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Review

Resistance to Bt Crops; Influence, mechanisms and management strategies

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The genetically engineered insect-resistant crops, Bt crops, were first commercially grown in 1996 and adopted in different countries. The economic benefits of Bt crops are reducing the use of insecticides and more safe to environment, however, development of resistance by insects might reduce their efficacy. Unfortunately, the field population evolved resistance to different Bt toxins and the number of resistant species is going to increase, which threat the continuous success of Bt crops. Thus, understanding the Bt resistance mechanisms, including the molecular basis of resistance is important for well-resistance control in Bt crops. This review paper displayed the mechanisms of insect pests resistance to Bt crops and appropriate strategies to delay and manage the resistance in Bt crops.

Key words: Field-evolved resistance, molecular mechanism, resistance to Bt toxins, resistance management strategies, transgenic crops.

INTRODUCTION

In 1948, the first case of insecticide resistance has been reported in synthetic insecticide (DDT) within 6 years of its introduction. Unfortunately, the number of resistance insects increased dramatically, and over 500 species evolved resistance to different kinds of insecticides (Denholm et al., 2002). Understanding the resistance mechanisms is important for insecticide resistance management, thus the resistance mechanisms have been studied in different insect's pest, for example, *Laodelphax striatellus, Nilaparvata lugens* and *Anopheles gambiae* (Ding et al., 2013; Elzaki et al., 2015; Mitchell et al., 2012).

Transgenic crops have been commercialized since 1996, which delivers *Bacillus thuringiensis* (Bt) toxins to kill certain insect pests and thus can decrease dependence on synthetic insecticides (Wu et al., 2008) in cotton, corn, peanut, soybean, and vegetables (James, 2010). Bt toxins disrupts the midgut membranes by binding to specific target sites and finally kill the insects (Morin et al., 2003). Cry1A family is the most commonly used Bt toxins, especially Cry1Ac in transgenic Bt cotton and Cry1Ab in transgenic Bt corn (Tabashnik et al., 2003).

Transgenic crops delivering Bt toxins are grown in millions of hectares. Although, the Bt crops increased the yield and reduced the use of conventional insecticide, however, their effectiveness would be decreased by evolution of resistance by insect pests (Ferré and Van

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Rie, 2002; Tabashnik et al., 2013, 2003. The number of resistant species has been increased worldwide, 13 cases of field-developed resistance to 5 Bt toxins in transgenic corn and cotton. Most of the resistance reported cases belong to Cry1A family (Tabashnik et al., 2013, 2014). Insect pests developed resistance to Bt crops by different mechanisms (Tabashnik, 2001). Therefore, understanding of the molecular and genetic basis of resistance to Bt could help in designing a suitable management approaches to delay the resistance development in the insect pests (Ferré and Van Rie, 2002).

This review focusing on the development of resistance to Bt crops and its underlying mechanisms, and discuss the significance of better understanding of these mechanisms, and resistance management strategies.

HISTORY OF RESISTANCE TO BT CROPS IN FIELD POPULATIONS

The first case of insect-resistance to Bt crops was reported in Mississippi and Arkansas between 2003 and 2006 in bollworm *Helicoverpa zea*. The bollworm resistance was discovered when an entomologist's team form University of Arizona investigated published data from monitoring studies of six main caterpillar pests of Bt crops in U.S, Australia, China and Spain. This case was reported after 7 years after being introduced by Bt cotton (Jensen, 2008). Then, different cases of resistance to Bt toxins has been stated in different Bt crops, such as, pink bollworm *Pectinophora gossypiella* evolved resistance to Cry1Ac in Bt cotton (Dennehy et al., 2004; Tabashnik et al., 2002, 2000; Zhang et al., 2012), *Spodoptera frugiperda* to Cry1F in Bt corn, *Busseola fusca* (Fuller) to Cry1Ab in Bt corn, *Helicoverpa punctigera* and *Helicoverpa armigera* to Cry2Ab in Bt cotton (Downes et al., 2010; Kruger et al., 2011; Mahon et al., 2007; Santos-Amaya et al., 2016; Van Rensburg, 2007). *Diabrotica virgifera virgifera* showed resistance to Cry3Bb1 in Bt maize (Gassmann et al., 2011). *S. frugiperda* evolved resistance to Cry1Fa toxin in Bt corn (Farias et al., 2015; Jakka et al., 2015; Monnerat et al., 2015).

