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□ Review Article □

Biology of SNU Cell Lines

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SNU (Seoul National University) cell lines have been established from Korean cancer patients since 1982. Of these 109 cell lines have been characterized and reported, i.e., 17 colorectal carcinoma, 12 hepatocellular carcinoma, 11 gastric carcinoma, 12 uterine cervical carcinoma, 17 B-lymphoblastoid cell lines derived from cancer patients, 5 ovarian carcinoma, 3 malignant mixed MIlerian tumor, 6 laryngeal squamous cell carcinoma, 7 renal cell carcinoma, 9 brain tumor, 6 biliary tract, and 4 pancreatic carcinoma cell lines. These SNU cell lines have been distributed to biomedical researchers domestic and worldwide through the KCLB (Korean Cell Line Bank), and have proven to be of value in various scientific research fields. The characteristics of these cell lines have been reported in over 180 international journals by our laboratory and by many other researchers from 1987. In this paper, the cellular and molecular characteristics of SNU human cancer cell lines are summarized according to their genetic and epigenetic alterations and functional analysis. ***(Cancer Research and Treatment 2005;37:1-19)***

Key Words: **SNU, Cell line, Cell culture, Cancer, Cancer research**

INTRODUCTION

Cell lines are important because they provide a consistent renewable source of cell material for study. Cell line models should reflect the properties of the original cancers, such as, the maintenance of histopathology when transplanted into immunodeficient mice, genotypic and phenotypic characteristics, gene expression, and drug sensitivity (1). Moreover, advances in cell culture methods have made it possible to establish a variety of human cancer cell lines from surgical tissues, body fluids, and biopsy specimens. Because pure cells in culture can be used in many studies that cannot be conducted using tissue specimens, permanent cell lines established from human cancers offer great experimental flexibility (2～5). The Laboratory of Cell Biology at the Cancer Research Institute of Seoul National University (SNU) College of Medicine, has consistently worked to establish cell lines from human cancers for over 20 years. And currently, 180 tumor cell lines have been established from 2,200 cancer tissues. Of these 109 have been characterized and described in the literature. These include, 17 colorectal carcinoma (4,6), 12 hepatocellular carcinoma (3,7), 11 gastric carcinoma (2,5), 12 uterine cervical carcinoma (8), 17 B-lymphoblastoid (9), 5 ovarian carcinoma (10), 3 malignant mixed Müllerian tumor (11), 6 laryngeal squamous cell carcinoma (12), 7 renal cell carcinoma (13), 9 brain tumor (14), 6 biliary tract (15) and 4 pancreatic carcinoma (16) cell lines (Table 1). We have also established several anticancer drug resistant cell lines in the hope of identifying genes associated with anticancer drug sensitivity or resistance (17～21) (Table 2). And in 1987, we established the Korean Cell Line Bank (KCLB, http://cellbank.snu.ac.kr) at Cancer Research Institute in Seoul National University College of Medicine to distribute suitable cell lines to life science researchers. The characteristics of SNU cell lines have been reported in over 180 international journals by our laboratory and by other researchers since 1987 (references to these studies are included in the Reference section). The genetic, epigenetic and expression alterations of genes in SNU cell lines are summarized in Tables 3～6. In fact, several characteristics of SNU cell lines were reported in 2002 (22). In addition, we have contributed to three text books on the establishment and characterization of gastric, colorectal, and renal cancer cell lines (23～25). In this paper, we summarize the more recently discovered cellular and molecular characteristics of these cell lines and include the characteristics of recently developed cell lines. We also provide a summary on the establishment of cancer cell lines.

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ESTABLISHMENT OF CANCER CELL LINES

This section provides a summary of the establishment of cancer cell lines, for more detail refer to references 23～25. Our laboratory has extensive experience of the use of serum-containing and fully-defined media for the establishment of

Table 1. The establishment and characterization of SNU cancer cell lines

Organ	No.	Cell lines	References	Year
Colorectal ca.	5	SNU-C1, SNU-C2A, SNU-C2B, SNU-C4, SNU-C5	(4)	1987
Gastric ca.	3	SNU-1, SNU-5, SNU-16	(2)	1990
HCC*	8	SNU-182, SNU-354, SNU-368, SNU-387, SNU-398 SNU-423, SNU-449, SNU-475	(3)	1995
Gastric ca.	8	SNU-216, SNU-484, SNU-520, SNU-601, SNU-620 SNU-638, SNU-668, SNU-719	(5)	1996
Cervical ca.	12	SNU-17, SNU-487, SNU-523, SNU-682, SNU-703 SNU-778, SNU-902, SNU-1000, SNU-1005 SNU-1160, SNU-1245, SNU-1299	(8)	1997
Ovarian ca.	5	SNU-8, SNU-119, SNU-251, SNU-563, SNU-840	(10)	1997
MMMT†	3	SNU-539, SNU-685, SNU-1077	(11)	1997
B lympho-blastoid	17	SNU-9, SNU-20, SNU-99, SNU-247, SNU-265 SNU-285, SNU-291, SNU-299, SNU-315, SNU-321 SNU-374, SNU-445, SNU-447, SNU-538, SNU-817 SNU-889, SNU-1103	(9)	1998
Colorectal ca.	12	SNU-61, SNU-81, SNU-175, SNU-283, SNU-407 SNU-503, SNU-769A, SNU-769B, SNU-1033 SNU-1040, SNU-1047, SNU-1197	(6)	1999
Laryngeal ca	6	SNU-46, SNU-585, SNU-899, SNU-1066 SNU-1076, SNU-1214	(12)	1999
HCC*	4	SNU-739, SNU-761, SNU-878, SNU-886	(7)	1999
Renal cell ca.	7	SNU-228, SNU-267, SNU-328, SNU-333 SNU-349, SNU-482, SNU-1271	(13)	2000
Brain tumor	9	SNU-201, SNU-444, SNU-466, SNU-489 SNU-626, SNU-738, SNU-791, SNU-1105, SNU-1118	(14)	2001
Pancreatic ca.	4	SNU-213, SNU-324, SNU-410, SNU-494	(16)	2002
Biliary tract ca.	6	SNU-245, SNU-308, SNU-478, SNU-869 SNU-1079, SNU-1196	(15)	2002

*Hepatocelluar carcinoma, † malignant mixed Müllerian tumor.

