Chapter 3
CRISPR-Cas9 Technology for Unlocking Immunity Against Infectious Pathogens

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ABSTRACT

The development of CRISPR-Cas9 has dramatically changed the field of genome engineering and its utilization in epigenome editing could have profound implications for precision medicine.This ability to precisely target epigenetic marks, including DNA methylation, histone modifications, and chromatin remodeling, allows for exciting therapeutic developments in cancer, neurodegenerative and autoimmune

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diseases. New developments such as CRISPRi, CRISPRa, and reversible CRISPR off/CRISPR on, allow for complex and multiplexed epigenetic reprogramming with improved specificity and safety. Nonetheless, there are some challenges to delivery off-target effects, stability of epigenetic modification, and moral lines, especially with inheritable epigenetic modification. The essential principles of CRISPR-Cas9-based epigenome editing, its therapeutic prospects for personalized medicine, and the consideration of technological, ethical, and policy aspects associated with epigenome editing are discussed

INTRODUCTION

Precision medicine is revolutionizing health care by enhancing the ability to personalize prevention, diagnosis, and treatment for an individual, based on their genetic, environmental, and lifestyle characteristics, with the role of gene regulation being particularly important. We can regulate genes not only at the DNA sequence level, but also at the epigenetic level as heritable, but reversible modifications, which do not change the underlying genetic code. Epigenetic dysregulation is being increasingly recognized in the pathology of an ever-expanding list of diseases, including, but not limited to, cancer, neurodegenerative diseases, autoimmune diseases, and metabolic disorders. The CRISPR-Cas9 system is based on a bacterial immune system and was developed as a genome-editing technology, and has most recently advanced to the realm of epigenome editing, which offers an exciting possibility for clinical application. Scientists have discovered that CRISPR can be coupled with a catalytically dead Cas9 (dCas9), to which the scientists then attach functional effector domains that enable targeted modulation of epigenetic marks (e.g., DNA methylation; histone modifications) in a compact and specific manner without permanently modifying the genome.

This is a significant advance over traditional epigenetic therapeutics, which often have non-specific effects that engage global epigenetic machinery. CRISPR-based epigenome editing technologies, including CRISPR interference (CRISPRi), CRISPR activation (CRISPRa), reversible systems such as CRISPRoff and CRISPRon have great potential to use in the treatment of diseases caused by aberrant expression of genes. These technologies provide an unprecedented level of precision to reprogram gene expression; thus, providing new avenues for treatments for cancers, neurodegenerative diseases, autoimmune diseases, and drug resistance. There are still challenges in developing the technology further to improve delivery efficiency, reduce off-target effects, determine the long-term stability of reversible modifications, and address ethical concerns raised in using germline editing. This chapter will provide a brief history and mechanism of CRISPR-Cas9, as this technology is applied in