杀虫剂的抗性研究*

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摘 要 本文综述了中国昆虫学家、杀虫剂毒理学研究者与植物保护专家及害虫防治工作者最近 20 年来在昆虫对杀虫剂的抗性研究方面的进展, 并就杀虫剂施用后害虫抗药性的发生、交互抗性的形成、杀虫剂增效剂的使用以延缓抗性的发展做了简要介绍, 特别对昆虫抗药性的产生机制, 包括靶标抗性、代谢抗性和穿透抗性在内的抗性机理, 尤其是细胞色素 P450 酶系、乙酰胆碱酯酶 (AChE)、谷胱甘肽巯基转移酶 (GST)、电压门控钠离子通道 (VGSC)、P-糖蛋白 (P-gp)、乙酰胆碱受体 (AChR)、表皮生长因子受体 (EGFR) 和 γ -氨基丁酸受体 (GABAR) 等与杀虫剂抗性相关的基因及其表达产物在昆虫抗药性形成中的作用的研究进行了系统性综述。

关键词 杀虫剂; 害虫抗药性; 毒性; 靶标抗性; 代谢抗性; 穿透抗性

Advances in insecticide toxicology in China in the last two decades II: Resistance of insects to insecticides

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Abstract Advances in research on the resistance of insects to insecticides made by entomologists, insecticide toxicologists, plant protection and pest control experts in China over the past 20 years is reviewed. Insecticide resistance, including cross-resistance and the delay, or prevention, of resistance by applying different insecticides with synergistic effects, is briefly introduced. Studies on the mechanisms of insecticide resistance in insects, including target resistance, metabolic resistance, and penetration resistance, especially the role of the genes such as cytochrome P450s, acetylcholinesterase (AChE), glutathione S-transferase (GST), voltage-gated sodium channel (VGSC), P-glycoprotein (P-gp), acetylcholine receptor (AChR), epidermal growth factor receptor (EGFR), and γ -aminobutyric acid receptor (GABAR), and their expression products in the development of resistance, are systematically reviewed.

Key words insecticide; insect resistance; toxicity; target resistance; metabolic resistance; penetration resistance

随着杀虫剂长期、大量、广泛使用, 很多昆虫都产生了抗药性。尽管在过去 20 年, 我国昆虫毒理学与杀虫剂毒理学研究者及植物保护工作者在杀虫剂的杀虫机理、杀虫剂的合理使用与

杀虫剂防控害虫的施药技术等方面开展了大量研究工作, 包括合理搭配不同杀虫剂施用以延缓害虫对杀虫剂抗性的发展或研制杀虫增效剂以削弱害虫已经形成的对杀虫剂的抗性, 但是,

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害虫对杀虫剂抗性的发展趋势仍在继续。

对于杀虫剂抗性的调查已开展多年,而抗性发生机理的研究近年来也有较大的进展。抗性的基本参数测定(半数致死量、抗性倍数测定)是杀虫剂抗性研究工作的基础,过去 20 年各地植物保护部门及卫生防疫部门做了大量工作,包括建立抗性品系昆虫的筛选方法用于抗性机理的研究等(刘泽文等, 2002)。这不仅为杀虫剂的合理使用提供科学依据,同时也为昆虫对杀虫剂抗性机理的研究奠定了基础。

1 害虫对杀虫剂的抗药性

1.1 卫生害虫

包括蚊、蝇、蟑螂等在内的卫生害虫在杀虫剂抗性研究中一直占有相当高的比例,疾病防控部门在这方面开展了比较多的工作。相关工作包括:与野生型或敏感型作对比,测定某些特定种群对某种杀虫剂的抗性指数,各地监测的卫生害虫对杀虫剂的抗性程度存在很大差异。例如:利用寡核苷酸基因芯片检测淡色库蚊,发现在溴氰菊酯(Deltamethrin)和氯氰菊酯(Cypermethrin)抗性品系中分别有 8 个和 5 个基因表达水平发生改变,其中 CYP6Z10 和 PSMB6 在抗性种群高表达(Chen *et al.*, 2010)。针对埃及伊蚊 *Aedes aegypti* 对氯氰菊酯和三氟氯氰菊酯(Cyhalothrin)的抗性研究表明,蚊虫对拟除虫菊酯类杀虫剂的抗性机制包括表皮穿透抗性、靶标抗性和代谢抗性,其中代谢抗性机制较为普遍,与昆虫对多种杀虫剂的交互抗性关系密切(Li *et al.*, 2015)。最近,研究人员调查中国东部地区按蚊种群击倒抗性的多态性及地理分布,发现大多数中华按蚊种群对拟除虫菊酯类杀虫剂具有抗性(Tan *et al.*, 2019)。