Table 2. Induced anticancer drug resistant SNU gastric cancer cell lines

Organ/drug	No.	Cell lines	References
Doxorubicin	5	SNU-1-DOX, SNU-16-DOX, SNU-620-DOX SNU-668-DOX, SNU-719-DOX	(17,18,21)
5-FU	4	SNU-620-5FU, SNU-638-5FU SNU-668-5FU, SNU-719-5FU	(17)
Cisplatin	3	SNU-620-CIS, SNU-638-CIS, SNU-668-CIS	(17,20)

permanent cell lines from human cancers. Most of the SNU cancer cell lines developed were cultured initially in ACL-4 medium supplemented with 5% heat-inactivated FBS (AR5). ACL-4 is a fully defined medium, which was formulated for the selective growth of human lung adenocarcinoma cells, and which proved to be useful during the establishment of colorectal cancer cell lines. ACL-4 is a complex medium, and consists of 12 additives including basal medium (Table 7).

Human cancer cell lines can be established from ascitic effusions, metastatic tissues (regional lymph nodes and distant metastatic sites), and from primary tumors. The establishment of cell lines from ascitic effusions has proven to be more efficient than their establishment from primary tumors, because the cancer cells are rich, free-floating, and primed for in vitro growth. However, effusions usually contain mesothelial cells and lymphocytes. The former can attach more easily to flasks than cancer cells and generally survive for more than one year, whereas lymphocytes can inhibit cancer cell growth. Moreover, the enzymatic digestion of solid primary tumor tissues may result in the poor recovery of viable cells and in the overgrowth of the contaminating faster growing stromal cells. The mechanical spillout method provides a simpler, faster, and less traumatic method of obtaining cells for culture. This method minimizes stromal cell contamination, because stromal cells are not easily detached from tissue matrix by mechanical means.

Solid tumors (primary tumors and tumors in lymph nodes) must be carefully and aseptically excised from pathologically proven human cancer samples and transferred to a cell culture laboratory in RPMI1640 medium. Whenever possible, invasive

Table 3. Genetic alterations of genes in SNU cancer cell lines

Amplification of genes Cell lines	Genes	Status
SNU-16	*c-myc*	amplification [2]
SNU-16	*FGFR2* (*KSAM*)	amplification [92]
	FGFR2 and *FGFR4*	overexpression [112]

p53 gene Cell lines	Codon	n.t. change	a.a. change
SNU-5	262～269	24bp del	8 a.a del [132]
SNU-16	205	TAT to TTT	Tyr to Phe [132]
SNU-46	245	GGC to TGC	Gly to Cys [12]
SNU-61	175	CGC to CAC	Arg to His [6]
SNU-119	151	CCC to GCC	Pro to Ala [10]
	132	1bp del	frameshift [10]
SNU-182	215	AGT to ATT	Ser to Ile [152]
SNU-201	int 4, agTA to aaTA, splicing		variants [14]
SNU-213	175	CGC to CAC	Arg to His [16]
SNU-216	216	GTG to ATG	Val to Met [5]
SNU-251	255～256	3bp in frame del	[10]
SNU-267	219	1 bp del	frameshift [13]
SNU-354	72	CGC to CCC	Arg to Pro [152]
SNU-368	106	AGC to AGG	Ser to Arg [152]
SNU-387	164	AAG to TAG	Lys to Stop [152]
SNU-398	215	AGT to ATT	Ser to Ile [152]
SNU-423	intron5/exon5 junction,		AG to GG [152]
	inframe deletion, a.a. 126～132		[152]
SNU-444	275	TGT to TAT	Cys to Tyr [14]
SNU-449	138	AAG to AGG	Lys to Arg [152]
	161	GCC to ACC	Ala to Thr [152]
SNU-475	239	AAC to GAC	Asn to Asp [152]
	275	TGT to CGT	Cys to Arg [152]
	288	AAT to AGT	Asn to Ser [152]
SNU-478	266～267	insertion T	frameshift [15]
SNU-484	266	GGA to GAA	Gly to Glu [5]
SNU-494	238	TGT to TAT	Cys to Tyr [16]
SNU-503	273	CGT to CTT	Arg to Leu [6]
SNU-539	239	AAC to GAC	Asn to Asp [11]
SNU-563	282	CGG to GGG	Arg to Gly [10]
SNU-585	273	CGT to CTT	Arg to Leu [12]
SNU-601	273	CAT to CGT	Arg to Leu [5]
SNU-620	homozygous deletion of exon 5		[5]
SNU-626	77	CCA to CCG	Pro to Arg [14]
SNU-638	282	TGG to CGG	Trp to Arg [5]
SNU-668	215	AGT to AAT	Ser to Asn [5]
SNU-739	215	AGT to AGG	Ser to Arg [152]
SNU-761	313～323, 32bp del		frameshift [152]
SNU-869	48	GAC to GGT	Asp to Gly [15]
SNU-878	251	ATC to AAC	Ile to Asn [152]
SNU-886	219	CCC to CC	frameshift [152]
SNU-1033	190	CCT to CTT	Pro to Leu [6]
SNU-1040	248	CGG to TGG	Arg to Trp [6]
SNU-1047	254	ATC to ACC	Leu to Thr [6]
SNU-1066	46 bp del at exon 5		frameshift [12]

Table 3. Continued (1)

p53 gene Cell lines	Codon	n.t. change	a.a. change
SNU-1105	158	CGC to GGC	Arg to Gly [14]
SNU-1118	157	del 1 bp	frameshift [14]
SNU-1196	273	CGT to TGT	Arg to Cys [15]
SNU-1197	175	CGC to CAC	Arg to His [6]
SNU-C5	218		Val to Leu [62]
	248		Arg to Trp [62]

p16 gene Cell lines	Codon	n.t. change	a.a. change
SNU-46	106	CCC to CAC	Pro to His [12]
SNU-201	genomic deletion, exons 1～2		[14]
SNU-324	22	GCG to GTG	Ala to Val [16]
SNU-410	genomic deletion, exons 1～2		[16]
SNU-444	genomic deletion, exons 1～2		[14]
SNU-466	genomic deletion, exon 2		[14]
SNU-478	genomic deletion, exons 1～2		[15]
SNU-494	genomic deletion, exons 1～2		[16]
SNU-585	42	CAG to CGG	Gln to Arg [12]
	145	GAC to TAC	Asp to Tyr [12]
SNU-738	genomic deletion, exons 1～2		[14]
SNU-1066	84	1bp del	frameshift [12]
SNU-1076	106	CCC to CAC	Pro to His [12]
SNU-1079	genomic deletion, exons 1～2		[15]
SNU-1105	genomic deletion, exons 1～2		[14]
SNU-1196	genomic deletion, exons 1～2		[15]
SNU-1214	72	CGA to TGA	Arg to Stop [12]

