Snippets of virus integrated into human genome suggests possibility of CRISPR-like adaptive immune system in human cells

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Abstract

Snippets of virus that infect humans have been shown to be incorporated into the human genome. Could such virus snippets provide a form of adaptive immunity similar to that offered by CRISPR to bacterial cells? To answer the question, RNA-seq could be used to provide a broad view of the RNA transcribed from DNA in the genome. Using known genome sequence of viruses that infect humans as template, reads obtained from RNA-seq would be profiled for virus snippets integrated into human genome and subsequently transcribed as part of an adaptive immune system. Subsequently, viruses corresponding to the virus snippets in human genome would be used to infect human cell lines to obtain direct evidence of how virus snippets mediate an adaptive immune response at the cellular level. Specifically, successful defence of the cell by virus snippets triggering an adaptive immune response would manifest as viable cells compared to lysed cells unable to mount an immune response. Following demonstration of cell viability under viral challenge, *in vitro* biochemical assays using cell lysate would interrogate the specific proteins and enzymes that mediate possible cutting of the foreign DNA or RNA. To this end, beads immobilized with virus snippets would serve as bait for binding to complementary viral DNA or RNA as well as potential endogenous endonuclease protein. Following precipitation and recovery of beads, possible endonuclease that bind to both viral DNA or RNA and virus snippets immobilized on beads would be isolated through gel electrophoresis and subsequently purified. Purified endonuclease would be assayed for activity against a variety of nucleic acids (both DNA and RNA) from various sources with and without added virus snippets. This provides important information on substrate range and specificity of the potential endonuclease. Amino acid sequencing of the purified endonuclease would help downstream bioinformatic search for candidate protein in the human genome. Finally, cryo-electron microscopy could help determine the structure of the endonuclease in complex with viral nucleic acids and virus snippets. Such structural information would provide more insights into mechanistic details describing the binding and cleavage of viral DNA or RNA in a CRISPR-like adaptive immune response in human cells. Overall, tantalizing clues have emerged that a CRISPR-like adaptive immune response may exist in human cells for defending against viral attack. Combination of cell biological, biochemical and structural tools could lend insights into the potential endonuclease that mediate double strand break of foreign DNA or RNA using virus snippets transcribed from the human genome as guide RNA. If demonstrated to be true for a variety of human viruses across different cell lines, the newly discovered viral defence mechanism in human cells hold important implications for understanding the adoption and evolution of CRISPR in eukaryotic cells.

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Conflicts of interest

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