关于蚊虫对杀虫剂的抗性机理参见本文第 1.4.3 节“靶标抗性”。

1.2 农业害虫

包括稻飞虱 *Nilaparvata lugens*、棉铃虫 *Helicoverpa armigera*、小菜蛾 *Plutella xylostella* 及各种蚜虫在内的农业害虫(又称农作物害虫)

近年来对杀虫剂的抗性越来越普遍,且抗性程度越来越高。田间采样实测数据显示, Bt 抗性棉铃虫的比例从 2010 年到 2013 年增长了近 6 倍!对棉铃虫 Bt 抗性的预测建模研究显示,设立天然避难区域或可延缓棉铃虫 Bt 抗性的发展(Jin *et al.*, 2015)。

对于拟除虫菊酯类杀虫剂的抗性,早在 20 世纪 90 年代,研究人员就在河北定州开展了调查,发现抗性综合治理有助于控制棉铃虫对菊酯类杀虫剂抗性的发展(Yang *et al.*, 2004, 2005)。曾对江西省 5 个蔬菜产区小菜蛾田间种群对啉虫酰胺的抗性水平进行测定,发现该地区小菜蛾抗性不明显或呈低水平(Cao and Han, 2006)。然而,研究发现,褐飞虱 *Nilaparvata lugens* 对不同杀虫剂的敏感性存在很大差异。田间种群对新烟碱类杀虫剂的抗性水平不一,对吡虫啉的抗性高,对噻虫嗪的抗性较低(Wang *et al.*, 2008a, 2008b)。甜菜夜蛾 *Spodoptera exigua* 的田间种群在室内经过多代筛选后对氯虫苯甲酰胺的抗性大幅度增加(Lai and Su, 2011)。原本对噻虫嗪和烯啶虫胺敏感的褐飞虱田间种群在经过连续 30 代室内抗性筛选后抗性上升几十倍(烯啶虫胺)甚至数百倍(噻虫嗪)(Zhang *et al.*, 2017)。

研究者通过西花蓟马 *Frankliniella occidentalis* 对噻虫嗪的抗性选育及抗性风险评估,揭示了噻虫嗪与其他药剂的交互抗性水平及西花蓟马对噻虫嗪的作用机制(Gao *et al.*, 2014)。调查了 7 省 19 地二化螟 *Chilo suppressalis* 对杀虫剂的抗性,发现各地二化螟地理种群之间对氯虫苯甲酰胺和氟苯虫酰胺的抗性差异较大(Yao *et al.*, 2017)。此后又对我国 7 个省份 23 个地区采集的 37 个二化螟田间种群对氯虫苯甲酰胺等 7 种杀虫剂的抗药性开展调查。结果显示,田间二化螟种群的抗性水平存在明显的地理差异,采自浙江、江西及湖南省的二化螟种群属高抗性;而江苏、四川省的二化螟种群相对敏感(Lu *et al.*, 2017; Sun *et al.*, 2018; Wei *et al.*, 2019)。

近年来对陕西关中地区小麦田禾谷缢管蚜 *Rhopalosiphum padi* 对氯氰菊酯等 7 种常用杀虫剂的抗性测定发现,由于存在高抗性问题,高效氯氰菊酯被认为已不适合用于关中地区禾谷缢

管蚜防治(黄彦娜等, 2019)。另有研究者从我国多个地区收集小菜蛾田间种群, 发现这些小菜蛾对溴虫腈产生了高水平抗性(Wang *et al.*, 2019)。

关于农业害虫对杀虫剂抗性的机制研究详见本文第 1.5 节。

1.3 杀虫剂抗性类型

按照目前学界共识, 昆虫对杀虫剂的抗性主要可被分为靶标抗性、代谢抗性和穿透抗性三大类, 此外, 也有研究者提出非特异性抗性 & 行为抗性等抗性类型。

1.3.1 代谢抗性 代谢抗性一直是杀虫剂抗性研究的热点。杀虫剂在昆虫体内被解毒酶代谢降解而降低毒性。这些代谢酶(有称解毒酶)主要包括谷胱甘肽巯基转移酶(GST)、乙酰胆碱酯酶(AChE)及细胞色素 P450(以下简称 P450)介导的多功能氧化酶(MFO)等。近 20 年大量的研究工作围绕杀虫剂的代谢抗性机制展开。P450 可介导抗性进化可塑性, 同种昆虫的不同种群在相同种类杀虫剂的胁迫下, 进化选择出抗性相关的 P450 也有所不同, 抗性的产生也可以是几种不同 P450 协同作用的结果(邱星辉等, 2008)。早期有报道抗啮虫酰胺的小菜蛾体内酯酶和 MFO 活性均比敏感品系高。提示这可能与小菜蛾对啮虫酰胺的抗性有关(Cao and Han, 2006)。研究发现, MFO 在甜菜夜蛾对虫酰肼的抗性中起重要作用(Jia *et al.*, 2009)。已有多篇论文揭示褐飞虱对吡虫啉的抗性与 P450 单加氧酶的活性增强有关(Liu *et al.*, 2003; Liu and Han, 2006; Wen *et al.*, 2009)。野外采集的白背飞虱 *Sogatella furcifera* 种群对氟虫腈具有抗性, 其体内酯酶和 P450 单加氧酶活性增加(Tang *et al.*, 2010)。B 型烟粉虱 *Bemisia tabaci* 对噻虫嗪的抗性与 P450 单加氧酶及羧酸酯酶(CarE)有关(Feng *et al.*, 2010)。甜菜夜蛾对氰氟虫腈(Metaflumizone)的抗性与黄素依赖性单加氧酶(FMOs)的活性增加有关(Tian *et al.*, 2014)。棉铃虫对茚虫威(Indoxacarb)产生抗性的重要原因是 P450 活性的增强(Cui *et al.*, 2018); 同