VHL gene Cell lines	Codon	n.t. change	a.a. change
SNU-349	37	GCT to GCA	Ala to Ala [13]
	108	1bp del	frameshift [13]
SNU-1272	186	CAC to CAA	His to Gln [13]

p15 gene Cell lines	n.t. change
SNU-201	genomic deletion, exons 1～2 [14]
SNU-410	genomic deletion, exons 1～2 [16]
SNU-444	genomic deletion, exons 1～2 [14]
SNU-466	genomic deletion, exons 1～2 [14]
SNU-478	genomic deletion, exons 1～2 [15]
SNU-494	genomic deletion, exons 1～2 [16]
SNU-503	genomic deletion, exons 1～2 [6]
SNU-769A	genomic deletion, exons 1～2 [6]
SNU-1079	genomic deletion, exon 1 [15]
SNU-1105	genomic deletion, exons 1～2 [14]
SNU-1196	genomic deletion, exons 1～2 [15]

IGFIIR gene Cell lines	n.t. change	a.a. change
SNU-1047	-1/wt in poly G8 tract	frameshift [36]
SNU-C2A	-1/wt in poly G8 tract	frameshift [36]

Table 3. Continued (2)

PTEN gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-626	130	CGA to CAA	Arg to Gln [14]
SNU-1108	genomic deletion, exons 4～9 [14]		
hMSH2 gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-407	281	TCA to TGA	Ser to Stop [6]
SNU-769A	genomic deletion, exons 7～16 [6]		
SNU-769B	genomic deletion, exons 7～16 [6]		
SNU-1118	324	CAG to CAA	Gln to Gln [14]
hMLH1 gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-1	226	CGA to TGA	Arg to Stop [119]
SNU-251	723	GCC to GAC	Ala to Asp [10]
SNU-324	233	TGT to CGT	Cys to Arg [16]
	384	GTT to GAT	Val to Asp [16]
SNU-349	711	1bp deletion	frameshift [13]
SNU-478	384	GAT to GTT	Asp to Val [15]
SNU-482	376	GAT to GAC	Asp to Asp [13]
SNU-1040	725	CGC to TGC	Arg to Cys [6]
TGF-βRII			
Cell lines	Codon	n.t. change	a.a. change
SNU-1	-1/wt in poly A10 tract		frameshift [86]
SNU-46	+1/+1 in poly A10 tract		frameshift [12]
SNU-324	+1/-1 in poly A10 tract		frameshift [16]
SNU-333	389	AAC to AAT	Asn to Asn [13]
SNU-407	+1/-1 in poly A10 tract		frameshift [36]
SNU-410	genomic deletion [16]		
SNU-638	-1/-2 in poly A10 tract		frameshift [86]
SNU-769A	-2/-2 in poly A10 tract		frameshift [36]
SNU-769B	-1/-2 in poly A10 tract		frameshift [36]
SNU-899	389	AAC to AAT	Asn to Asn [12]
SNU-1047	-1/-1 in poly A10 tract		frameshift [36]
SNU-1066	409	TCT to TTT	Ser to Phe [12]
SNU-1214	389	AAC to AAT	Asn to Asn [12]
SNU-1272	121	TGC to CGC	Cys to Arg [13]
	389	AAC to AAT	Asn to Asn [13]
SNU-C4	-1/-1 in poly A10 tract		frameshfit [36]
BRCA1			
Cell lines	Codon	n.t. change	a.a. change
SNU-251	1815	TGG to TGA	Trp to Stop [10]
hMSH3 gene			
Cell lines	n.t. change		a.a. change
SNU-324	wt/-1 in poly A8 tract		frameshift [16]
SNU-349	wt/-1 in poly A8 tract		frameshift [13]

Table 3. Continued (3)

hMSH3 gene		
Cell lines	n.t. change	a.a. change
SNU-769A	-1/-1 in poly A8 tract	frameshift [36]
SNU-769B	-1/wt in poly A8 tract	frameshift [36]
SNU-1040	-1/wt in poly A8 tract	frameshift [36]
SNU-1047	-1/wt in poly A8 tract	frameshift [36]
SNU-C4	-1/-1 in poly A8 tract	frameshift [36]
BAX gene		
Cell lines	n.t. change	a.a. change
SNU-324	-1 in poly G8 tract	frameshift [16]
SNU-407	+1/-1 in poly G8 tract	frameshift [36]
SNU-769A	+1/-1 in poly G8 tract	frameshift [36]
SNU-769B	+1/-1 in poly G8 tract	frameshift [36]
SNU-1040	-1/wt in poly G8 tract	frameshift [36]
SNU-1047	-1/wt in poly G8 tract	frameshift [36]
SNU-C4	-1/-1 in poly G8 tract	frameshift [36]

APC gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-61	1450	CGA to TGA	Arg to Stop [6]
SNU-81	360	TTA to TGA	Leu to Stop [6]
SNU-769A	1462～1463, GA del		frameshift [6]
SNU-769B	1462～1463, GA del		frameshift [6]
SNU-1033	mutant, confirmed only by PTT [6]		
SNU-1040	360	TTA to TGA	Leu to Stop [6]
SNU-1047	1369	1bp del	frameshift [6]
SNU-1197	mutant, confirmed only by PTT assay [6]		

K-ras gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-61	12	GGT to GAT	Gly to Asp [6]
SNU-175	59	GCA to ACA	Ala to Thr [6]
SNU-213	12	GGT to GTT	Gly to Val [16]
SNU-407	12	GGT to GAT	Gly to Asp [6]
SNU-410	12	GGT to GTT	Gly to Val [16]
SNU-494	12	GGT to GTT	Gly to Val [16]
SNU-601	12	GGT to GAT	Gly to Asp [5]
SNU-668	61	CAA to AAA	Gln to Lys [5]
SNU-1033	12	GGT to GAT	Gly to Asp [6]
SNU-1197	12	GGT to GAT	Gly to Asp [6]

β-catenin gene			
Cell lines	Codon	n.t. change	a.a. change
SNU-407	41	ACC to GCC	Thr to Ala [6]
SNU-1047	45	TCT to TTT	Ser to Phe [6]
SNU-601	int2, splice acceptor site, 343 bp del [148]		
SNU-638	41	ACC to GCC	Thr to Ala [148]
SNU-719	34	GGA to GTA	Gly to Val [148]

