Published OnlineFirst September 7, 2017; DOI: 10.1158/0008-5472.CAN-17-0775

Microenvironment and Immunology

Cancer Research

Transplantation of iPS-Derived Tumor Cells with a Homozygous MHC Haplotype Induces GRP94 Antibody Production in MHC-Matched Macaques

Hirohito Ishigaki[1], Toshinaga Maeda[2], Hirokazu Inoue[3], Tsuyoshi Akagi[4], Takako Sasamura[1], Hideaki Ishida[1], Toshiro Inubushi[5], Junko Okahara[6], Takashi Shiina[7], Misako Nakayama[1], Yasushi Itoh[1], and Kazumasa Ogasawara[1]

Abstract

Immune surveillance is a critical component of the antitumor response *in vivo*, yet the specific components of the immune system involved in this regulatory response remain unclear. In this study, we demonstrate that autoantibodies can mitigate tumor growth *in vitro* and *in vivo*. We generated two cancer cell lines, embryonal carcinoma and glioblastoma cell lines, from monkey-induced pluripotent stem cells (iPSC) carrying a homozygous haplotype of major histocompatibility complex (MHC, Mafa in Macaca fascicularis). To establish a monkey cancer model, we transplanted these cells into monkeys carrying the matched Mafa haplotype in one of the chromosomes. Neither Mafa-homozygous cancer cell line grew in monkeys carrying the matched Mafa haplotype heterozygously. We detected in the plasma of these monkeys an IgG autoantibody against GRP94, a heat shock protein. Injection of the plasma prevented growth of the tumor cells in immunodeficient mice, whereas plasma IgG depleted of GRP94 IgG exhibited reduced killing activity against cancer cells *in vitro*. These results indicate that humoral immunity, including autoantibodies against GRP94, plays a role in cancer immune surveillance. *Cancer Res; 77(21); 6001–10. ©2017 AACR.*

Introduction

The establishment of an experimental monkey model of cancer is important to develop new treatments for cancer. Cynomolgus macaques are genetically closer to humans than are mice, and the structures of biologically relevant molecules in monkeys and the organization of the hematopoietic system in macaques are similar to those in humans. Indeed, more than half of the antibodies against human molecules react to molecules of cynomolgus monkeys (1, 2). Furthermore, recent genomic studies have revealed that several monkey cytochrome P450s, which work in drug metabolism, are apparently orthologous to human P450s (3). Therefore, a cancer model in cynomolgus macaques may be more useful than a cancer model in mice for preclinical experiments (4, 5). However, spontaneous neoplasms and malignant tumors in cynomolgus monkeys are uncommon (6). In addition, no cancer model in cynomolgus monkeys has been established by transplantation of tumor cell lines as in mouse cancer models because there is no inbred line in cynomolgus monkeys. To solve this problem, we established major histocompatibility complex (MHC) homozygous tumor cell lines of cynomolgus macaques for transplantation to MHC-matched heterozygous monkeys.

We established induced pluripotent stem cells (iPSC) from fibroblasts of a cynomolgus macaque carrying homozygous MHC genes by introduction of the four Yamanaka factors (Oct3/4, Sox2, Klf4, and c-Myc; refs. 7, 8) and colonies of cynomolgus macaques carrying the identical MHC haplotype heterozygously (7, 9). From an immunological aspect, cells derived from MHC homozygous iPSCs are more acceptable than MHC-mismatched cells by hosts carrying identical MHC genes. This strategy enables the establishment of various types of tumor models transplantable to cynomolgus macaques as various somatic cells have been developed from iPSCs including neural cells, hematopoietic cells, and pancreatic cells (10–14).

We established cancer cell lines from iPSCs of a cynomolgus macaque carrying a homozygous MHC haplotype; however, MHC-matched hosts rejected these cell lines after transplantation. We found antibodies reacting to the cancer cells in plasma of the macaques that rejected transplanted cells. The plasma also reacted to other immortalized cells transduced with oncogenes that were not transplanted. The IgG in plasma recognized glucose-regulated protein (GRP) 94, a kind of heat shock proteins that is considered as a target of tumor therapy. GRP94 is a common antigen of oncogene-transduced cells that we

[1]Division of Pathology and Disease Regulation, Department of Pathology, Shiga University of Medical Science, Otsu, Shiga, Japan. [2]Central Research Laboratory, Shiga University of Medical Science, Otsu, Shiga, Japan. [3]Division of Microbiology and Infectious Diseases, Department of Pathology, Shiga University of Medical Science, Otsu, Shiga, Japan. [4]KAN Research Institute, Kobe, Hyogo, Japan. [5]Biomedical MR Science Center, Shiga University of Medical Science, Otsu, Shiga, Japan. [6]Central Institute for Experimental Animals, Kawasaki, Kanagawa, Japan. [7]Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Isehara, Kanagawa, Japan.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Corresponding Author: Hirohito Ishigaki, Shiga University of Medical Science, Setatsukinowa-Cho, Otsu, Shiga 520-2192, Japan. Phone: 81-77-548-2172; Fax: 81-77-548-2423; E-mail: ihiro@belle.shiga-med.ac.jp

doi: 10.1158/0008-5472.CAN-17-0775