样, P450 单加氧酶的解毒作用增强与棉蚜对甲氧嘧啶的抗性有关(Ma *et al.*, 2019)。而烟草夜蛾幼虫体内 P450 还原酶的表达水平影响其对辛硫磷及其他杀虫剂的敏感性(Ji *et al.*, 2019)。

野外采集的小菜蛾体内 CarE 活性与多杀菌素抗性呈正相关(Gong *et al.*, 2013)。CarE 基因 CpCE-1 的表达在苹果蠹蛾 *Cydia pomonella* 不同发育阶段存在明显差异, 该基因可能参与毒死蜱与高效氟氯氰菊酯的解毒作用(Yang, 2016)。棉蚜 *Aphis gossypii* 对螺虫乙酯的耐受性增强可能是由于 CarE 活性增加而加快了螺虫乙酯的代谢所致(Gong *et al.*, 2016)。研究发现, 在抗氧乐果的棉蚜中 CarE 活性及其表达水平比对氧乐果敏感的棉蚜要高, 认为 CarE 表达的增加或 CarE 基因突变与棉蚜对氧乐果的抗性有关(Cao *et al.*, 2008; Gong *et al.*, 2017)。经多代筛选获得对茚虫威抗性的棉铃虫, 其体内 CarE 和 P450 活性增强是其重要的解毒机制(Cui *et al.*, 2018)。

研究发现, 中国西北地区的苹果蠹蛾种群对毒死蜱和西维因不敏感的主要原因是 GST 活性增加(Yang and Zhang, 2015); 在以家蚕为实验对象的研究中发现, 经甲氰菊酯与辛硫磷处理后, BmGSTe2 表达水平改变可参与幼虫对多种杀虫剂的耐受性, 而 GST 活性和 BmGSTe2 的表达水平可作为有机磷和拟除虫菊酯类杀虫剂的毒性标记(Zhou *et al.*, 2015; Hu *et al.*, 2016)。此外还发现, 抗茚虫威的小菜蛾体内 GST 及 P450 单加氧酶活性升高, 提示其抗性与 GST 具有相关性(Zhang *et al.*, 2017)。

1.3.2 穿透抗性 穿透抗性机制可延缓杀虫剂进入昆虫体内尤其是到达靶标部位的时间, 并使杀虫剂在体内有更多机会被降解。通过室内汰选获得对氟虫腈抗性的稻纵卷叶螟 *Cnaphalocrocis medinalis*, 发现增效醚对微粒体去甲基化酶的抑制作用在敏感品系要比抗性品系高, 且氟虫腈与增效醚产生协同效应在两个品系间的差别主要是抗性品系降低了氟虫腈的穿透(Huang *et al.*, 2010)。表皮穿透性降低机制在家蝇、埃及伊蚊、致倦库蚊 *Culex quinquefasciatus*、淡色库蚊 *Culex*

pipiens pallens 等均有发现(孙雅雯和郑彬, 2015)。研究者以果蝇幼虫为测试对象, 探索其对阿维菌素穿透抗性的分子机制, 发现外排转运蛋白 P-糖蛋白(P-glycoprotein, P-gp)在抗阿维菌素的幼虫表皮中过表达, 阿维菌素可直接与表皮生长因子受体(EGFR)相互作用, 诱导几丁质合成酶, 导致几丁质层增厚, 穿透性降低, 这为深入了解抗药性的分子机制提供了新的见解(Chen et al., 2016b)。德国小蠊 *Blattella germanica* 对高效氯氰菊酯的抗性品系中的 CYP4G19 的高表达与几丁质层较高的碳氢含量呈正相关, 敲减 CYP4G19 基因可以降低几丁质层碳氢含量。因此, 与碳氢产量有关的 CYP4G19 基因被认为在德国小蠊对杀虫剂的穿透抗性中起重要作用(Chen et al., 2020)。

1.3.3 靶标抗性 靶标抗性已在多种昆虫对杀虫剂的抗性中被发现。涉及 AChE 对有机磷和氨基甲酸酯类杀虫剂的抗性, 电压门控钠离子通道(VGSC)对滴滴涕(DDT)和拟除虫菊酯的击倒抗性以及 γ -氨基丁酸受体(γ -aminobutyric acid receptor, GABAR)对环戊二烯类杀虫剂的抗性。

