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MICRO-REVIEW

CncC/Maf-mediated xenobiotic response pathway in insects

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Abstract

Insects have evolved resistance to almost all insecticides developed for their control. Multiple mechanisms of resistance, including enhanced metabolism and excretion of insecticides, target-site insensitivity, reduced penetration of insecticides, and avoidance behavior, have been reported. The genes coding for proteins involved in resistance have been identified in numerous insects. The enzymes and transporters required for all three phases of insecticide metabolism and excretion including cytochrome P450 monooxygenases, glutathione S-transferases, UDP-glucuronosyltransferases, carboxylesterases, and ATP-binding cassette transmembrane transporters have been identified. Recent research in multiple insect species identified CNC-bZIP transcription factor superfamily members as regulators of genes coding for enzymes and transporters involved in insecticide metabolic resistance. The information on the pathway including reactive oxygen species, cap "n" collar isoform-C, and its heterodimer partner, muscle aponeurosis fibromatosis transcription factors involved in overexpression of enzymes and transporters involved insecticide resistance will be summarized.

KEYWORDS
CncC, Maf, P450, ROS, xenobiotic response

1 | INTRODUCTION

There is a constant battle between humans and other animals, including insects, for scarce resources available on earth. Some insects are beneficials and provide resources such as honey or silk, and services such as pollination or destruction of pest insects, and disease vectors. While others are pests that compete with humans for food, fiber, timber, and other natural resources, destroy dwellings and transmit deadly diseases. As a result, humans have developed methods to control insect pests and disease vectors. However, insects developed ways to overcome methods employed by humans to control them. For example, insects have developed resistance to almost all classes of chemicals introduced to control them (Ffrench-Constant, 2013; Ffrench-Constant, Daborn, & Le Goff, 2004; Hemingway, 1999; Hemingway & Ranson, 2000; Liu, 2015). Enhanced metabolism of insecticides, target-site insensitivity, altered behavior, and reduced penetration of insecticides are among the major mechanisms insects employ to resist insecticides used to control them (Liu, 2015; Liu, Li, Gong, Liu, & Li, 2015). Insects use detoxification enzymes that increase oxidation, epoxidation, dehydrogenation, hydrolysis and reduction (Phase I), conjugation (Phase II), and excretion (Phase III) of both natural and synthetic toxic compounds referred to as xenobiotics to protect themselves from the toxicity exerted by these chemicals. Constitutive or induced overexpression of genes coding for enzymes involved in detoxification (e.g., cytochrome P450 monooxygenases [P450s]), conjugation (e.g., glutathione S-transferases [GSTs]), UDP-glucuronosyltransferases) or further detoxification (e.g., carboxylesterases) and excretion (e.g., ATP-binding cassette [ABC] transmembrane transporters) have been reported in insects that developed resistance to most classes of insecticides introduced for their control (Scott, 1999; Scott, Liu, & Wen, 1998). However, the mechanisms employed by insecticide-resistant insects for overexpression of these genes were not identified until recently. Studies in multiple insect species during the past few years showed that insects co-opted a xenobiotic stress response pathway involving reactive oxygen species (ROS), cap "n" collar isoform-C (CncC) and its heterodimer partner, muscle aponeurosis fibromatosis (Maf) transcription factors for overexpression of enzymes and transporters involved insecticide resistance. (Figure 1).