Resistance to pyramid Bt crops

Pyramids Bt crop is a transgenic Bt crops producing two or more Bt toxins to kill the same pest and have been used widely to delay the development of pest resistance. While, a few cases of study in laboratory and field populations showed that the insect could evolve resistance to pyramid crops (Bernardi et al., 2015; Brévault et al., 2013; Fabrick et al., 2015; Wei et al., 2015; Welch et al., 2015). However, study by Carrière et al. (2015) who reported that the resistance to pyramids is due to similarity of amino acid sequence between Bt toxins, which affect the cross-resistance when the resistance is associated with mutations, that reduce binding to midgut receptor. This study provides a valuable information that should be taken into consideration for designing pyramid crops and the development of sustainable management tactics for resistance in Bt crops (Carrière et al., 2015).

Molecular mechanisms of resistance

Understanding the resistance mechanism to Bt toxins is a key factor for resistance management in transgenic crops. The insect pests showed resistance to Bt crop by different mechanisms. For example, *H. armigera* conferred resistance to Cry1Ac by mutation in the promoter region of HaTryR. The insect adapted to Cry1Ac by decreasing the expression of trypsin, because the activation of trypsin is a critical step in toxicity for protoxin. Therefore, the durability of Bt transgenic crops might increase with activated toxins rather than protoxins (Liu et al., 2014a).

In the field populations of *P. gossypiella,* resistance to Cry1Ac in Bt cotton has been connected with 3 mutant alleles of a cadherin encoding gene (Morin et al., 2003; Ocelotl et al., 2015). *Bombyx mori* resistance to Cry1Ab has been conferred by a single amino acid mutation in ATP-binding cassette transporter gene (Atsumi et al., 2012).

The cadherin gene plays an important role in resistance to Bt crops. For example, *Manduca sexta* resistance to Cry1Ab was increased by silencing cadherin gene (Soberón et al., 2007). Similarly, in *Heliothis virescens,* resistance to Cry1Ac was associated with cadherin gene (Tabashnik, 2001). In *H. armigera*, resistance was associated with recessive cadherin mutations in filed populations of cotton bollworm (Zhang et al., 2012). In *Sexigua*, resistance to Cry1Ac and Cry2Aa was related to cadherin gene (Qiu et al., 2015).

In addition, the *Trichoplusia ni* evolved resistance to Cry1Ac by differential alteration of two midgut aminopeptidases N (APN1 and APN6) (Tiewsiri and Wang, 2011).

Moreover, loss of a carbohydrate modifying enzyme creates resistance to Bt toxin, this mechanism is more threatening than a mutation in single receptor. In nematode *Caenorhabditis elegans,* resistance to Cry5B conferred by losing bre-5 in the intestine. Bre-5 mutants exhibited resistance to Cry14A in nematodes and insects. Loss of a particular general modifier could affect the binding of various Bt toxins to several receptors, which cause a high level of resistance to a single toxin as well as cross-resistance to other Bt toxins (Griffitts et al., 2001).

Furthermore, in armyworm, *S. frugiperda* resistance to Cry1Fa in Bt corn was related to reduced toxin binding and expression of midgut alkaline phosphatase (Jakka et al., 2015). In *H. armigera* and *H. punctigera,* resistance to Cry2Ab was conferred by mutations in ABC transporter (Coates and Siegfried, 2015; Tay et al., 2015).

RESISTANCE MANAGEMENT STRATEGIES

Refuges strategy

Providing refuges is considered as a primary strategy for delaying pest resistance to Bt crops. This strategy allowed the susceptible insects mating with resistant insects, which led to reduce the resistance allele in the pest population and led to delay the resistance (Gould, 1998; Hutchison et al., 2010; Liu et al., 1999; Shelton et al., 2000; Tabashnik et al., 2003, 2005; Tabashnik and Gould, 2012). The refugee strategy is most commonly used to delay resistance in Bt crops (Jin et al., 2015; Shelton et al., 2000; Tabashnik et al., 2008).

Pyramided plants

Pyramided plants delivering two or more Bt toxins targeting one pest are more essential for pest management and resistance management. Nowadays, pyramided plants have been broadly used to delay the development of insect-resistance (Carrière et al., 2015; Jin et al., 2015; Moar and Anilkumar, 2007; Roush, 1998; Tabashnik et al., 2015; Zhao et al., 2002, 2003).