Table 3. Continued (4)

Microsatellite instability Cell lines	Microsatellite markers
SNU-1	BAT-25 and BAT-26 [36,86]
SNU-638	BAT-26 [86]
SNU-175	BAT-25 and BAT-26 [36]
SNU-324	BAT-25 and BAT-26 [16]
SNU-349	BAT-25 and BAT-26 [13]
SNU-407	BAT-25 and BAT-26 [36]
SNU-769A	BAT-25 and BAT-26 [36]
SNU-769B	BAT-25 and BAT-26 [36]
SNU-1040	BAT-25 and BAT-26 [36]
SNU-1047	BAT-25 and BAT-26 [36]
SNU-C2A	BAT-25 and BAT-26 [36]
SNU-C4	BAT-25 and BAT-26 [36]

del=deletion; n.t.=nucleotide; a.a.=aminoacid; frameshift, results in stop codon and truncated protein.

Table 4. Epigenetic alterations of genes in SNU cancer cell lines

p16 gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [106]
SNU-61	no protein	hypermethylation [6]
SNU-81	no protein	hypermethylation [6]
SNU-601	no mRNA	hypermethylation [106]
SNU-620	no mRNA	hypermethylation [106]
SNU-638	no mRNA	hypermethylation [106]
SNU-719	no mRNA	hypermethylation [106]
SNU-1197	no protein	hypermethylation [6]
COX-2 gene Cell lines	Expression	Promoter status
SNU-601	no mRNA	hypermethylation [105]
SNU-620	no mRNA	hypermethylation [105]
SNU-719	no mRNA	hypermethylation [105]
RUNX3 gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [151]
SNU-61	no mRNA	no hypermethylation [35]
SNU-81	no mRNA	hypermethylation [35]
SNU-175	no mRNA	no hypermethylation [35]
SNU-769A	no mRNA	no hypermethylation [35]
SNU-769B	no mRNA	no hypermethylation [35]
SNU-1047	no mRNA	hypermethylation [35]
SNU-C5	no mRNA	hypermethylation [35]
DLC-1 gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [103]
SNU-16	no mRNA	hypermethylation [103]

Table 4. Continued (1)

DLC-1 gene Cell lines	Expression	Promoter status
SNU-601	no mRNA	hypermethylation [103]
SNU-620	no mRNA	hypermethylation [103]
SNU-719	no mRNA	hypermethylation [103]
Integrin α4 gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [104]
SNU-5	no mRNA	hypermethylation [104]
SNU-601	no mRNA	hypermethylation [104]
SNU-638	no mRNA	hypermethylation [104]
SNU-668	no mRNA	hypermethylation [104]
SNU-719	no mRNA	hypermethylation [104]
AKAP12A gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [100]
SNU-16	no mRNA	hypermethylation [100]
SNU-601	no mRNA	hypermethylation [100]
SNU-620	no mRNA	hypermethylation [100]
SNU-638	no mRNA	hypermethylation [100]
SNU-719	no mRNA	hypermethylation [100]
AKAP12B gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [100]
SNU-484	no mRNA	hypermethylation [100]
SNU-601	no mRNA	hypermethylation [100]
SNU-620	no mRNA	hypermethylation [100]
SNU-719	no mRNA	hypermethylation [100]
E-cadherin gene Cell lines	Expression	Promoter status
SNU-1	no mRNA	hypermethylation [101]
SNU-478	no mRNA	hypermethylation [15]
SNU-1079	no mRNA	hypermethylation [15]

areas from the serosal surface should be selected for primary tumor cultures, to reduce the possibility of microbial contamination. The RPMI1640 medium used to transport the specimen should contain antibiotics, such as penicillin-streptomycin, to prevent bacterial contamination, and ascitic effusions should be collected in sterile glass bottles or syringes. Heparin (5 ug/ml) may be added to collected fluids to prevent clotting, if the effusions contain many erythrocytes. Cancer cells can grow either as floating aggregates, firmly, as loosely adherent colonies, or as both adherent and floating subpopulations. If cancer cells are adherent or grow as floating aggregates, the medium is changed

Table 5. Expression alterations of genes in SNU cancer cell lines

hMLH1 gene	
Cell lines	Expression status
SNU-1	no protein expression [119]
SNU-216	no protein expression [119]
SNU-484	no protein expression [119]
SNU-520	no protein expression [119]
SNU-638	no protein expression [119]
SNU-668	no protein expression [119]
TGF-βRII gene	
Cell lines	Expression status
SNU-1	no expression [87]
SNU-5	truncated [87]
SNU-16	expression [87]
SNU-484	no expression [87]
SNU-601	overexpression [87]
SNU-638	no expression [87]
SNU-668	truncated [87]
SNU-719	overexpression [87]
Smad 3 gene	
Cell lines	Expression status
SNU-1	low to undetectable [150]
SNU-484	low to undetectable [150]
MDR1 gene	
Cell lines	Expression status
SNU-354	overexpression [43]
SNU-368	overexpression [43]
SNU-C4	overexpression [45]
DCC gene	
Cell lines	Expression status
SNU-201	no mRNA [14]
SNU-466	no mRNA [14]
SNU-489	no mRNA [14]
SNU-626	no mRNA [14]
SNU-738	no mRNA [14]
SNU-791	no mRNA [14]
SNU-1118	no mRNA [14]

Table 6. Virus infection in SNU cell lines

Hepatitis B virus

Cell lines	Virus	Status
SNU-182	HBV	integration [3]
SNU-387	HBV	integration [3]
SNU-398	HBV	integration [3]
SNU-354	HBV	integration, HBVX transcripts [3]
SNU-368	HBV	integration, HBVX transcripts [3]
SNU-449	HBV	integration [3]
SNU-475	HBV	integration [3]
SNU-739	HBV	integration [7]
SNU-761	HBV	integration [7]
SNU-878	HBV	integration [7]
SNU-886	HBV	integration [7]

Human papilloma virus

Cell lines	Virus	Status
SNU-17	HPV16	integration [8]
SNU-487	HPV18	integration [8]
SNU-523	HPV16	episome [8]
SNU-682	HPV33 [8]	
SNU-703	HPV16	integration [8]
SNU-778	HPV31 [8]	
SNU-902	HPV16	integration [8]
SNU-1000	HPV16	integration and episome [8]
SNU-1005	HPV16	integration [8]
SNU-1160	HPV18	integration [8]
SNU-1245	HPV18	episome [8]
SNU-1299	HPV16	integration [8]