2 | XENOBIOTIC RESPONSE SYSTEM

Animals evolved an elaborate three-phase system to detoxify xenobiotics, including pesticides, pollutants, natural toxins, and pharmaceuticals. The genes coding for enzymes and transporters that function in detoxification and excretion of xenobiotics are induced by toxic compounds that enter the body via multiple routes. In mammals, transcription factors belonging to the nuclear receptor superfamily (e.g., pregnane X receptor [PXR]; constitutive androstane receptor [CAR]; FXR, VDR, and HNF4), the basic helix–loop–helix (bHLH)-PAS domain transcription factors superfamily (e.g., aryl hydrocarbon receptor [AHR], AHR nuclear translocator [ARNT]) and the NF-E2-related factor 2 [Nrf2] CNC-bZIP transcription factor family (e.g., CncC) play key roles in induction of xenobiotic response genes (Hankinson, 1995; Higgins & Hayes, 2011; Maglich et al., 2002; Pascussi et al., 2008; Rowlands & Gustafsson, 1997; Sonoda, Rosenfeld, Xu, Evans, & Xie, 2003; Sykiotis & Bohmann, 2010; Vorrink & Domann, 2014). Recent studies employing advanced molecular methods including RNA sequencing, RNA interferences, and cell-based reporter assays identified nuclear receptor, bHLH-PAS domain and CNC-bZIP transcription factor superfamily members as regulators of genes coding for enzymes and transporters involved in insecticide resistance in various pest insects. A recent publication reviewed antioxidant response elements and the transcription factors that bind to these elements (Wilding, 2018). Due to the word limit and space restrictions, the scope of this microreview will be limited to CNC-b-ZIP transcription factors.

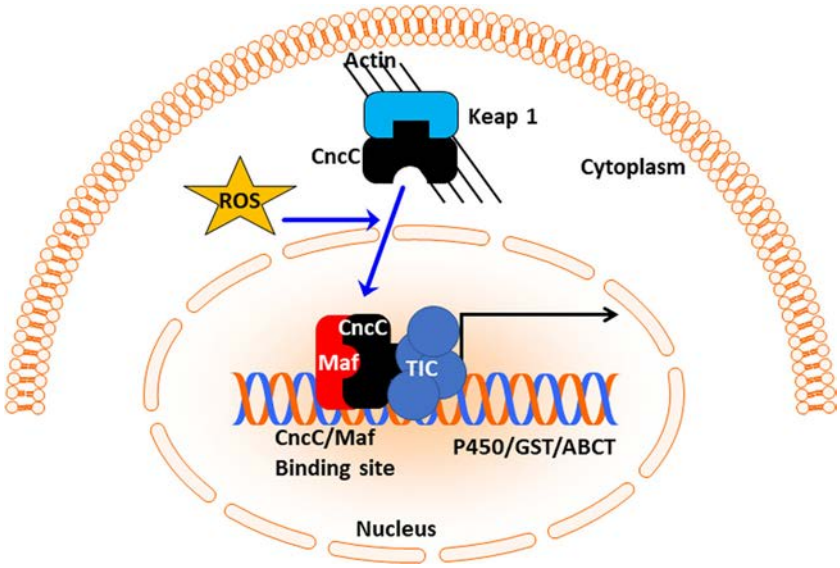

FIGURE 1 A model for CncC and Maf regulation of xenobiotic response genes. CncC heterodimerizes with Keap1 and stays in cytoplasm anchored to actin filaments. Under xenobiotic stress conditions, ROS or other molecules induce dissociation of CncC and Keap1 allowing CncC to translocate to the nucleus and heterodimerize with Maf. The heterodimer binds to CncC/Maf response elements located in the promoter of xenobiotic response genes and induce their expression. ABCT, ATP-binding cassette (ABC) transmembrane transporters; CncC, cap "n" collar isoform-C; GST, glutathione S-transferases; Keap1, Kelch-like ECH-associated protein 1; Maf, muscle aponeurosis fibromatosis; P450, cytochrome P450 monooxygenases; ROS, reactive oxygen species; TIC, transcription initiation complex