杀虫剂尤其是有机磷与氨基甲酸酯类杀虫剂的抗性很多都与 ace 基因突变有关, 例如: 棉蚜对有机磷杀虫剂的抗性与其体内 Ace1/Ace2 突变有关(Li and Han, 2004); 禾谷缢管蚜对有机磷和氨基甲酸酯的抗性与 Ace2 中的 F368(290)L、V435(356)A 和 Ace1 中的 S329(228)P 的突变有关(Chen et al., 2007); 烟粉虱对毒死蜱的抗性与其体内 ace1 基因的 F392W 突变有关(Zhang et al., 2012b); 二化螟对克百威的抗性与 AChE 分子中的氨基酸取代(E101D、A314S 和 R667Q)有关(Chang et al., 2014); 褐飞虱对毒死蜱的抗性与其体内 ace1 基因的 G119S、F331C 和 I332L 的点突变有关(Zhang et al., 2017); 而绿盲蝽 *Apolygus lucorum* 对毒死蜱的抗性与 AChE-1 基因的 A216S 突变有关(Wu et al., 2015; Zhen et al., 2016)。龟纹瓢虫 *Propylaea japonica* 对有机磷杀虫剂抗性品系中的 ace1 基因中有 5 种氨基酸

与敏感品系的不同, 分析发现, 其位于乙酰基结合口袋位置的氨基酸的突变(F358S)可能对有机磷杀虫剂的抗性起到至关重要的作用(Wang et al., 2018)。另外, 抗有机磷杀虫剂的中华按蚊体内 Ace1 的 119S 位点具有较高的突变频率(Fang et al., 2019)。

关于 VGSC 在昆虫抗性中的作用研究主要集中于蚊虫对拟除虫菊酯类杀虫剂的抗性研究, 例如: 埃及伊蚊对拟除虫菊酯类杀虫剂的抗性与 kdr 基因的 V1016G 突变有关(Li et al., 2015); 白纹伊蚊 *Aedes albopictus* 对溴氰菊酯及 DDT 的抗性与 VGSC 的 F1534S 突变有关(Chen et al., 2016a; Xu et al., 2016), 该位点突变被认为可作为白纹伊蚊击倒抗性的监测标志(Zhu et al., 2019)。尖音库蚊 *Culex pipiens* 和中华按蚊对拟除虫菊酯类杀虫剂溴氰菊酯的抗性主要与 kdr 基因 L1014F/C、L1035S/F 突变有关(Chen et al., 2010; Zhao et al., 2014); 而淡色库蚊对氯菊酯和氯菊酯抗性至少涉及 VGSC 的 R954Q、L1023F、S1775G 和 A1989E 共 4 个位点突变(Xu et al., 2017)。除此之外, 绿盲蝽和桃蚜 *Myzus persicae* 对菊酯类杀虫剂的抗性也与 L1015(1014)F 突变有关(Zhen and Gao, 2016; Tang et al., 2017)。Kdr 基因 L1014(1015)F 位点突变被认为可作为淡色库蚊抗菊酯类杀虫剂的分子标记(Liu et al., 2019)。

对蚊虫以外的其他昆虫 VGSC 的研究很少, 有报道广东地区小菜蛾对茚虫威呈现高抗性, 其 VGSC 的两个突变(F1845Y 和 V1848I)分别出现, 或可作为小菜蛾抗性的分子标记(Wang et al., 2016)。棉蚜对拟除虫菊酯类杀虫剂的抗性被认为与 VGSC 的 M918L 点突变伴随解毒代谢有关(Chen et al., 2017)。

1.3.4 非特异性抗性 非特异性抗性与含有 ATP 结合盒(ATP-binding cassette)的转运载体蛋白(如: P-gp)等 ABC 转运蛋白相关。研究发现, 阿维菌素可通过钙调蛋白/Relish(NF- κ B)通路上调 P-gp 转运蛋白的表达, 增强其活性, 加速外源性物质外排, 提高对杀虫剂的抗性(Luo et al., 2013b); 抗阿维菌素果蝇中的 P-gp 增加

受 dEGFR 和 dAkt 途径的调节, 而 P-gp 的表达增加可以增强昆虫对阿维菌素的抗性 (Luo *et al.*, 2013a); 阿维菌素可激活 EGFR/AKT/ERK 通路, 诱导 P-gp 的过表达导致抗性增加 (Chen *et al.*, 2016b)。对 ABC 转运蛋白 ABCC1 在禾谷缢管蚜的不同发育阶段及体内不同部位的表达水平进行测定发现, 在抗吡虫啉和抗毒死蜱的种群中, ABCC1 的表达高于敏感种群 (Kang *et al.*, 2016)。ABC 转运蛋白在小菜蛾抗性中也可能发挥作用, 研究发现抗性品系小菜蛾的中肠和马氏管中 ABC 转运蛋白的高表达基因占优势 (Qi *et al.*, 2016)。德国小蠊 *Blattella germanica* 对毒死蜱的抗性也与 P-gp 有关, P-gp 表达增强与 ATP 酶活性的升高可能是该抗性的重要机制 (Hou *et al.*, 2016)。

