Wolbachia—a foe for mosquitoes

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1. Introduction

More than half of the world population live under the risk of insect–borne diseases, predominantly those transmitted by mosquitoes. The mosquitoes are vectors of a broad range of harmful viral and parasitic diseases affecting both humans and animals. Mosquitoes are the causative agents of diseases such as malaria, lymphatic filariasis, dengue, chikungunya and West Nile fever. Estimations made by the World Health Organization show that 247 million people in tropical and subtropical regions of the world become ill and about one million people died because of mosquito–borne diseases[1]. So far insecticide–based control programs targeting mosquitoes have been the most successful method of controlling the disease, but it is often expensive and also the effectiveness of such program has been greatly reduced because of the development of insecticide resistance in mosquitoes. This has prompted the need to use more expensive alternative compounds. The massive unjudicial use of chemical insecticides has led to environmental...
degradation and biomagnification in ecosystems[2].

Wolbachia is an intracellular maternally inherited endosymbiotic bacteria found in arthropods. It manipulates its host reproduction in many ways, all of which favour infected females in nature. Wolbachia was first discovered in the reproductive tissues of mosquitoes Culex pipens by Hertig and Wolbach in 1924 and the species was later named Wolbachia pipiens[3,4]. Wolbachia infections are widespread within insect species[5–8]. One of the reproductive manipulation induced by Wolbachia is cytoplasmic incompatibility, which has received considerable attention in biological control of insect vectors and diseases. Cytoplasmic incompatibility results in the generation of unviable offspring when an uninfected female mates with a Wolbachia–infected male[9].

Wolbachia is responsible for inducing a number of reproductive modifications that enables its spread and maintenance in natural populations. Wolbachia–induced cytoplasmic incompatibility has received considerable attention as a mechanism to control insect vectors and diseases[10,11]. Recently, there has been a substantial increase in Wolbachia research related to the interactions of Wolbachia with its hosts and its impact on parasite transmission. Fruit fly Drosophila melanogaster (D. melanogaster) Wolbachia strains can invade and sustain themselves in mosquito populations, reduce adult lifespan, affect mosquito reproduction and interfere with pathogen replication. Such endosymbiotic bacterial strains have been introduced in Aedes aegypti (Ae. aegypti) mosquito populations to reduce their life span, thereby reducing the extrinsic incubation period. The other prospect of exploiting Wolbachia is using its ability to interfere with viruses and parasites. Wolbachia is known to interact with a wider range of pathogens in transfected mosquitoes including dengue and chikungunya viruses[12]. A recent study showed that Plasmodium falciparum development in Anopheles gambiae (An. gambiae) is suppressed transiently as a result of Wolbachia infection. This reproductive parasite is known to indirectly support and up-regulate the insect–host immune system and suppress the pathogen[13]. A major advantage of Wolbachia–based control approach for mosquitoes is that cytoplasmic incompatibility acts as a self–spreading mechanism for Wolbachia to rapidly invade populations from the release of relatively small numbers of individuals. Wolbachia provides a biological method to manipulate mosquito populations and reduce disease transmission[14]. Findings have prompted researchers to aid in the control of mosquito–transmitted diseases. It has the benefit of being more environment–friendly than insecticide–based approaches[15,16].

2. Wolbachia inhibits dengue and chikungunya virus replication in mosquitoes

Evidence from several recent studies indicates that a strain of life–shortening Wolbachia has been detected in the fruit fly Drosophila. This virulent Wolbachia strain wMelPop is responsible for the shortening of life span in D. melanogaster[17]. In Drosophila, the wMelPop and another closely related Wolbachia strains have the ability of protecting against RNA virus infection by delaying the mortality of flies infected with a range of pathogenic viruses[18,19]. The Wolbachia wMelPop infection in D. melanogaster induces antiviral response to the Drosophila C virus in their hosts, cricket paralysis, Nora and Flock House viruses[20]. These observations in Drosophila has made researchers to introduce this bacterial strain into the dengue virus mosquito vector Ae. aegypti artificially. The introduction of walbB strain reduces the proliferation of dengue virus when compared with uninfected mosquito population. The Wolbachia strain not only reduced the virus replication but also reduced the adult life span. The life–shortening Wolbachia exerts its effect by altering the extrinsic incubation period of dengue virus, thereby inhibiting its transmission to new host. Meanwhile life–shortening Wolbachia may offer a new technology to control the chikungunya virus as well. These results may offer a potential new method to control vector–borne diseases like dengue and chikungunya virus from Ae. aegypti[21].