Pyramided Bt crops have been employed in different countries. For example, United States and Australia, totally replaced single-toxin Bt cotton. Pyramided Bt crops are expected to become even more dominant in the future, because they can enhance resistance management as well as pest control (Brévault et al., 2013).

The resistance in diamondback moth was delayed after the selection for Bt broccoli plants producing two toxins Cry1Ac and Cry1C (Zhao et al., 2005, 2003).

Modified Bt toxin

One promising way to develop modified Bt toxin is to determine how the target pests evolved resistance to particular toxins, then modify these toxins so that resistance must happen in another manner. This would probably increase the time for resistance development and increase the life expectation of insect-resistance to Bt crops.

Modified toxins, Cry1AbMod and Cry1AcMod killed *M. sexta* and *P. gossypiella* that had cadherin deletion mutations. These toxins could be valuable for delaying or countering pest resistance to Cry1A toxins (Soberón et al., 2007).

Resistance of greenhouse-selected strains of *T. ni*, to *B. thuringiensis* subsp. *kurstaki* was countered by genetically modified toxins Cry1AbMod and Cry1AcMod lack of helix α-1 (Franklin et al., 2009).

The strength of the modified toxins was commonly higher against the most resistant strains in *Diatraea saccharalis, H. virescens, H. armigera, Plutella xylostella* and *Ostrinia nubilalis* (Tabashnik et al., 2011).

The engineering plants possessed a fusion protein linking the-endotoxin Cry1Ac and the galactose-binding domain of the nontoxic ricin B-chain (RB). This offers the toxin with extra binding domains, hence the potential number of interfaces at the molecular level in target insects. Maize and rice plants which have been engineered to produce the fusion protein were significantly more potent. The fusion genes have potential effect on resistance sustainability, crop improvement and biosafety (Mehlo et al., 2005).

RELEASE OF STERILE INSECTS

Release of sterile insect method is well-known for decades, which has been successfully used in different insect pests (Gould and Schliekelman, 2004; Krafsur, 1998). The application of this technique to suppress pests resistant to transgenic crops was first reported by Tabashnik et al. (2010) using computer stimulation study, which showed that the resistance of pink bollworm in Bt cotton was suppressed by release of sterile moths (Tabashnik et al., 2010).

Released male-selecting (MS) transgenes was effective by preventing survival of female offspring, and offer a substitute resistance management approach by introgression of susceptibility alleles in the target pest populations. MS insects was provided an active and appropriate management option against *P. xylostella* and potentially could be useful for other pests (Harvey-Samuel et al., 2015).

Natural enemies

The preservation of natural enemies could delay resistance development in Bt crops. Study showed that *P. xylostella* populations were reduced when the *Corymbia maculata* were used with unsprayed non-Bt refuge plants. These study exhibited that natural enemies could delay the resistance to Bt plants and have significant effects on integrated pest management (IPM) in Bt crops (Liu et al., 2014b).

Seed mixtures

Seed mixtures strategy is also used to delay resistance to Bt crops, planting seed mixtures yielding random disseminations of non-Bt corn plants and pyramided Bt plants within fields, were effective only on pests with little inherent susceptibility to Bt toxins (Carrière et al., 2016).

Different study reported that the seed mixtures strategies had low efficiency in delaying resistance in pests with movable larvae and inherently low susceptibility to Bt toxins (Brévault et al., 2015). Thus, seed mixture strategies might be suitable for delaying resistance when used with other strategies.

CONCLUSION AND FUTURE PROSPECT

Bt is the most successfully used bio-pesticide in the agriculture sector, and its insecticidal protein genes are used to control insect pests in transgenic crops. Although, transgenic plants provide distinct opportunities for management of pest populations, but the development of insect-resistance threatens the continuous success of the transgenic crops delivering Bt toxins. The resistance to Bt crops could affect the long-term future of Bt applications. Therefore, tactics for resistance management should be conducted. Moreover, understanding the molecular mechanism of resistance is a key factor for Bt resistance management. Although, this review displayed the reported molecular resistance mechanisms in Bt crops, but still more study showed be conducted for well-resistance management to ensure the continuous use of Bt crops.

Furthermore, different strategies have been used to increase pest control efficiency and delay the evolution of resistance to Bt crops. This review displayed the most promising resistance management strategies. By using these strategies resistance management could be achieved for the sustainable use of transgenic plants delivering insecticidal proteins from Bt.

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Conflict of interests

The author has not declared any conflict of interests.

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