1.3.5 交互抗性 交互抗性是指昆虫由于系统抗性或相似作用机理, 对某种已产生抗性的杀虫剂以外的其他从未使用过的杀虫剂也产生抗性的现象。例如: 田间采得的小菜蛾抗啉虫酰胺品系对阿维菌素、氯虫苯甲酰胺、氟虫双酰胺和茚虫威有中低水平的交互抗性 (Cao and Han, 2006)。研究者收集了白背飞虱的田间种群, 经过测定发现它们对氟虫腈具有 50 倍的抗性, 与敏感品系相比, 抗性品系对磷酸三苯酯、顺丁烯二酸二乙酯、增效醚也有显著的交互抗性 (Tang *et al.*, 2010)。经过筛选获得的抗毒死蜱的灰飞虱 *Laodelphax striatellus* 与敌敌畏有交互抗性 (Wang *et al.*, 2010), 而采自野外的抗毒死蜱的灰飞虱田间种群对溴氰菊酯、二嗪农、灭多威、丁硫克百威、乙酰甲胺磷和吡虫啉也都有交互抗性 (Xu *et al.*, 2014)。抗辛硫磷的西花蓟马对毒死蜱、氯氟氰菊酯、灭多威有较高的交互抗性 (王圣印等, 2012)。抗多杀菌素的小菜蛾田间种群对高效氯氟菊酯也有一定的抗性 (Gong *et al.*, 2013), 通过对采自中国南方的斜纹夜蛾 *Spodoptera litura* 的 17 个野外种群的测定, 发现氯虫苯甲酰胺与溴氰虫酰胺具有交互抗性, 这种抗性可能不涉及解毒酶的作用 (Sang *et al.*, 2016)。褐飞虱对氟啶虫胺腈具有较低的抗性水平, 但这种抗性与褐飞虱对所有测试的新烟碱类

杀虫剂的反应具有显著相关性, 提示褐飞虱存在潜在的交互抗性模式 (Liao *et al.*, 2017)。抗氯虫苯甲酰胺和氟苯虫酰胺的二化螟田间种群对溴氰虫酰胺、四氯虫酰胺及氯氟氰虫酰胺具有交互抗性 (Yao *et al.*, 2017)。抗茚虫威的小菜蛾虽然对氰氟虫腈、高效氯氟菊酯、溴虫腈有交互抗性, 但对氰虫酰胺、氯虫苯甲酰胺、阿维菌素、多杀菌素和丁醚脲无交互抗性 (Zhang *et al.*, 2017)。总体上, 田间种群交互抗性比较常见, 但有些文献中报告的数据尚不能完全排除田间用药所产生的交互影响。

1.3.6 抗性管理 简单的抗性治理包括设法提高杀虫剂的防控效果。生产实际中的常用方法是将几种杀虫剂混用以延缓抗药性的形成或使用增效剂改善已经产生抗药性的杀虫剂的防治效果。研究发现, 增效剂胡椒基丁醚 (又名增效醚) 对多杀菌素抗性品系的小菜蛾具有明显的协同作用 (Wang *et al.*, 2006)。增效剂磷酸三苯酯和增效醚对小菜蛾啉虫酰胺抗性品系均有显著增效作用 (Cao and Han, 2006)。增效醚对瓢虫低毒性, 但对寄生蜂高毒, 对甲胺磷、氰戊菊酯、氟虫腈、阿维菌素等杀虫剂有高效协同作用 (Wu *et al.*, 2007), 此外, 增效醚还可以抑制对氟虫腈具有抗性的白背飞虱体内的酯酶和 P450 单加氧酶活性, 这可能是其增效作用的机理 (Tang *et al.*, 2010)。最新的研究发现, 杀虫增效剂胡椒基丁醚可明显提高对吡虫啉具有抗性的烟粉虱的防治效果 (Zhou *et al.*, 2020)。

1.4 昆虫对杀虫剂抗性的分子机制

随着现代生物学技术的发展, 越来越多的分子生物学技术用于昆虫抗性的研究, 并逐渐揭示昆虫对杀虫剂抗性的发生机制。大量文献涉及与代谢抗性和靶标抗性相关的酶 (如: AChE、P450、GST 等) 和受体 (如: EGFR、GABAR 等) 这类抗性基因的突变或表达异常的研究。