3. Wolbachia and host immune gene up–regulation

Researchers recently found that the presence of wMelPop in mosquitoes up–regulated the host immune gene expression, resulting in inhibition of pathogen replication or multiplication. The up–regulated six immune genes observed in wMelPop infected An. gambiae are LRIM1, TEP1, CEC1, DEF1, CTL4 and CLIP3 as shown by genome analysis[21]. When Wolbachia strain wMelPop was transinfected into An. gambiae, up–regulation of immune genes LRIM1 and TEP1 has been found, inhibiting the Plasmodium development by interfering in the opsonization pathway[22,23]. Fascinatingly, similar results have been seen in the avian malarial parasites Plasmodium gallinaeum and Plasmodium berghei[24]. The infection of wMelPop strain in mosquito Ae. aegypti induces up–regulation of several immune effector molecules, namely, thio–ester containing proteins, C–type lectins, defensin, dipterisin, GNBP1, SPZ1A, cactus and cecropin[25]. The up–regulation of immune effector molecules in Wolbachia–infected mosquitoes may be responsible for the resistance to pathogen virus proliferation[26]. Natural Wolbachia strains infected in Culex quinquefasciatus mosquitoes have shown resistance to West Nile virus[27]. This evidence is more prominent when compared to Wolbachia strains infected mosquitoes.

4. Wolbachia and malaria parasite (Plasmodium) inhibition

Malaria is one of the deadliest infectious disease caused by protozoan parasite Plasmodium transmitted by vector
Anopheles mosquitoes. There are estimated 500 million cases of malaria annually and 1 to 3 million deaths primarily associated with Plasmodium\textsuperscript{28}. When life shortening Wolbachia strain wMelPop transinfects into An. gambiae, several immune genes are activated, resulting in inhibition of Plasmodium parasite development\textsuperscript{29}. Several recent studies in Drosophila has shown that the immune genes involved in inhibition of Plasmodium are LRIM1 and TEP1, and they are likely to inhibit the human malarial parasite Plasmodium, if stable infection is transmitted vertically to Anopheles\textsuperscript{30}. The evidence for pathogen suppression was reported in Ae. aegypti, with induced resistance to bacterial pathogen Pseudomonas aeruginosa, by reducing the number of Plasmodium gallinaceum oocysts by triggering the co-expression of two antimicrobial peptides cecropin A and defensin A, and completely blocking transmission of this avian malaria parasite to native chickens\textsuperscript{31}. The density and tissue distribution of Wolbachia infections in mosquitoes is an important factor in inhibiting Plasmodium\textsuperscript{32}.

5. Conclusion

The Wolbachia–based technology will assess a novel strategy for mosquito control by using virulent Wolbachia. It will also deliver new tools for the accurate assessment of the impact on population age structure in mosquitoes based on Wolbachia interventions. To summarize, it is opined that Wolbachia provides a biological method to manipulate mosquito population and reduce disease transmission and health burden in humans.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

The mosquitoes are vectors of a broad range of harmful viral and parasitic diseases affecting both humans and animals. Mosquitoes are the causative agents of diseases such as malaria, lymphatic filariasis, dengue, chikungunya and West Nile fever. The use of insecticides targeting mosquitoes has been the most successful method, but contentious use of insecticides has led to development of insecticide resistance in mosquitoes. In recent years, potential application of Wolbachia endosymbiont to control of mosquito borne diseases has emerged as a more environmental friendly, cost effective biocontrol tool against mosquitoes.

