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Is antibacterial PNA the answer for combating multidrug resistant bacterial infections?

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Abstract

The emergence of multidrug resistant bacterial infections is a serious problem. Treatment options are limited to patients those are infected with multidrug resistant bacteria. We are in a desperate need of new antibiotics. Antisense oligomers of PNA (Peptide Nucleic Acid) were introduced in late 90's as antibacterial agents in an intention to create a new class of bacterial specific antibiotic. Followed by several studies have demonstrated that antibacterial PNA oligomers are effective in a verity of pathogenic bacterial strains. Development of PNA-based drugs (PNA antibiotics) will help us to combat infections of drug resistant bacterial strains.

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The number of multidrug resistant bacteria is increasing at an alarming rate. This is happening mainly due to the uncontrolled use of antibiotics and transfer of resistance genes within bacteria. The majority of previously discovered antibiotics are now not useful in eradicating multidrug resistant bacterial infections, although, in some cases, the combination of antibiotics still work. There are very few antibiotics such as ceftobiprole, linezolid, daptomycin, amikacin, etc. that are effective on multidrug resistant bacterial strains.

The number of deaths associated with multidrug resistant bacterial infections is increasing everywhere in the world, indicating that we are not too far to reach the post-antibiotic era. Since the discovery of penicillin, not many new classes of antibiotic were discovered (Lewis, 2013); although, in recent years, the initiatives of discovering new antibacterial drugs have increased steadily. The need of new kinds of antibiotic is paramount.

PNA oligomers were first introduced as antisense antibacterial agents in late 90's (Good and Nielsen, 1998). A few years later, it was shown that peptide conjugated PNA oligomers (antibacterial PNA) are capable of killing bacteria by inhibiting the function of *acpP* gene and provide protection from *E. coli* infection (Good *et al*, 2001). Thereafter, several studies have demonstrated the potential of antibacterial PNAs in inhibiting the growth of many human pathogenic bacteria (Ghosal, in press; Ghosal, 2012). Further, it was shown that antibacterial PNAs are capable of reducing bacterial load in infection mice models (Tan *et al*, 2005; Bai *et al*, 2012). Antibacterial PNAs also inhibit the growth of *Pseudomonas aeruginosa* (Ghosal and Nielsen, 2012), and anti-*acpP*PNAs are effective in inhibiting the growth of different strains of *Pseudomonas aeruginosa*. Furthermore, *Pseudomonas aeruginosa* LESB58 strain (a clinical isolate) showed sensitivity to lower doses of antibacterial PNAs compared to antibiotic ofloxacin and ceftazidime. A just-published study, which characterizes a Pseudomonas specific antibacterial PNA, highlighted that antibacterial PNA is capable of reducing the production of pro-inflammatory cytokines in an *in vitro* cell culture infection model (Montagner *et al*, 2017).

The potency of antibacterial PNA molecules depends on the properties of conjugated peptide and the PNA oligomer. The conjugated peptide helps in transportation of PNA oligomer into the bacterial cytosol; inside the bacterial cytosol, antisense PNA oligomer binds to the target RNA. In some cases, conjugated peptides degrade in bacterial periplasm after crossing the outer membrane (Gram-negative bacteria), and from periplasm, PNA oligomers transport to cytoplasm by inner membrane transporters, while some peptides remain attached to the PNA oligomers after crossing the bacterial membrane (Ghosal *et al*, 2013).

Properties of antibacterial PNAs provide an advantage to design bacterial specific antibiotics. Designing of bacterial specific antibiotics is always advantageous as it lives other beneficial bacteria unharmed.

The human body is colonized by a vast number of microorganisms where majority of them are represented by bacteria (Bäckhed *et al*, 2005). Recently, it has shown that bacteria secrete RNA, and these secreted RNA have the potential to alter the behavior of host cells (Ghosal *et al*, 2015; Fritz *et al*, 2016; Koeppen *et al*, 2016). It would be relatively easy to design PNA-based inhibitors against those effector RNA molecules.

Despite several advantages, delivery of antibacterial PNA oligomers is still a challenge; it requires a vehicle to get into the bacterial cell. Several studies need to be done to take antibacterial PNAs to the clinics. Further, instead of using antibacterial PNA alone as an antibiotic, it would also be advantageous to use antibacterial PNA in combination with commonly used drugs where antibacterial PNA will be used to sensitize multidrug resistant bacteria to the drugs.

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