3 | DISCOVERY OF CncC AS A XENOBIOTIC TRANSCRIPTION FACTOR IN *DROSOPHILA MELANOGASTER*

Constitutive or induced overexpression of genes coding for enzymes and transporters involved in insecticide detoxification and excretion in resistant strains have been reported in many insect species, including the fruit fly, *D. melanogaster*. To identify transcription factors responsible for overexpression of xenobiotic response genes, the function of the single *D. melanogaster* ortholog of mammalian xenobiotic nuclear receptors (PXR and CAR) the DHR96, was studied by mutagenesis experiments. These studies showed that only 10% of genes induced by xenobiotic phenobarbital required DHR96 (King-Jones, Horner, Lam, & Thummel, 2006), suggesting that other transcription factors may be involved in the regulation of xenobiotic-responsive genes in the fruit fly and other insects. Subsequent studies in the fruit fly identified that the CncC/Kelch-like ECH-associated protein 1 (Keap1) pathway plays a key role in the xenobiotic response (Misra, Horner, Lam, & Thummel, 2011). These studies showed that CncC regulates 70% of the genes induced by phenobarbital. Also, constitutive activation of the CncC/Keap1 pathway conferred resistance to the insecticide malathion. These studies established CncC as the central regulator of the xenobiotic response in the fruit fly. The CncC/Keap1 pathway was also found to be constitutively active in two DDT-resistant strains of *D. melanogaster* (91R and RDDTR) in inducing expression of multiple genes coding for enzymes involved detoxification of DDT (Misra, Lam, & Thummel, 2013; Table 1)

TABLE 1 Examples of CncC/Maf-regulated metabolic resistance genes

Insect/mite name	Transcription factor identified	Targets	References
Drosophila melanogaster	CncC Keap1	P450 and GST	Misra et al. (2011)
	CncC	P450	Misra et al. (2013)
Tribolium castaneum	CncC Maf	P450	Kalsi and Palli (2015)
	CncC	P450	Kalsi and Palli (2017a)
Leptinotarsa decemlineata	CncC	P450	Kalsi and Palli (2017b)
	CncC	P450, GST, and ABCT	Gaddelapati et al. (2018)
Aphis gossypii	CncC	P450	Peng et al. (2016)
Anopheles gambiae	Maf	P450 and GST	Ingham et al. (2017)
Spodoptera exigua	CncC,Maf, AhR, and ARNT	GST	Hu, Hu et al. (2019); Hu, Huang et al. (2019)
Spodoptera litura	CncC and Maf	P450	Lu et al. (2020)
Bactrocera dorsalis	Maf	P450 and GST	Tang et al. (2019)
Tetranychus cinnabarinus	CncC and Maf	P450	Shi et al. (2017)

4 | DISCOVERY OF CncC/Maf TRANSCRIPTION FACTORS AS THE MAJOR CONTRIBUTORS TO METABOLIC RESISTANCE TO INSECTICIDES IN BEETLES

The red flour beetle, *Tribolium castaneum* strain (QTC279) developed resistance to pyrethroids through constitutive overexpression of P450 genes including CYP6BQ9 (Zhu et al., 2010). RNAi-mediated knockdown of genes coding for candidate nuclear receptor, bHLH-PAS domain transcription and the Nrf2 CNC-bZIP transcription factor family members, identified CncC and Maf as the key regulator of P450 genes responsible for pyrethroid resistance in the QTC279 strain (Kalsi & Palli, 2015). The promoters of these genes contain binding sites for CncC and Maf. These studies identified for the first time that the CncC and Maf transcription factors are responsible for overexpression of P450 genes in insecticide-resistant pest insects. To identify other genes coding for enzymes and transporters involved in detoxification of pyrethroid insecticides in the QTC279 strain, these beetles were injected with dsRNA targeting CncC or a gene coding for green fluorescence protein (GFP, control). RNA isolated from these beetles was sequenced, and differential gene expression analysis was performed. These studies identified 662 upregulated and 91 downregulated genes in CncC knockdown beetles (Kalsi & Palli, 2017a). Twenty-one of the downregulated genes coded for enzymes and transporters with potential function in xenobiotic detoxification identified previously (Zhu, Moural, Shah, & Palli, 2013). The function of genes coding for CYP4G7, CYP4G14, GST-1 and four ABC transporters, ABCA-UB, ABCA-A1 and ABCA-A1L and ABCA-9B identified as CncC targets were tested by RNAi knockdown and insecticide efficacy bioassays. These studies showed that these gene products are involved in the detoxification of pyrethroids. These studies also identified CncC as the transcription factor involved in the regulation of genes coding for enzymes and transporters involved in all three phases of insecticide detoxification.

