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G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

① 特許出願中 特願2004-363681「癌の新規診断法」（安井）

② HBV DNAの高感度定量系の開発（申請準備中）（大石）

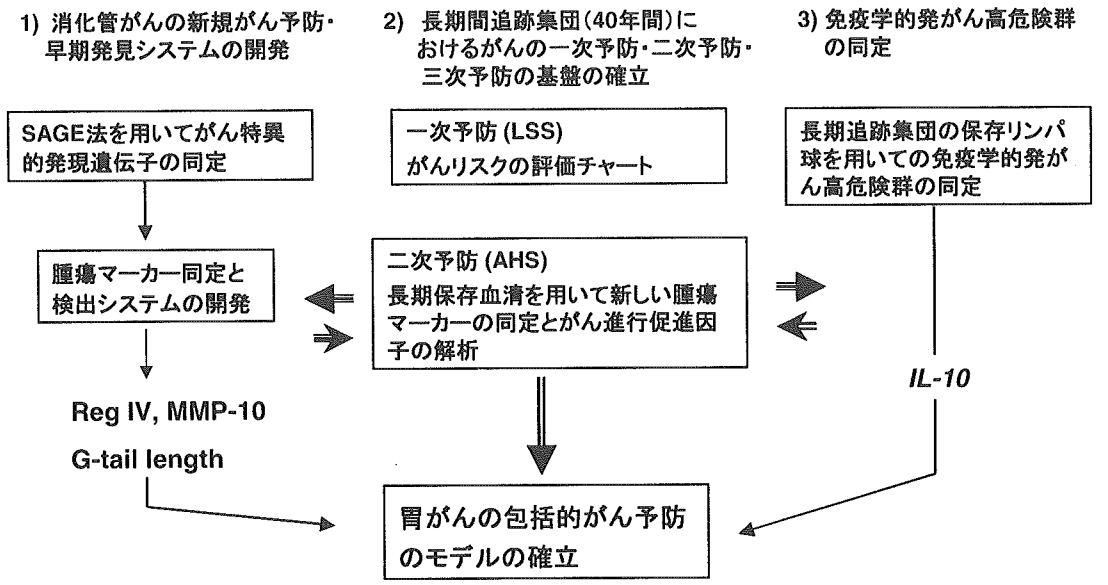
2. 実用新案登録

なし

3. その他

なし

図1. 新規がん予防・早期発見システムを用いた包括的ながん予防の開発研究（田原班）
（H17－3次がん－012）



II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

＜平成 17 年（2005 年）度＞

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著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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Smith M, Hold GL, Tahara E, El-Omar EM.	Cellular and molecular aspects of gastric cancer.	The World Journal of Gastroenterology		In press
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Recent Advances in Molecular Pathobiology of Gastric Carcinoma

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Introduction

Cancer is a chronic proliferative disease with multiple genetic and epigenetic alterations, namely, disease with altered gene expression. Integrated research in molecular pathology over the past 15 years has uncovered the molecular mechanism of the development and progression of gastric cancer [1–5]. Multiple genetic and epigenetic alterations involve inactivation of tumor suppressor genes, activation of oncogenes, abnormalities of DNA repair genes, cell-cycle regulators, cell adhesion molecules, growth factors/receptors, matrix metalloproteinases, and so on. Gastric carcinoma is histologically classified into two types, well-differentiated and poorly differentiated types, and the former can be further classified into those with gastric and intestinal phenotypes. Some of these alterations occur commonly in both well-differentiated and poorly differentiated types whereas some differ depending on the histological types or mucin phenotypes. Recent advances in genomic science have enabled revealing the molecular mechanism of stomach carcinogenesis more in detail; these include global analysis of gene expression by microarray or other techniques and study of the association of genetic polymorphism with cancer risk. A better knowledge of the molecular bases of gastric cancer may lead to new approaches to diagnosis, treatment, and prevention.

This chapter presents an overview of the classical pathway of molecular stomach carcinogenesis, mechanism of epigenetic alterations, importance of genetic polymorphism, search for novel genes specific in gastric carcinoma through global analysis of gene expression, and the clinical implications.