Epstein-Barr virus

Cell lines	Virus	Status
SNU-20	EBV	B lymphoblastoid cell line [9]
SNU-99	EBV	B lymphoblastoid cell line [9]
SNU-247	EBV	B lymphoblastoid cell line [9]
SNU-265	EBV	B lymphoblastoid cell line [9]
SNU-285	EBV	B lymphoblastoid cell line [9]
SNU-291	EBV	B lymphoblastoid cell line [9]
SNU-299	EBV	B lymphoblastoid cell line [9]
SNU-315	EBV	B lymphoblastoid cell line [9]
SNU-374	EBV	B lymphoblastoid cell line [9]
SNU-445	EBV	B lymphoblastoid cell line [9]
SNU-447	EBV	B lymphoblastoid cell line [9]
SNU-538	EBV	B lymphoblastoid cell line [9]
SNU-719	EBV	gastric cancer cell line [149]
SNU-817	EBV	B lymphoblastoid cell line [9]
SNU-889	EBV	B lymphoblastoid cell line [9]
SNU-1103	EBV	B lymphoblastoid cell line [9]

weekly until a substantial outgrowth of cells is observed. Cancer cells are isolated when heavy tumor-cell growth is observed. The key features for successful culture are as follows: 1) nonenzymatic or minimal dissociation of tumor tissue; 2) seeding cultures as explants and at high cell densities; 3) the removal of contaminating fibroblasts, usually after they have aided culture initiation; 4) delaying passage until high cell densities have been achieved and 5) plating cells at high density.

Several methods can be employed to isolate pure cancer cells. After establishing cancer cell lines, initial passages are performed when heavy tumor-cell growth and large colonies are observed. Subsequent passages are performed 1 or 2 weekly. ACL-4 medium supplemented with heat inactivated 5% FBS, which is used in primary cell culture can be also used to propagate cancer cell lines. This medium must be used until the isolated cancer cells are considered a cell line. It is recommend

that early passages, whenever passaged, are frozen in cryoprotective medium to prevent loss of the cell lines due to contamination or other laboratory accidents. After cells have been fully established, AR-5 medium can be replaced with RPMI 1640 medium supplemented with 10% heat inactivated FBS (Fig. 1). The growth characteristics of some cultured SNU cell lines are shown in Fig. 2.

CHARACTERISTICS OF SNU CANCER CELL LINES

1) SNU colorectal cancer cell lines

SNU colorectal carcinoma cell lines have become items in the research field (22,26～44). Seventeen cell lines (SNU-C1, SNU-C2A, SNU-C2B, SNU-C4, SNU-C5, SNU-61, SNU-81, SNU-175, SNU-283, SNU-407, SNU-503, SNU-769A, SNU-769B, SNU-1033, SNU-1040, SNU-1047, and SNU-1197) have now been established and characterized (4,6). These cell lines have been used for many research purposes, including, multidrug resistance (45) and anticancer drug screening (29,30,38,42, 46～54), and in investigations into microsatellite instability (36, 55), CEA expression (37), mutations in mismatch repair genes (6), the TGF-β signaling pathway (36), and many others (56～61).

The resistance of cultured cells to drugs, such as, the vinca alkaloids and the anthracyclins is frequently due to the expression of P-glycoprotein, which is encoded by the *MDR1* gene in humans. P-glycoprotein functions as an energy-dependent drug efflux pump. In SNU gastric and colorectal cancer cell lines, using a slot blot assay, relatively low levels of *MDR1* RNA were found to be present in the SNU-1, SNU-5, and SNU-16 gastric cancer cell lines, whereas high levels were found in the SNU-C4 colorectal carcinoma cell line (45).

Rand *et al.* (62) found two missense mutations of the p53 gene in the SNU-C5 colorectal carcinoma cell line, and identified two mutations located at codons 218 and 248 of separate alleles. SNU-C5 cells exhibited complete loss of normal p*53*

Table 7. Composition of media for primary cell culture

RPMI 1640 medium:	RPMI1640 powder, 25 mM HEPES buffer, 20 mM sodium bicarbonate, antibiotics (streptomycin-penicillin, usually 100 units/ml), filter through 0.22μm bottle top filter
ACL-4 medium:	RPMI1640 as basal medium, 20 ug/ml insulin, 10 ug/ml transferrin, 25 nM sodium selenite, 50 nM hydrocortisone, 1 ng/ml epidermal growth factor, 10 uM ethanolamine, 10 uM phosphorylethanolamine, 100 pM triiodothyrosine, 2 mg/ml bovine serum albumin, 2 mM glutamine, 0.5 mM sodium pyruvate
Initiation and growth medium (AR-5 medium):	ACL-4 medium supplemented with 5% heat-inactivated FBS