The Colorado potato beetle (CPB), *Leptinotarsa decemlineata* is a major pest on solanaceous plants, co-evolution with these plants containing high levels of glycoalkaloid toxins helped this pest to develop an efficient detoxification system. As a result, this pest developed resistance to almost every insecticide introduced for its control. Several genes coding for enzymes involved in detoxification and overexpressed in insecticide-resistant strains have been identified

(Zhu, Moural, Nelson, & Palli, 2016). For example, the imidacloprid-resistant CPB employs P450 enzymes to detoxify this insecticide. Knockdown of four of these genes (CYP6BJa/b, CYP6BJ1v1, CYP9Z25, and CYP9Z29) reduced resistance to imidacloprid. RNAi studies showed that CncC and Maf transcription factors are required for overexpression of these P450 genes in resistant beetles (Kalsi & Palli, 2017b). In addition, binding sites for CncC and Maf were identified in the promoters of these P450 genes suggesting that these transcription factors play an important role in constitutive overexpression of P450 genes in the imidacloprid-resistant CPB (Kalsi & Palli, 2017b).

Sequencing of RNA isolated from the imidacloprid-resistant CPB injected with dsCncC or dsGFP followed by differential gene expression analysis identified 1,798 genes regulated by CncC (Gaddelapati, Kalsi, Roy, & Palli, 2018). Interestingly, 1,499 out of 1,798 differentially expressed genes were downregulated in CncC knockdown beetles. These include 79% of P450 genes identified as overexpressed in imidacloprid-resistant beetles. Some of the genes coding for GSTs, carboxylesterases and ABC transporters that are overexpressed in imidacloprid-resistant CPB also require CncC for their expression (Gaddelapati et al., 2018). These studies identified CncC as a major transcription factor responsible for overexpression of genes coding for enzymes and transporters involved in detoxification of insecticide in imidacloprid-resistant CPB.

5 | CncC/Maf TRANSCRIPTION FACTORS AS THE MAJOR CONTRIBUTORS TO METABOLIC RESISTANCE IN OTHER INSECTS AND MITES

Recent studies in the African malaria vector, *Anopheles gambiae* showed that the transcription factor Maf-S regulates expression of genes coding for multiple detoxification enzymes including CYP6M2 and GSTD1 (Ingham, Pignatelli, Moore, Wagstaff, & Ranson, 2017). RNAi-mediated knockdown of Maf-S resulted in a decrease in the expression of genes coding for detoxification enzymes and a significant increase in mortality caused by the pyrethroid insecticides and DDT. In another mosquito species, *Aedes aegypti*, CncC was shown to affect intestinal homeostasis, insecticide resistance, and Zika virus susceptibility (Bottino-Rojas et al., 2018).

The expression of CYP6DA2 in the cotton aphid, *Aphis gossypii* increases after feeding on cotton plants containing gossypol. Reporter assays showed that CncC binds to elements in the promoter of CYP6DA2 gene and induce it's expression (Peng et al., 2016). RNAi-mediated knockdown in the expression of CncC gene resulted in a decrease in the expression of CYP6DA2 gene and an increase in the toxicity to gossypol. These studies showed that CncC is involved in the regulation of xenobiotic response to the plant toxin, gossypol.

In *Bactrocera dorsalis*, resistance to insecticide, abamectin occurs as a result of an increase in the expression of GSTZ2 and *CYP473A3* (Tang et al., 2019). Interestingly, the gene coding for *MafB* transcription factor also showed an increase in its expression in the resistant strain. Knockdown of CncC and MafB genes resulted in a decrease in the expression of *GSTZ2* and *CYP473A3* gene as well as resistance levels to abamectin in the resistant strain. These data suggest that MafB is a key player in constitutive over of expression of genes coding for metabolic enzymes in abamectin resistant strain of *B. dorsalis*.

Constitutive overexpression of six P450 genes contributes to fenpropathrin resistance in the spider mite, *Tetranychus cinnabarinus* (Shi et al., 2017). After evaluating six transcription factors for their ability to regulate expression of P450 genes responsible for fenpropathrin resistance using RNAi, CncC and Maf were identified as the major players in constitutive overexpression of P450 genes in the fenpropathrin-resistant strain of *T. cinnabarinus* (Shi et al., 2017). Interestingly, CncC and Maf genes are expressed at higher levels in the fenpropathrin-resistant strain of *T. cinnabarinus* when compared to their expression levels in the susceptible strain. CncC/Maf binding sites were identified in the promoters of P450 genes and overexpressed in the fenpropathrin-resistant strain of *T. cinnabarinus*. These experiments demonstrated that CncC and Maf regulate expression of P450 genes and influence the susceptibility of *T. cinnabarinus* to acaricide, fenpropathrin.

