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Review

Diversity, evolution, and therapeutic applications of small RNAs in prokaryotic and eukaryotic immune systems

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Abstract

Recent evidence supports that prokaryotes exhibit adaptive immunity in the form of CRISPR (Clustered Regularly Interspersed Short Palindromic Repeats) and Cas (CRISPR associated proteins). The CRISPR–Cas system confers resistance to exogenous genetic elements such as phages and plasmids by allowing for the recognition and silencing of these genetic elements. Moreover, CRISPR–Cas serves as a memory of past exposures. This suggests that the evolution of the immune system has counterparts among the prokaryotes, not exclusively among eukaryotes. Mathematical models have been proposed which simulate the evolutionary patterns of CRISPR, however large gaps in our understanding of CRISPR–Cas function and evolution still exist. The CRISPR–Cas system is analogous to small RNAs involved in resistance mechanisms throughout the tree of life, and a deeper understanding of the evolution of small RNA pathways is necessary before the relationship between these convergent systems is to be determined. Presented in this review are novel RNAi therapies based on CRISPR–Cas analogs and the potential for future therapies based on CRISPR–Cas system components.

Contents

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1. Introduction

1.1. Prokaryotes and eukaryotic immune systems

Living organisms have evolved into three domains: Bacteria, Archaea, and Eukaryota. Two of these three domains – the Bacteria and the Archaea – consist of generally unicellular organisms that lack a cell nucleus and other membrane-bound organelles. These organisms are known as prokaryotes. On the other hand, the eukaryotes of domain Eukaryota contain DNA and metabolic sites enclosed within membranes.

All large, complex organisms, such as plants and animals, are eukaryotes, and can sport varied and multifaceted immune systems. Traditionally, the immune system can be divided into two main systems: the innate and adaptive. The distinguishing characteristics of the two systems contrast greatly. The innate immune system is natural, non-specific, non-anticipatory, non-clonal, germ line, and does not retain memory of past exposures. This type of immune system is found throughout the animal and plant kingdoms. The adaptive immune system is acquired, specific, anticipatory, clonal, somatic, and allows for memory of past exposures [27]. Differences in animal evolution and morphology have led to associations with either or both of these systems. Primarily, vertebrates employ some combination of the two systems, while invertebrates tend only to have access to the innate immune system [25,27]. Invertebrates do not possess a T-cell-like recognition system, whereas vertebrates have a highly specialized recognition system against non-self components [28]. Often when both systems are present they are highly interrelated [26,27]. Innate mechanisms can be viewed as a part of a continuum of adaptive immune system responses [29].

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