研究成果の刊行に関する一覧表

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An improved method for detection of replication-competent retrovirus in retrovirus vector products

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Abstract

Contamination by replication-competent retrovirus (RCR) is one of the most important safety issues of retrovirus vector products for gene therapy clinical research. To improve the sensitivity of RCR detection and to shorten the assay period, we have developed a novel RCR detection method (infectivity RT-PCR method) based on real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) in combination with virus infection and a novel virus concentration method using polyethyleneimine (PEI)-conjugated magnetic beads. In this method, permissive cells were infected with RCR samples, and amplified RCR in the culture supernatants was adsorbed by PEI-beads. Then RCR RNA extracted from PEI-beads was quantified by real-time RT-PCR. We demonstrated that 1 infectious unit (iu) of RCR spiked in 10^6 cfu/ml of vector products could be detected within 3 days, and the sensitivity for viral detection was increased 3- to 10-fold compared with the direct S + L− assay. By this method, the presence of retroviral vector interfered with RCR detection only slightly. In conclusion, infectivity RT-PCR conducted in conjunction with virus concentration using PEI-beads can detect RCR more sensitively and rapidly than the conventional infectivity assay.

1. Introduction

Retrovirus vectors are widely used in human gene therapy to treat genetic diseases, cancer, and other conditions. The retroviral vector products currently used in gene therapy clinical researches are replication-defective retroviruses, and the primary safety concern associated with the use of retroviral vector products is contamination by replication-competent retrovirus (RCR). RCR is the major risk factor for insertional mutagenesis, and exposure to retrovirus vector contaminated with a high titer of RCR has been shown to lead to lymphoma in rhesus monkeys [1].

The most likely source of RCR is the vector-packaging sequence. Since RCR can arise by homologous recombination during the production of retroviral vector supernatants, sensitive assays for the screening of RCR in vector products are required. The U.S. Food and Drug Administration (FDA) has developed guidelines for testing of RCR in clinical grade vectors and transduced cells, as well as for monitoring patients

Abbreviations: RCR, replication-competent retrovirus; RT-PCR, reverse transcription-polymerase chain reaction; PEI, polyethyleneimine; iu, infectious units; cfu, colony forming units; MLV, murine leukemia virus; AMLV, amphotropic MLV.

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