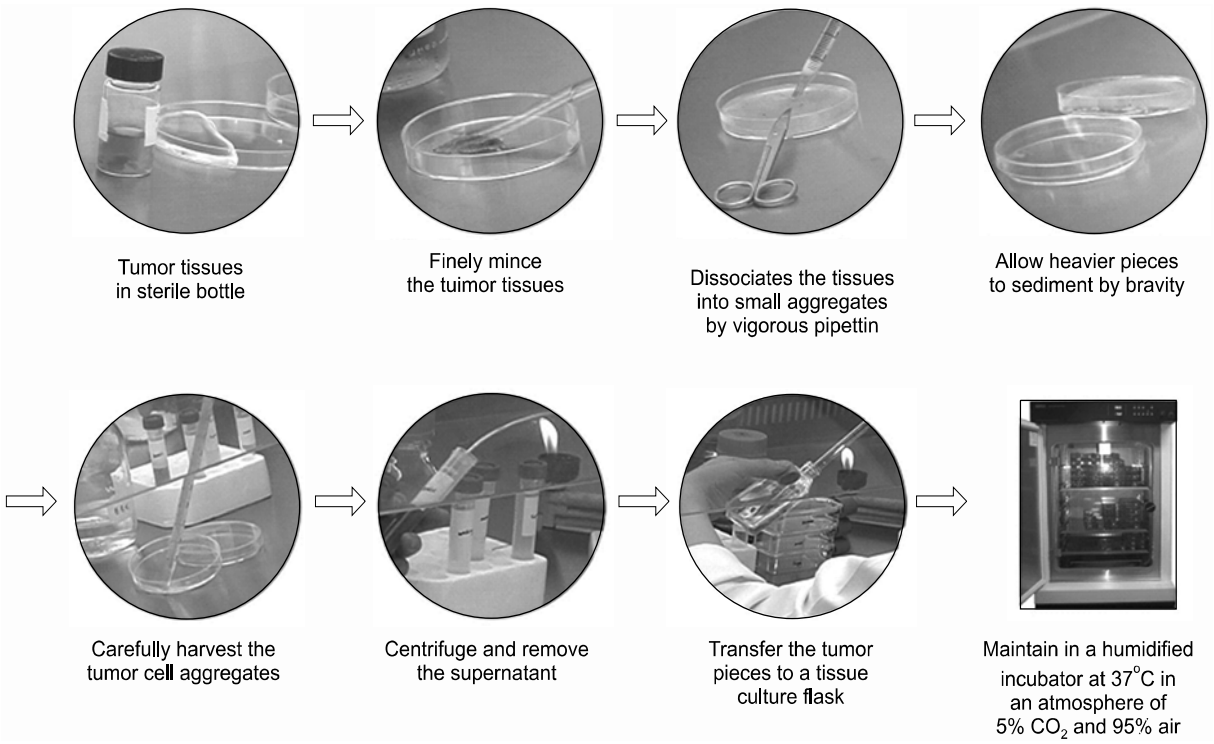

Fig. 1. Procedure for the establishment of cancer cell lines.

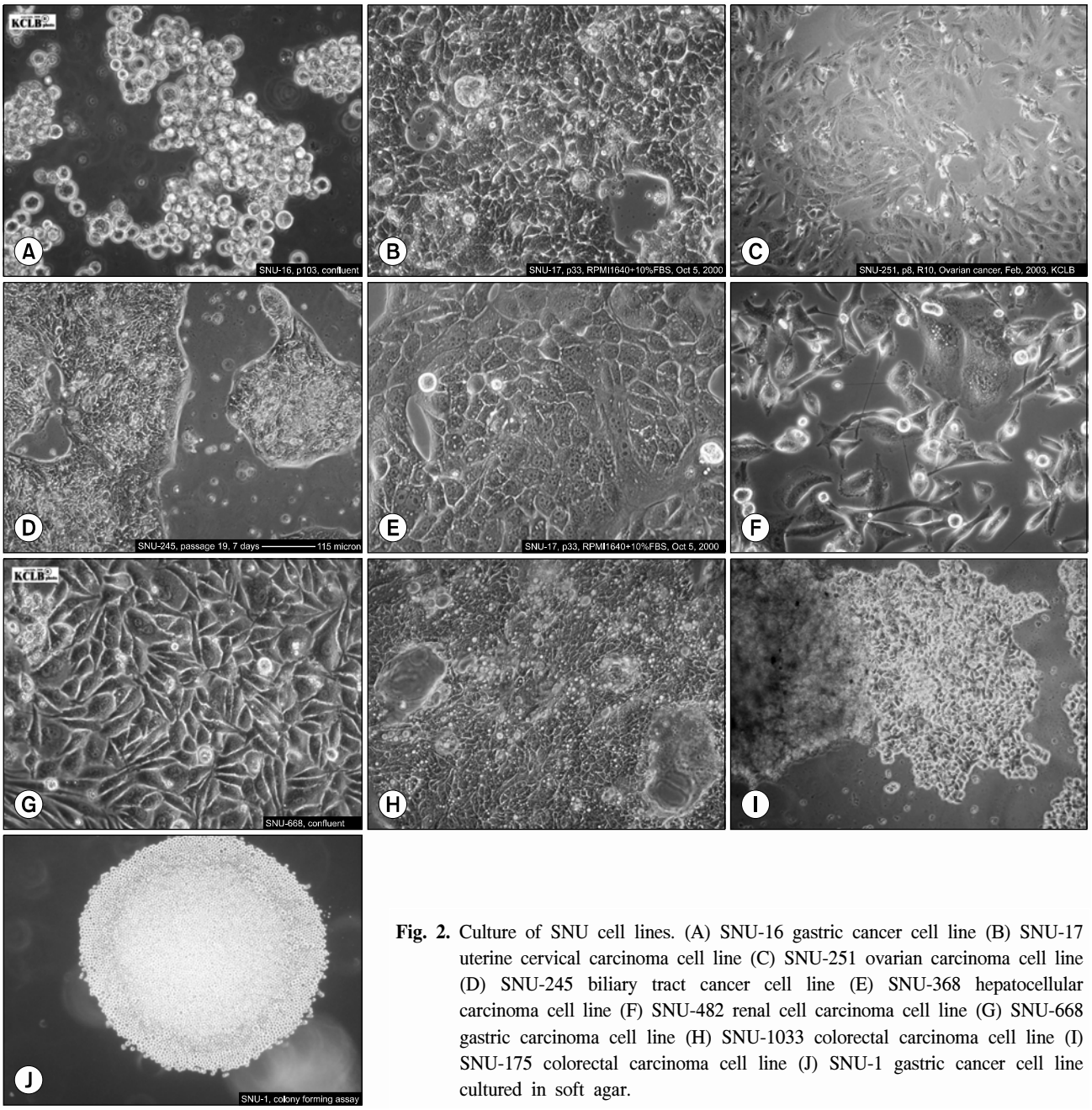

Fig. 2. Culture of SNU cell lines. (A) SNU-16 gastric cancer cell line (B) SNU-17 uterine cervical carcinoma cell line (C) SNU-251 ovarian carcinoma cell line (D) SNU-245 biliary tract cancer cell line (E) SNU-368 hepatocellular carcinoma cell line (F) SNU-482 renal cell carcinoma cell line (G) SNU-668 gastric carcinoma cell line (H) SNU-1033 colorectal carcinoma cell line (I) SNU-175 colorectal carcinoma cell line (J) SNU-1 gastric cancer cell line cultured in soft agar.

function, as evidenced by the overexpression of p53 and its by the failure to induce p53, p21, and mdm-2 in response to DNA damaging agents.

