Development of Gene Targeting Technique Using Radiolabeled Antisense DNA

2001 Fiscal Year Final Research Report Summary

Development of Gene Targeting Technique Using Radiolabeled Antisense DNA

Research Project

Project/Area Number

10470194

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

Radiation science

Research Institution

Kanazawa University

Principal Investigator

TONAMI Norihisa Kanazawa University Graduate School of Medical Sciences, Professor, 大学院・医学系研究科, 教授 (60019940)

Co-Investigator(Kenkyū-buntansha)

SHIBA Kazuhiro Kanazawa University Radioisotope Center, Associate Professor, アイソトープ総合センター, 助教授 (40143929)
YOKOYAMA Kunihiko Kanazawa University Hospital, Lecturer, 医学部・附属病院, 講師 (60230661)

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1998 – 2000

Keywords

antisense DNA / oligonucleotide / radioisotope / imaging diagnosis / gene imaging / delivery system / induced hypertension

Research Abstract

Using radiolabeled antisense oligonucletides (DNA), lesions of amplified mRNA can be imaged with gamma cameras. For this approach, the stable radiometal chelates, which are appropriate for oligonucletide, is required. We have developed the in vivo model system where nude mice xenografted tumor cells express P-glycoprotein (P-gp). To image multidrug resistant tumors caused by P-gp, we designed the 15mer of antisense DNA sequence for the mdr1 gene coding P-gp. The 5'-end of the oligonucleotide was modified with the thiol group and the maleimido-C6-benzyl-EDTA chelate was reacted. The final product was identified as the objective compound by ODS chromatography. Further investigation was warranted. The small molecules like oligonucleotides tend to be cleared very rapidly from the blood and therefore, the

absolute tumor uptake of this kind of the tracer is limited. We have tried to increase the tumor uptake of radiolabeled antibodies by modifying the delivery system to the tumor tissue. The combination usage of angiotensin-II, continuously infused at 2μg/kg/min, and a kininase inhibitor, enalapril maleate, 30 μg increased the mouse blood pressure from 95/61 to 153/67. And the tumor uptake was also increased by the factor of 1.62 with little change in normal organ distribution. The autoradiography showed that more homogeneous distribution of the radiolabeled antibody in the tumor because of recanalization of vascular beds and increased vascular permeability. In conclusions, enhanced tumor uptake was achieved by manipulating hemodynamics and vascular permeability of the tumor tissue and this technique can be applied for smaller molecule as the oligonucleotides.

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