1.4.1 P450 涉及抗性机理比较多的是关于 P450 酶系的研究 (邱星辉, 2014)。与抗性相关的 P450 酶系包括 CYP6A1、CYP6A2、CYP6A8、CYP6A9、CYP6B2 和 CYP6B1 等多

个基因。P450 基因的过表达是昆虫对吡虫啉产生抗性的重要机制。研究 2 种 P450 基因 CYP6AY1 与 CYP6ER1 如何参与褐飞虱对吡虫啉的抗性时发现, CYP6AY1 可更有效地分解代谢吡虫啉, 而 CYP6ER1 基因可能更容易被吡虫啉调控到更高的水平 (Bao *et al.*, 2016; Elzaki *et al.*, 2020)。此外, 这 2 种基因的表达水平对不同剂量吡虫啉的反应不同 (Yang *et al.*, 2018)。赤拟谷盗 *Tribolium castaneum* 幼虫在暴露于吡虫啉后, CYP4BR3 和 CYP345A1 的表达显著增加, 对于其他杀虫剂诱导的抗药性也有类似现象, 研究显示, CYP4G7 和 CYP345A1 表达水平可被氯氰菊酯、氯菊酯和氟氯氰菊酯诱导增加 (Liang *et al.*, 2015)。P450 基因 CYP340W1 的过表达在小菜蛾对阿维菌素的抗性中起着重要作用 (Gao *et al.*, 2016); 而在斜纹夜蛾对毒死蜱和氯氰菊酯的抗性中, CYP321B1 起着重要作用 (Wang *et al.*, 2017)。通过研究褐飞虱体内 CYP6ER1 基因过表达与噻虫胺抗性之间的关系发现, 在用 RNA 干扰技术降低 CYP6ER1 表达后褐飞虱对噻虫胺的敏感性显著增加, 提示 CYP6ER1 的高表达可能是褐飞虱对噻虫胺抗性的原因 (Jin *et al.*, 2019)。另有研究结果提示, 烟粉虱对吡虫啉的抗性也涉及 P450 单加氧酶, 通过对采自我国 12 个省的抗吡虫啉烟粉虱种群与 5 个 P450 基因表达之间的关联进行评估, 发现抗性水平与 P450 基因 CYP6CM1 和 CYP4C64 的表达相关, 而与 CYP6CX1, CYP6CX4 或 CYP6DZ7 的表达无关 (Wang *et al.*, 2009; Yang *et al.*, 2013), 最近的研究发现, 抗吡虫啉烟粉虱体内 P450 基因中有 4 个基因 (CYP4CS3、CYP6CX5、CYP6DW2 和 CYP6CM1) 表达显著增强 (Zhou *et al.*, 2020)。进一步研究发现, 烟粉虱通过丝裂原活化蛋白激酶 (MAPK) 调控转录因子 cAMP 应答元件结合蛋白 (CREB), 增强 P450 基因 CYP6CM1 的表达, 导致对吡虫啉类杀虫剂抗药性的形成 (Yang *et al.*, 2020)。此外, 其他相关研究显示: 麦蚜对吡虫啉的抗性也与 P450 基因 CYP6CY3-1 和 CYP6CY3-2 的表达水平显著增加有关 (Wang *et al.*, 2018)。对苹果

蠹蛾的研究发现, P450 的 CYP6B2 基因参与了甲基谷硫磷和溴氰菊酯类杀虫剂的抗性 (Wan *et al.*, 2019)。通过对噻虫嗪、溴氰菊酯、敌敌畏、百草枯的测试, 发现有 4 个 P450 基因 (Acc301A1、Acc303A1、Acc306A1 和 Acc315A1) 在中华蜜蜂 *Apis cerana cerana* 对杀虫剂的解毒中起重要作用 (Zhang *et al.*, 2019)。

1.4.2 AChE、GST、CarE 和 AChR AChE 是有机磷和氨基甲酸酯类杀虫剂的作用靶标, 其基因发生突变后, AChE 对杀虫剂敏感度降低。此外, 乙酰胆碱受体 (Acetylcholine receptor, AChR) 的分子结构改变也可导致昆虫对有机磷和氨基甲酸酯类杀虫剂的敏感性改变, 这些都是杀虫剂靶标抗性产生的重要基础。例如: 早期研究发现, AChE 的丙氨酸到酪氨酸的突变可能是棉铃虫对久效磷不敏感的原因 (Ren *et al.*, 2002)。分子生物学分析发现, 抗有机磷和氨基甲酸酯的果蝇体内 AChE 分子结构的峡部的柔韧性比敏感果蝇的 AChE 的要低很多, 正是其第 W83 和 I161 位的构象改变导致对杀虫剂的降解速度加快 (Fan *et al.*, 2009)。水稻二化螟对三唑磷的抗性与 Ace1 的突变 A314S 有关 (Jiang *et al.*, 2009)。棉蚜对氧乐果的抗性与其体内 Ace1 基因转录下调及 Ace1 和 Ace2 的突变有关 (Pan *et al.*, 2010)。菜蛾啮小蜂 *Oomyzus sokolowskii* 对甲胺磷的抗性与其 AChE 基因中的氨基酸残基的替换导致对 AChE 的不敏感有关 (Zhuang *et al.*, 2014)。调查发现, 小菜蛾对毒死蜱抗性相关的 Ace1 基因有两个突变, 且受温度影响 (Zhang *et al.*, 2015)。在以马铃薯甲虫为对象的研究中发现, 编码功能性 nAChR 一个亚基的 Ld α 1 基因的下调可能是马铃薯甲虫对吡虫啉和噻虫嗪产生抗性的重要机制 (Qu *et al.*, 2016)。