In 1999, we reported upon 12 new colorectal carcinoma cell lines derived from 6 primary tumors and 6 metastatic sites in 11 Korean colorectal-carcinoma patients, their morphologies *in vivo* and *in vitro* were described as were mutations of *K-ras2, p15, p16, p53, APC,β-catenin, hMLH1,* and *hMSH2* genes in vitro (6). All 12 lines were found to express surface carcinoembryonic antigen and to secrete it into the supernatant fluid. Morphological correlations between the original tumors and cultured cells suggested that mucinous adenocarcinoma correlated with floating aggregates in culture, and that the degree of desmoplasia in the original tumor correlated with attached growth in culture. Five of the 12 cell lines showed mutations in the *K-ras2* gene, and 6 lines showed mutations in the *p53* gene. The *p15* gene was deleted in 2 cell lines, and the *p16* gene was hypermethylated in 3 cell lines. Moreover, mutations of the mismatch-repair genes (*hMLH1* and *hMSH2*) were found in 4 cell lines, and the *APC* and*β-catenin* genes were mutated in 9 and 2 lines, respectively.

Using these newly developed colorectal carcinoma cell lines, we assayed mutations in the mononucleotide repeat tract in the coding region of the *TGF-β RII* gene. Four lines were found

to contain deletion or insertion mutations in the 10 base pair adenine repeat tracts. These 4 lines also showed microsatellite instability (36).

A RT-PCR analysis of *FGFR3* from human colorectal carcinomas revealed novel mutant transcripts caused by aberrant splicing and by the activation of cryptic splice sequences. Two aberrantly spliced transcripts were detected at high frequency in 50% of 36 primary tumors and in 60% of 10 human colorectal cancer cell lines. Most transcripts used normal splice sites and either skipped or included exons 8 and 9. The predicted translation products are expected to exhibit frameshifts and a premature termination codon in exon 10 (63).

Promoter hypermethylation of the *RUNX3* gene was investigated in 16 SNU colorectal cancer cell lines. *RUNX3* is not expressed in SNU-61, SNU-81, SNU-175, SNU-769A, SNU-769B, SNU-1047, or SNU-C5 cell lines. Using primers for methylated DNA amplification on bisulfite modified DNA, DNA fragments were amplified from SNU-81, SNU-1047, and SNU-C5 cell lines. In all these cell lines, the 24 individual CpG sites (located between -270 and -121, relative to the transcription initiation site of exon 1 of *RUNX3*) were found to be fully methylated. In four SNU cell lines (SNU-61, SNU-175, SNU-769A, and SNU-769B cell lines), which did not express RUNX3 mRNA, bisulfite PCR products were not amplified by methylated DNA-specific PCR. *RUNX3* mRNA was re-expressed in SNU-81, SNU-1047, and SNU-C5 cell lines after treating them with the demethylating agent, 5-aza-2'-deoxycytidine (35).

2) SNU gastric carcinoma cell lines

In general, gastric carcinoma cell lines have proven to be more difficult to establish in long-term culture than esophageal or colorectal-carcinoma cell lines (25). A total of 11 gastric carcinoma cell lines (SNU-1, SNU-5, SNU-16, SNU-216, SNU-484, SNU-520, SNU-601, SNU-620, SNU-638, SNU-668, and SNU-719 cell lines) have been established and reported (2,5). SNU gastric carcinoma cell lines are among the most popular in use today. These cell lines have been used in various research fields including multidrug resistance (43,45), anticancer drug screening (47,51,64～81), the establishment and characterization of anticancer drug resistant gastric cancer cell lines (17,18,20,21,82), TGF-β signaling pathway (68,83～91), gene amplification (92～98), telomerase assays (21,99), methylation studies (100～107), cytogenetic studies (108～110), the mutational and expression analysis of FGF receptors (111,112), responsiveness of gastric cancer cells after *Helicobacter pylori* infection (113～117), studies on mismatch repair genes (118, 119), mechanism of apoptosis (71,72,120～124), invasion assays of gastric cancer cells (125～130), mutational analysis of genes (131～135), cDNA and oligonucleotide microarrays (17, 131,136～138), proteomic analysis in gastric cancer cell lines (20), and in other studies (139～144).

SNU-16 line has been used as source of amplified DNA sequences (92～96). This line was amplified for the *c-myc* protooncogene and found to contain four homogeneously staining regions (HSR). c-myc was found to be amplified 50-fold more than in other cell lines (2) and *FGFR2* (KSAM) was amplified in extrachromosomal double minute chromosomes (DMS) (92). Fibroblast growth factor (FGF) is fundamentally involved in embryonic development, angiogenesis, and tumorigenesis, and Shin *et al.* (112) found fibroblast growth factor receptors -2, -3 and 4 were amplified and *FGFR2* and *4* were overexpressed in the SNU-16 gastric cancer cell line. They also found that acidic FGF, keratinocyte growth factor (KGF) treatment enhanced the invasive potential of SNU-16 cells versus a control cell line.

Park *et al.* (87) found several genetic changes in *TGF-βRII* in SNU gastric carcinoma cell lines resistant to the growth inhibitory effect of TGF-β. This was the first report that TGF-β resistance to cancer cells is associated with genetic changes in the *TGF-βRII* gene in human gastric carcinoma cell lines. The cell lines SNU-1, SNU-5, and SNU-719 resistant to TGF-β showed no expression or overexpression of the *TGF-βRII* gene.

Myeroff *et al.* (86) also reported that mutations in the 10 base pair polyadenine repeat tract (BAT-RII) of the *TGF-βRII* gene are common in gastric cancer, and demonstrated microsatellite instability using the SNU gastric carcinoma cell lines Concerning the SNU gastric carcinoma cell lines, mutations have been found in BAT-RII of the *TGF-βRII* gene in SNU-1 and SNU-668. SNU-638 gastric carcinoma cell line showed microsatellite instability (MSI) and frameshift mutations in BAT-RII of the *TGF-βRII* gene (83). The wild type *TGF-βRII* transfected SNU-638 cell line responded to TGF-β and tumorigenicity was reduced and delayed when it was transplanted into nude mice. These results suggest a strong association between the expression of wild type *TGF-βRII* and the degree of malignancy of human gastric cancer cells.

It is known that MutL proteins form the MutL-alpha complex, *hPMS2* and *hMLH1*. Using the SNU-1 cell line, which lacks *hMLH1*, Leung *et al.* (145) proved the existence of other MutL protein, namely, the MutL-beta complex, *hPMS1* and *hMLH1*. Moreover, in the SNU-1 cell line, these workers found that lower levels of *hMLH1* were associated with markedly lower levels of *hPMS2* and *hPMS1* proteins, but that the RNA levels of *hPMS1* and *hPMS2* were normal. They found that *hPMS2* and *hPMS1* are present in the cells bound to *hMLH1*, but that *hPMS1* and *hPMS2* do not associate with each other.