Research frontiers

Fruit fly D. melanogaster Wolbachia strains can invade and sustain themselves in mosquito populations, reduce adult lifespan, affect mosquito reproduction and interfere with pathogen replication. Such endosymbiotic bacterial strains have been introduced in Ae. aegypti mosquito populations to reduce their life span, thereby reducing the extrinsic incubation period. The other prospect of exploiting Wolbachia is using its ability to interfere with viruses and parasites. Wolbachia is known to interact with a wider range of pathogens in transfected mosquitoes including dengue and chikungunya viruses. A recent study showed that Plasmodium falciparum development in An. gambiae is suppressed transiently as a result of Wolbachia infection. This reproductive parasite is known to indirectly support and up-regulate the insect–host immune system and suppress the pathogen.

Related reports

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Innovations & breakthroughs

The transinfection of life shortening Wolbachia from fruit fly, invades mosquitoes by reducing the adult life span and triggering immune responses, thereby inhibiting pathogen replication.

Applications

This review paper has given more emphasis on the use of Wolbachia endosymbiont, which is benefit of being more environmental friendly, cost effective than insecticide based approaches in biocontrol of mosquito borne disease.

Peer review

The Wolbachia–based technology will assess a novel control strategy for mosquito control by using fruit fly virulent Wolbachia. It will also deliver new tools for the accurate assessment of the impact on population age structure in mosquitoes based on Wolbachia interventions. To summarize, it is opined that Wolbachia provides a
biological method to manipulate mosquito population and reduce disease transmission and health burden in humans.

References

[1] World Health Organization. World malaria report. Geneva: World Health Organization; 2010. [Online] Available from: http://www.who.int/malaria/publications/atoz/9789241564106/en/index.html. [Accessed on 14th August, 2013]

[2] Service MW. Mosquito ecology: field sampling methods. 2nd ed. London: Chapman & Hall; 1993.

[3] Hertig M, Wollbach SB. Studies on rickettsia-like microorganisms in insects. J Med Res 1924; 44(3): 329–374.

[4] Hertig M. The rickettsia, Wolbachia pipiens (gen. et sp.n.) and associated inclusions of the mosquito, Culex pipiens. Parasitology 1936; 28(4): 435–486.

[5] Werren JH, Jaenike J. Wolbachia and cytoplasmic incompatibility in mycophagous Drosophila and their relatives. Heredity (Edinb) 1995; 75(1 Pt 3): 320–326.

[6] Jeyaprakash A, Hoy MA. Long PCR improves Wolbachia DNA amplification: wsp sequence found in 76 of sixty–three arthropod species. Insect Mol Biol 2000; 9(4): 393–405.

[7] Hilgenboecker K, Hammerstein P, Schlattmann P, Telschow A, Werren JH. How many species are infected with Wolbachia? – a statistical analysis of current data. FEMS Microbiol Lett 2008; 281(2): 215–220.

[8] Sumithra, Guruprasad NM, Pattaraju HP. A comparative analysis of long PCR and standard PCR technique in detecting the Wolbachia endosymbiont. Curr Trends Biotechnol Pharm 2012; 6(4): 472–478.

[9] Guruprasad NM, Mouton L, Pattaraju HP. Effect of antibiotic, temperature curing of Wolbachia and seasonal variation on the reproductive fitness of the Uzifly Exorista sorbillans (Diptera: Tachinidae). Synbiosis 2011; 54(3): 151–158.

[10] Saridaki A, Bourtzis K. Wolbachia–induced reproductive parasitism and applications. Entomol Hell 2009; 18: 3–16.

[11] Guruprasad NM, Jalali SK, Pattaraju HP, Wolbachia and its perspectives in biological control of insect pests and diseases vectors. Appl Entomol Zool 2013; doi: 10.1007/s13355–013–0178-2.

[12] Breilsford CL, Dobson SL. An update on the utility of Wolbachia for controlling insect vectors and disease transmission. Asian Pac J Mol Biol Biotechnol 2011; 19(3): 85–92.

[13] Pinto SB, Mariconti M, Bazzocchi C, Bandi C, Sinkins SP. Wolbachia surface protein induces innate immune responses in mosquito cells. BMC Microbiol 2012; 12(Suppl 1): S11.

[14] Iturbe–Ormaetxe I, Walker T, O’Neill SL. Wolbachia and the biological control of mosquito–borne disease. EMBO Rep 2011; doi: 10.1038/embo.2011.84.

[15] Walker T, Moreira LA. Can Wolbachia be used to control malaria? Mem Inst Oswaldo Cruz 2011; 106(Suppl 1): S212–S217.

