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CRISPR-Cas9: Promising Platform for Prospective Antimicrobial Therapy

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Introduction

Infectious diseases are the leading cause of death worldwide, which requires novel therapeutics to battle against the infectious agents [1]. In recent years, the development of most powerful genome editing tool based on a bacterial CRISPR associated protein 9 nuclease (Cas9) provides considerable excitement to precisely manipulate genomes of infectious agents, which enabled clinical researchers to execute inexpensive and high throughput investigation of gene functions associated with infections. In general, the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and Cas genes, function as critical components in adaptive immunity of certain bacteria and archaea, enabling them to resist against invading genetic materials such as DNA from viruses and plasmids [2, 3]. In CRIPSR mechanisms, the invading foreign DNA was cut into fragments and inserted into CRISPR locus, which were then transcribed to produce small RNAs (CRIPSR RNA or crRNA) that act as a guide molecule directing effector endonucleases to specifically target invading DNA based on sequence complementarity [4]. In recent past, CRISPR/Cas9 system advances as a new tool for molecular biology that comprised of synthetic guide RNA (sgRNA) requiring specifically programmed Cas9 endonuclease to guide targeted gene alteration in genome [5].

The greater simplicity and versatility of CRISPR/Cas9 system with minimal requirement of three components including Cas9, crRNA and tracRNA, makes this technology more amenable to adaption for precise genome editing. Furthermore, CRISPR/Cas9 system is highly efficient, effective and affordable, which all added benefits for exploiting this system for targeted genome engineering [6]. Till date, CRISPR/Cas9 system has been successfully used to target genes in cell lines and organisms including human, mice, zebrafish, rabbits, pigs, viruses and bacteria [7]. Moreover, this system can be specifically utilized for precision genome engineering of infectious agents as a potent prophylactic and therapeutic antimicrobial strategy that can impaired with pathogen multiplication and infections. Recently, researchers have successfully used this technology to limit herpes virus infection during the latent and productive stage of the viral life cycle, by inducing efficient genome editing in human herpes viruses that resulted in impaired production of new infectious particle from human cells [8]. Studies have also shown that RNA-directed gene editing using CRISPR/Cas9 technology specifically eliminates the HIV-1 integrated genome and prevents new HIV-1 infection [9]. CRISPR/Cas9 system has also been implemented to efficiently repress diverse set of essential genes in mycobacterial species, which opened up new doors to completely eradicate multidrug- and extensively drug-resistant cases of tuberculosis [10]. Thus, CRISPR approach has been proven to be effective in selectively killing of pathogenic microbes, which added advantages for using this technology to develop antimicrobials.

CRISPR/Cas9 technology represents a novel form antimicrobial therapy or strategy that offers an attractive platform to target gene(s) encoding antibiotics resistance, virulence factors and other disease relevant sequences of interest. Further, the combination of inducible and multiplex genome editing approaches would provide new pathways for easy genome editing with uniform temporal control, less off-target effects and multiplex targeting [11]. Therefore, devising specific guide (g) RNAs sequences that are complementary to the vital parts of the pathogen genome in combination with 'molecular scissors' as a part of CRISPR-Cas9 system can induce specific cuts and mutations in the genome that would cripple pathogen from causing infection. More importantly, this technology can be combined with other existing antimicrobial strategies towards successful eradication of infectious diseases.

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