

Establishment of novel molecular cancer therapy targeting telomerase and its clinical application to gynecologic tumors

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2004 Fiscal Year Final Research Report Summary

Establishment of novel molecular cancer therapy targeting telomerase and its clinical application to gynecologic tumors

Research Project

Project/Area Number

15390501

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

Obstetrics and gynecology

Research Institution

Kanazawa University

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Project Period (FY)

2003 - 2004

Keywords

hTERT / Telomerase / Telomere / siRNA / gene therapy / cervical cancer

Research Abstract

Telomerase activation plays critical roles in tumor growth and progression in part through the maintenance of telomere structure. Indeed, the ubiquitous expression of telomerase in human cancers makes telomerase a promising target for cancer therapy. Genetic, pharmacologic and antisense methods to inhibit telomerase have been described ; however, in most cases, cancer cell death was observed only after many cell divisions. Here, using retroviral delivery of small interfering RHAs specific for the human telomerase reverse transcriptase (hTERT), we successfully inhibited telomerase activity in cervical cancer cell lines. Cells lacking hTERT expression exhibited significantly decreased telomerase activity and showed shortened telomeres and telomeric 3'-overhangs with passage. These cells entered the replicative senescence after

considerable number of cell divisions. Notably, the proliferative rate of these cells was significantly impaired, compared to control cells with telomerase activity, even in low passage cells (PD 5). Likewise, colony-forming ability and tumorigenicity in mice were attenuated in low passage cells lacking hTERT. We further examined the effects of chemotherapy and ionizing radiation of cells in which hTERT expression is suppressed. Cells lacking hTERT showed a significantly increased sensitivity than control cells to ionizing radiation or chemotherapeutic agents that induce DNA double strand breaks, such as topoisomerase inhibitors or bleomycin. These findings suggest that a siRNA-based strategy can be applied to the development of novel telomerase inhibitors, whose anti-tumor effects may be enhanced in combination with ionizing radiation and chemotherapy.

Research Products (10 results)

All	2004	2003	Other
All	Journal Article		

- [Journal Article] Visualization of intrathoracically disseminated solid tumors in mice with optical imaging by telomerase-specific amplification of a transferred green fluorescent protein gene **2004** ▾
- [Journal Article] EWS/ETS fusions activate telomerase in Ewing's tumors **2003** ▾
- [Journal Article] Efficient inhibition of hTERT expression by RNA interference sensitizes cancer cells to ionizing radiation and chemotherapy ▾
- [Journal Article] Relief of p53-mediated telomerase suppression by p73 ▾
- [Journal Article] Therapeutic efficacy of PUMA for malignant glioma cells regardless of the p53 status ▾
- [Journal Article] Enhanced oncolysis by OBP-405, a tropism-modified telomerase-specific replication-selective adenoviral agent ▾
- [Journal Article] Efficient inhibition of hTERT expression by RNA interference sensitizes cancer cells to ionizing radiation and chemotherapy ▾
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