6 | ROS, THE INDUCER OF CncC/Maf XENOBIOTIC RESPONSE SYSTEM?

There needs to be some signal to induce CncC/Maf xenobiotic response system after the xenobiotic compounds enter the insect through multiple routes. Recent studies in *Spodoptera exigua and Spodoptera litura* suggest that these signaling molecules could be ROS. In *S. exigua* genes coding for multiple GSTs involved in resistance to chlorpyrifos and cypermethrin are overexpressed in the resistant strain (Hu, Huang et al., 2019). In this strain transcription factors, CncC/Maf and AhR/ARNT are expressed at higher levels when compared to their levels in the susceptible strain. The transcription factors play an important role in the upregulation of genes coding for GSTs that are involved in chlorpyrifos and cypermethrin resistance (Hu, Huang et al., 2019). Another study by the same group found that seven out of 31 GST genes showed an increase in their expression after exposure to lambda-cyhalothrin, chlorpyrifos and chlorantraniliprole (Hu, Hu et al., 2019). CncC/Maf binding sites were identified in the promoters of all seven GST genes. Reporter assays showed that the CncC/Maf binding sites are required for insecticide induced increase in expression of these genes. Interestingly, the same three insecticides increased the ROS levels and ROS inhibitor *N*-acetylcysteine (NAC) blocked insecticide-induced reporter gene under the control of GST promoter (Hu, Hu et al., 2019). These studies point to the involvement of ROS in CncC/Maf mediated insecticide induction of GST gene expression.

In the tobacco cutworm, *S. litura* λ-cyhalothrin induces expression of the gene coding for *CYP6AB1.2* (Lu et al., 2020). λ-Cyhalothrin also induced the expression of the gene coding for CncC and Maf, hydrogen peroxide (H_2O_2) levels and antioxidant enzyme activity. Knockdown of *CncC* gene reduced *CYP6AB12* expression and increased tolerance to λ-cyhalothrin. The CncC agonist curcumin induced *CYP6AB12* expression and enhanced insecticide tolerance. Treatment with ROS scavenger NAC reduced H_2O_2 accumulation, expression of *CncC*, *Maf*, *CYP6AB12* and tolerance to λ-cyhalothrin (Lu et al., 2020). These studies suggest that ROS may initiate CncC/Maf pathway involved in the induction of *CYP6AB12* by the insecticide.

7 | PROPOSED MODEL FOR INSECTICIDE-ROS-CncC/Maf-METABOLIC ENZYMES/TRANSPORTER-INSECTICIDE DETOXIFICATION PATHWAY

In animals, Nrf2 transcription factor is a major player in mediating the response to oxidative stress (Sykiotis & Bohmann, 2010). Under normal conditions, Nrf2 is localized in the cytoplasm as a heterodimer with the actin-binding protein Keap1. Stress conditions disrupt the Nrf2/Keap1 heterodimer allowing translocation of Nrf2 into the nucleus. Upon entering the nucleus, Nrf2 heterodimerizes with Maf and binds to response elements located in the promoters of antioxidant response genes and induce their expression (Sykiotis & Bohmann, 2008, 2010). A similar mechanism of action could occur in insecticide-resistant insects for induced and constitutive overexpression of genes coding for detoxification enzymes and transporters (Figure 1). ROS might sense insecticide signals or other forms of stress in insecticide-resistant insects and induce dissociation of CncC and Keap1, allowing CncC translocation into the nucleus. Upon entering the nucleus, CncC may then heterodimerize with Maf and binds to CncC/Maf binding sites located in the promoters of genes coding for detoxification enzymes and transporters and induce their expression. This results in the production of detoxification enzymes and transporters, which then could aid in detoxification and excretion of insecticides leading to tolerance of insects to the insecticides.

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