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TABLE 1. Footprint of molecular research on gastric cancer

Cancer in general		Gastric carcinoma	
1911	Rous sarcoma virus	1983	*Helicobacter pylori*
1914	Fijinami sarcoma virus		
1953	DNA double helix structure		
1956	Viral transformation	1984	c-*myc* amplification
1969	Oncogene theory	1985	Establishment of TMK-1
	Normal phenotype by cell fusion	1986	EGF overexpression
1970	Reverse transcriptase		H-*ras* altered expression
1971	Knudson's two-hit theory	1986	Identification of *HST-1*
1972	Epidermal growth factor (EGF)	1988	EGFR overexpression
	Apoptosis		*HER-2*/c-*er*bB2 amplification
1973	DNA transfection	1990	K-*sam* amplification
1975	Southern blot analysis	1991	Loss of E-cadherin
1976	Proto-oncogene c-*src*		Multiple loss of heterozygosity (LOH)
1979	Transformation by cellular DNA	1992	*p53/APC* mutations
	c-*src* encodes tyrosine kinase		c-*met* amplification
1982	Human H-*ras* oncogene		Cancer–stromal interaction
1983	Polymerase chain reaction (PCR) method	1993	Genetic changes in intestinal metaplasia
	Platelet-derived growth factor (PDGF) as c-*sis*, EGFR as v-*erb*B		Interleukin 1 (IL-1) as an autocrine growth factor
1986	*Rb* as a tumor suppressor gene		Molecular diagnosis
	Transcription factor Sp1	1994	Microsatellite instability in multiple cancer
1987	Cell adhesion molecule E-cadherin	1995	Increased telomerase activity

1988 Vogelstein's model for colon cancer
1989 *p53* as a tumor suppressor
1990 Cell-cycle regulator $p34^{CDC2}$
Microsatellite assay
Gene therapy for melanoma
1991 *APC* as a causative gene for famalial adenomatous polyposis (FAP)
Angiogenesis: VEGF
1993 *hMSH2* as a causative gene for hereditary nonpolyposis colorectal carcinoma (HNPCC)
p53 as transcription factor for p21
1994 TRAP assay for telomerase
1995 DNA microarrray technology
Serial analysis of gene expression
CpG island methylation of p16
1996 Laser capture microdissection
1997 Histone deacetylation
Human telomerase reverse transcriptase (hTERT)
1999 DNA demethylase
Chrosome 22 whole genome sequence
2001 Draft sequence of human genome
2003 Complete sequence of human genome

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Cyclin E gene amplification
1996 Reduced p21 expression
Microsatellite instability in precancerous lesion
1997 Reduced p27 expression
1998 E-cadherin germline mutation
hTERT expression
IL-8 and VEGF expression
1999 *hMLH1* hypermethylation
p73 genomic imbalance
2000 Hypoacetylation of histones
2002 23040 gene expression profile by microarray
2004 Serial analysis of gene expression (SAGE) libraries of gastric cancer

Overview of the Classical Pathway of Molecular Stomach Carcinogenesis

Footprint of Molecular Research on Gastric Carcinoma

We have learned from the footprint of cancer research that the history of cancer research is a repetition of establishment of hypothesis, development of new technologies, and discovery of novel findings (Table 1). For instance, Todaro and Huebner [6] hypothesized the oncogene theory in 1969 and Knudson [7] proposed the two-hit theory in 1971. After several years, methods of DNA transfection, Southern blotting, and polymerase chain reaction (PCR) amplification were developed and enabled them to verify and identify c-*src* as an oncogene and *Rb* as a tumor suppressor gene. Microarray is a powerful technique to reveal gene expression profiles of individual cancers. As of April 2003, the human genome sequence has been completed, and this is now the era of postgenome sequence and genomic medicine.

The history of molecular research on gastric carcinoma began only 20 years ago when c-*myc* amplification was found in primary gastric carcinoma in 1984 [8]. The first oncogene of gastric carcinoma, *HST-1*, was isolated from a primary gastric cancer in 1986 in the National Cancer Center in Tokyo [9]. In the late 1980s and 1990s, extensive analyses of molecular pathogenesis had been performed and the role and significance of novel genes and molecules, identified in other tumors or systems, had been clarified in gastric carcinoma with minimal time lag [4]. Examples include epidermal growth factor (EGF), EGF receptor (EGFR), E-cadherin, *p53*, cyclin E, $p27^{Kip1}$, human telomerase reverse transcriptase (*hTERT*), and *hMLH*1. The importance of DNA methylation and genetic instability during stomach carcinogenesis was also proved. In 1993, a routine system of molecular diagnosis on pathology specimens was established and this useful information was given to clinics [2,10]. Furthermore, the molecular mechanism of cancer–stromal interaction and genetic changes in intestinal metaplasia was explored, and the HGF/c-*met* system and mutations of *p53* and *APC*, respectively, were found to be involved [4]. Recently, dissection of gene expression profiles has been carried out using miroarray or other technology, and vast amounts of information regarding carcinogenesis, biological behavior, and chemosensitivity have been obtained, information that is directly connected with diagnosis and treatment.