对蚊虫的研究发现, 酯酶 B1 基因突变 (W224L) 可增加蚊虫对马拉硫磷的抗性 (Cui *et al.*, 2007, 2011)。淡色库蚊对氯氰菊酯和氯菊酯抗性除了涉及 VGSC 的点突变外, 还与 GST 的转录水平升高有关 (Xu *et al.*, 2017)。研究者测试了在氯氟氰菊酯、氟虫腈或硫丹胁迫下马

铃薯甲虫体内 20 种 GST 转录物的 mRNA 水平, 发现可通过不同 GST 的过表达而对不同种类的杀虫剂进行解毒 (Han *et al.*, 2016)。研究发现, 转录因子 MafB 可调节桔小实蝇的 GSTz2 基因表达, 后者上调后可降低对阿维菌素的敏感性 (Tang *et al.*, 2019)。通过对斜纹夜蛾的研究发现至少有 3 个 GST 基因受转录因子 CncC/Maf 和 AhR/ARNT 的协同调控导致对毒死蜱和氯氰菊酯的抗性 (Hu *et al.*, 2019)。

1.4.3 GABAR 早期研究发现, 抗氟虫腈小菜蛾体内 rdlGABAR 基因 PxRdl 点突变 (A302S) 对抗性的发生可能起作用 (Li *et al.*, 2006)。小菜蛾对多杀菌素的敏感性也与 GABAR 有关 (Yin *et al.*, 2016)。敲减亲离子型 GABAR-RDL 基因可降低灰飞虱对氟虫腈的敏感性: 提示 lsrdl 编码 RDL 功能亚单位, 介导对氟虫腈的抗性 (Wei *et al.*, 2015), 抗氟虫腈的灰飞虱也对另外 3 个苯基吡唑类杀虫剂有交互抗性, 进一步研究确定其抗性产生的原因是由于其 GABAR 亚单位发生了突变 (Wei *et al.*, 2017; Sheng *et al.*, 2018)。同样, 抗氟虫腈的褐飞虱体内也有 GABAR-RDL 基因点突变 (A302S 和 R300Q) (Zhang *et al.*, 2016), 提示稻飞虱抗氟虫腈的抗性与 GABAR-RDL 基因突变有关。通过分子对接分析褐飞虱对氟虫腈的抗性机理, 氟虫腈与抗氟虫腈的褐飞虱体内突变的 GABAR 的相互作用最弱, 发生突变时, 氟虫腈与之结合的姿态发生改变, 导致结合力降低 (Tian *et al.*, 2019)。

1.4.4 UGT 对于其他靶标酶的研究也有相关报道。例如: 对小菜蛾 UDP-糖基转移酶 (UDP-glycosyltransferase, UGT) 对氯虫苯甲酰胺的解毒能力的研究发现, 在所有对氯虫苯甲酰胺具有抗性的 4 个种群中, UGT2B17 处于过表达状态, 提示 UGT 基因表达水平与小菜蛾的杀虫剂抗性有关 (Li *et al.*, 2017)。对中华按蚊 UGT 基因表达与其对拟除虫菊酯抗性之间的关系进行分析, 发现 UGT308 与 UGT302 是与拟除虫菊酯抗性有关的两个主要基因, 前者参与拟除虫菊酯解毒过程, 而后者编码的氨基酸突变可导致更高的杀虫剂抗性 (Zhou *et al.*, 2019)。此外还通过

组学分析发现, 与敏感种群相比, 抗吡虫啉棉蚜田间种群中有 9 个 UGT 基因高表达, 敲低其中的 UGT344B4 或 UGT344C7 基因表达可增加抗性棉蚜对吡虫啉的敏感性 (Chen *et al.*, 2019); 进一步研究发现, 敲低这两个基因的表达也可增加吡虫啉敏感棉蚜种群对联苯菊酯 (Bifenthrin) 的敏感性 (Chen *et al.*, 2020)。