[16] Rasgon JL. Using predictive models to optimize Wolbachia–based strategies for vector–borne disease control. In: Aksoy S, editor. Transgenesis and the management of vector–borne disease. New York: Springer; 2008, p. 1–11.

[17] Min KT, Benzer S. Wolbachia, normally a symbiont of Drosophila, can be virulent, causing degeneration and early death. Proc Natl Acad Sci U S A 1997; 94(20): 10792–10796.

[18] Hedges LM, Brownlie JC, O’Neill SL, Johnson KN. Wolbachia and virus protection in insects. Science 2008; 322(5950): 702.

[19] Teixeira L, Ferreira A, Ashburner M. The bacterial symbiont Wolbachia induces resistance to RNA viral infections in Drosophila melanogaster. PLoS Biol 2008; 6(2): 2.

[20] Osborne SE, Leong YS, O’Neill SL, Johnson KN. Variation in antiviral protection mediated by different Wolbachia strains in Drosophila simulans. PLoS Pathog 2009; 5(11): 1000656.

[21] Moreira LA, Iturbe–Ormaetxe I, Jeffery JA, Lu G, Pyke AT, Hedges LM, et al. A Wolbachia symbiont in Aedes aegypti limits infection with dengue, chikungunya, and Plasmodium. Cell 2009; 139(7): 1268–1278.

[22] Blandin S, Shaio SH, Moita LF, Janse CJ, Waters AP, Kafatos FC, et al. Complement–like protein TEP1 is a determinant of vectorial capacity in the malaria vector Anopheles gambiae. Cell 2004; 116(5): 661–670.

[23] Povelones M, Waterhouse RM, Kafatos FC, Christophides GK. Leucine–rich repeat protein complex activates mosquito complement in defense against Plasmodium parasites. Science 2009; 324(5924): 258–261.

[24] Kambris Z, Blagborough AM, Pinto SB, Blagrove MS, Godfray HC, Sinden RE, et al. Wolbachia stimulates immune gene expression and inhibits Plasmodium development in Anopheles gambiae. PLoS Pathog 2010; 6(10): 1001143.

[25] Moreia LA, Saig E, Turley AP, Ribeiro JM, O’Neill SL, McGraw EA. Human probing behavior of Aedes aegypti when infected with a life shortening of Wolbachia. PLoS Negl Trop Dis 2009; 3(12): 568.

[26] Bian G, Xu Y, Lu P, Xie Y, Xi Z. The endosymbiotic bacterium Wolbachia induces resistance to dengue virus in Aedes aegypti. PLoS Pathog 2010; 6(4): 1000833.

[27] Glaser RL, Meola MA. The native Wolbachia endosymbionts of Drosophila melanogaster and Culex quinquefasciatus increase host resistance to West Nile virus infection. PLoS One 2010; 5(8); 11977.

[28] World Health Organization. World malaria report. Geneva: World Health Organization; 2008. [Online] Available from: http://www.who.int/malaria/publications/atoz/9789241564106/en/index.html. [Accessed on 16 August, 2013]

[29] Kambris Z, Cook PE, Phuc HK, Sinkins SP. Immune activation by life–shortening Wolbachia and reduced filarial competence in mosquitoes. Science 2009; 326(5949): 134–136.

[30] Hughes GL, Ren X, Ramirez JL, Sakamoto JM, Bailey JA, Jedlicka AE, et al. Wolbachia infections in Anopheles gambiae cells: transcriptomic characterization of a novel host–symbiont interaction. PLoS Pathog 2011; 7(2): 1001296.

[31] Kokoza V, Ahmed A, Woon Shin S, Okafor N, Zou Z, Raikhel AS. Blocking of Plasmodium transmission by cooperative action of cercopin A and defensin A in transgenic Aedes aegypti mosquitoes. Proc Natl Acad Sci 2010; 107(18): 8111–8116.

[32] Jin CY, Ren XX, Rasgon JL. The virulent Wolbachia strain wMelPop efficiently establishes somatic infections in the malaria vector Anopheles gambiae. Appl Environ Microbiol 2009; 75(10): 3373–3376.