Outline of Molecular Stomach Carcinogenesis

A variety of genetic and epigenetic alterations occur during multistep stomach carcinogenesis (Fig. 1) [1–5]; these include activation of oncogenes and growth factors/receptors, inactivation of tumor suppressor genes, DNA repair genes, and cell adhesion molecules, and abnormalities of cell-cycle regulators. Genetic alterations found in gastric carcinoma are gene amplification, point mutation, and loss of heterozygosity, whereas representative epigenetic changes are gene silencing by DNA methylation and overexpression at the transcriptional level [5]. Some alterations are found in both well- and poorly differentiated types, and others are unique depending on the histological type. The former may confer development of cancer whereas the latter may participate in tumor morphogenesis and biological behavior. Genetic

polymorphism predisposes to an endogenous cause and alters cancer susceptibility. Genetic instability, cytosine p guanine (CpG) island methylation, telomerase activation, and *p53* mutation commonly participate in the early steps of stomach carcinogenesis. Amplification and overexpression of the c-*met* and cyclin E genes are frequently associated with the advanced stage. Reduced expression of $p27^{Kip1}$ participates in both development and progression of gastric carcinoma. Overexpression of growth factors/cytokines confers progression through multiple autocrine loops. On the other hand, K-*ras* mutations, *HER*-2/c-*erb*B2 amplification, and *APC* mutation preferentially occur in the well-differentiated type. Precancerous lesions such as intestinal metaplasia and adenoma share alterations similar to those of the well-differentiated carcinomas. Loss of heterozygosity (LOH) of the *p73* gene occurs specifically in well-differentiated gastric carcinomas with foveolar epithelial phenotype. Inactivation of cadherins and catenins and amplification of the K-*sam* and c-*met* are frequently associated with poorly differentiated or scirrhous-type carcinomas.

Telomeric Repeats and Telomerase

The DNA sequence at telomeres consists of tandem repeats of TTAGGG, which protects chromosome ends from recombination and fusion and stabilizes the chromosome structure. Maintenance of the telomere by telomerase activation induces cellular immortalization [11]. Strong telomerase activity associated with hTERT expression is present in a majority of gastric carcinomas regardless of histological type and tumor staging [4]. Some intestinal metaplasia and adenomas express telomerase acvitity at certain levels. Telomerase activity is found in half of gastric adenomas at a level of activity about 10% of that in gastric carcinomas [12]. Hyperplasia of epithelial "stem cells" expressing hTERT and telomerase activity in precancerous lesion may be triggered by *Helicobacter pylori* (*H. pylori*) infection.

PINX1, a telomeric-repeat binding factor (TRF)1-binding protein, binds hTERT and inhibits its activity directly [13]. Reduced expression of PINX1 is detected in 70% of gastric carcinomas that show higher telomerase activity [13]. LOH of *PINX1* locus (8p23) is found in 33% of gastric carcinoma and is correlated significantly with reduced PINX1 expression. There are cases with reduced PINX1 expression but without LOH. Treatment with histone deacetylase inhibitor (HDAC) induces PINX1 expression, enhances histone H4 acetylation, and inhibits telomerase activity in gastric carcinoma cell lines. Therefore, reduced expression of PINX1 by LOH of PINX locus and hypoacetylation of histone H4 cause telomerase activation, resulting in cancer development.

POT1, a telomere end-binding protein, is proposed not only to cap telomeres but also to recruit telomerase to the ends of chromosomes [14]. POT1 expression levels are significantly higher in gastric carcinomas of advanced stage, and downregulation is frequently observed in those of early stage [14]. Reduced expression of POT1 is associated with telomere shortening and decreased telomerase activity. Inhibition of *POIT1* by antisense oligonucleotides increases telomere shortening, inhibits telomerase activity, and increases anaphase bridging, a sign of telomere dysfunction. Therefore, POT1 may play an important role in regulation of telomere length and that inhibition of POT1 may induce telomere dysfunction. Changes in POT1 expression levels may be associated with development and progression of gastric carcinoma.