1.4.5 其他与抗性相关的基因 热激蛋白 (Heat shock protein, HSP) 及鱼尼丁受体 (Ryanodine receptor, RyR) 也参与到昆虫对杀虫剂的抗性机制中, 有研究发现, 拟除虫菊酯抗性的中华按蚊种群中的 3 个 HSP 基因表达量显著高于敏感品系, 显示 HSP 基因与拟除虫菊酯抗性之间的相关性 (Si *et al.*, 2019)。此外, 研究发现小菜蛾的 RyR 蛋白表达量与二酰胺杀虫剂抗性有关, 与敏感种群相比, 田间采集的 5 个抗性种群中检测到 RyR 高表达; 使用 RNAi 抑制 RyR 表达可恢复其对杀虫剂的敏感性 (Li *et al.*, 2015)。为了解二化螟对双酰胺类杀虫剂产生抗性的机制, 研究者参照小菜蛾上发现的突变位点, 对二化螟抗性种群这些基因区域进行检测, 发现在 RyR 第 4753 位点 ATA 突变为 ATG, 而敏感种群中未发现该突变。因此推测 I4753M 突变可能与二化螟对双酰胺类药剂的抗性有关 (Lu *et al.*, 2017; Sun *et al.*, 2018; Wei *et al.*, 2019)。

在 Bt 抗性研究方面, 研究者通过建立 Bt 抗性棉铃虫品系发现了编码 Cry1Ac 钙粘蛋白基因, 该基因突变导致抗性发生 (Xu *et al.*, 2005; Xu and Wu, 2008)。随后, 从田间抗性的棉铃虫中鉴定出另外 2 个 Cry1Ac 抗性基因, 接着又分离出了另外 5 个新的等位基因 (Yang *et al.*, 2007; Zhao *et al.*, 2010), 实际上, 棉铃虫田间种群的 Bt 抗性等位基因存在遗传多样性 (Zhang *et al.*, 2012a)。进一步分析发现, 钙粘蛋白 1422-1440 位氨基酸若缺失, 便无法结合 Bt 毒素从而导致抗性产生 (Zhang *et al.*, 2017)。研究人员后来在抗性棉铃虫中发现一个突变基因, 敲除该基因可恢复抗性种群对 Cry1Ac 的敏感性 (Jin *et al.*, 2018)。最近的工作表明, ABC 跨膜转运蛋白也与棉铃虫的 Bt 抗性有关, 敲除

该基因或下调该基因的表达可导致鳞翅目昆虫对 Bt 的抗性 (Wang *et al.*, 2020a; Zhu *et al.*, 2020)。

实际上,昆虫抗药性通常并非单一基因起作用,很多时候,一种杀虫剂可以诱导多个基因表达水平发生改变。例如:对稻纵卷叶螟转录组学分析发现,360 个基因与杀虫剂的解毒或与杀虫剂靶标蛋白有关 (Yu *et al.*, 2015)。从抗氟虫双酰胺杀虫剂的亚洲玉米螟 *Ostrinia furnacalis* 中鉴定出包括 AChE、AChR、GABA、VGSC 在内与抗性有关的 25 个基因 (Cui *et al.*, 2017)。研究还发现,无论是家蝇还是禾谷缢管蚜对菊酯类杀虫剂的抗性机理都涉及 VGSC 的 *kdr* 突变及 P450 基因突变 (Pan *et al.*, 2018; Wang *et al.*, 2020b)。在抗阿维菌素等杀虫剂的烟粉虱田间种群中,既有 VGSC 和 *ace1* 突变也有 P450 和 GST 基因表达水平的增加 (Wang *et al.*, 2020c)。

2 结语

近 20 年来,我国科学工作者在昆虫毒理学与杀虫剂毒理学研究领域积极开展杀虫剂抗性的研究工作,不仅有对害虫抗药性基线测定及抗性倍数的野外调查,也有关于昆虫抗药性机理的实验研究。大量的文献集中于野外种群对常用杀虫剂抗性水平以及与其他杀虫剂的交互抗性水平的测定、室内汰选建立高抗性品系进行抗性机理分析等,很多研究根据对某类杀虫剂(如:拟除虫菊酯类杀虫剂、DDT 等)具有抗药性的昆虫体内基因突变频率,推测抗性的发生、迁移及进化方面的发展,大量的抗性频率调查集中于蚊虫等病媒昆虫。而关于抗性机理的研究,比较多的是对靶标酶和代谢酶活性的测定、其编码基因的表达水平及基因突变频率的测定等,也有利用转录组学进行基因分析,但研究结论多限于基因的突变或表达水平与抗性的相关与否或是表达上调/下调的基因与抗性的相关性等,有研究者通过检索专业数据库推测其所筛选的基因可能参与到昆虫体内的生理功能。较少有针对相关基因功能的深入研究以确认其在抗性中的作用机理,而对昆虫抗药性形成过程中多因素调控的理

论研究以及如何有效延缓或降低害虫抗药性的应用研究尚比较薄弱。这实际上也是我国在杀虫剂毒理学尤其是杀虫剂抗性研究方面今后需要给予更多关注的地方。

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