SNU-gastric carcinoma cell lines have also been used in a *Helicobacter pylori* studies (113-117). After infection with *H. pylori*, SNU-5 expressed several cytokines, including, interleukins, GM-CSF, MCP-1, and TNF-alpha. *H. pylori* infection of SNU-5 up-regulated the mRNA and protein levels of *COX-2* and stimulated the release of PGE2.

The overexpression of cyclooxygenase-2 has been reported in gastric cancer. However, Yamamoto *et al.* (146) found that SNU-1 (a gastric carcinoma cell line which is MSI and *hMLH1* defective) lacks *COX-2* expression, and that after treatment with aspirin or sulindac the MSI phenotype was reduced.

Grady *et al.* (101) found that several hereditary gastric cancers with germline mutation in the *E-cadherin* gene have no LOH or somatic mutation. These cancers with germline mutation do not express the *E-cadherin* gene and the promoter region of the *E-cadherin* gene proved to be methylated. Therefore, it was concluded that *E-cadherin* gene promoter methylation acts as a second genetic hit in hereditary gastric cancer. In this study SNU-1 was used as control cell line for *E-cadherin* promoter methylation. The *E-cadherin* promoter in SNU-1 proved to be methylated, and after treatment with the demethylating agent 5-aza-2'-deoxycytidine, *E-cadherin* expres-

sion was restored.

To investigate the genetic changes that occurred during the establishment of the 4 SNU gastric cancer cell lines, Bae *et al.* (147) examined microsatellite instability, loss of heterozygosity, and *p53* mutation. They found that MSI, LOH, and *p53* gene mutations were sustained during the establishment of the gastric cancer cell lines, and they suggested that minor genetic differences between original tumor tissues and the cancer cell lines could be attributed to tumor heterogeneity, because portions of the original tumor tissues showed similar variations

Fukuda *et al.* (109) examined 25 gastric cancer cell lines, including SNU cell lines, to detect aberrations in the DNA copy number used to identify chromosomal gains and losses, and investigated amplifications by comparative Genomic hybridization (CGH). Amplification within 11p13, which bears the *CD44* gene, was found in HSC series cell lines of Japanese origin. However, no such amplification was found in SNU gastric cancer cell lines, in which amplification within 8q was frequently observed.

β-catenin is a key molecule in Wnt/wingless signal transduction and in the *E-cadherin* pathway. Altered expression and mutations of the β-*catenin* gene have been identified in a number of human malignancies. Woo *et al.* (148) identified mutations of the β-*catenin* gene in three (SNU-601, SNU-638, and SNU-719) of the 11 SNU gastric cancer cell lines. Interestingly, β-catenin protein in these three cell lines was located in the cell nucleus, which suggests that β-catenin protein in these three cell lines is complexed with Tcf/lef and translocated to the nucleus from the cytoplasm.

Oh *et al.* (149) recently found that a naturally derived SNU-719 gastric cancer cell line is infected with type I Epstein-Barr Virus (EBV). EBNA1 and LMP2A were expressed, while LMP1 and EBNA2 are not expressed in this line. EBV infection was also shown in the original carcinoma tissue of this cell line. These findings suggest that SNU-719 cell line may serve as a valuable model system to clarify the precise role of EBV in gastric carcinogenesis.

Many chemotherapeutic agents have been used to treat gastric cancer patients, but the emergence of drug resistance has prevented successful treatment in many cases. The two major forms of drug resistance are intrinsic resistance, in which previously untreated tumor cells are inherently insensitive to the chemotherapeutic agent, and acquired resistance, in which treated tumor cells become insensitive after drug exposure. Our laboratory has developed anticancer drug resistant cell lines from SNU-620, SNU638, SNU-668, and SNU-719 gastric cancer cell lines, namely, four 5-FU-resistant gastric cancer cell lines (SNU-620-5FU, SNU-638-5FU, SNU-668-5FU, and SNU-719-5FU), 5 doxorubicin-resistant cell lines (SNU-1-DOX, SNU-16-DOX, SNU-620-DOX, SNU-668-DOX, and SNU-719-DOX), and 3 cisplatin-resistant cell lines (SNU-620-CIS, SNU-638-CIS, and SNU-668-CIS) (Table 3).

Kang *et al.* (17) performed global gene expression analysis in these acquired drug-resistant gastric cancer cell lines using an Affymetrix HG-U133A microarray after exposing them to the commonly used drugs 5-fluorouracil, doxorubicin, or cisplatin. They identified over 250 genes differentially expressed in these 5-fluorouracil-, cisplatin-, or doxorubicin-resistant gastric cancer cell lines. Expression analysis also identified eight multidrug resistance candidate genes that were associated with resistance to two or more of the chemotherapeutics tested. This investigation provided comprehensive gene information upon acquired resistance to anticancer drugs in gastric cancer cells and a basis for additional functional studies.

Comparative proteomics involving 2-dimensional gel electrophoresis (2-DE) and matrix-associated laser desorption ionization-mass spectroscopy (MALDI-MS) was performed by Yoo *et al.* on protein extracts from SNU-620 and SNU-638 gastric cancer cell lines and drug-resistant derivative lines to screen for drug resistance-related proteins (20). Pyruvate kinase M2 (PK-M2) was identified as a protein with lower expression in cisplatin-resistant cells than in parental cells. They also found that PK-M2 activity in 11 individual human gastric carcinoma cell lines was positively correlated with cisplatin sensitivity, and concluded that PK-M2 protein and activity levels are lower in cisplatin-resistant human gastric carcinoma cell lines than in their corresponding parental cell lines.

Han *et al.* (150) observed that *Smad3* was expressed at low to undetectable levels in SNU-1 and SNU-484 cell lines, and that it was detected in SNU-5, SNU-16, SNU-601, SNU-620, SNU-636, SNU-668 and SNU-719 cell lines. They found that the introduction of *Smad3* into the SNU-484 cell line restored TGF-β responsiveness, the induction of p21 and p15 gene expression, and the growth inhibition response to TGF-β. They also observed that Smad3-expressing cells showed markedly lower and delayed tumorigenicity in vivo.

The aberrant methylation of normally unmethylated CpG islands located in the 5' promoter region of genes is associated with transcriptional inactivation, which is as effective as inactivation by gene mutation or deletion. The aberrant methylation status of some genes was examined in SNU gastric cancer cell lines. Song *et al.* (106) found that the *p16* gene was not expressed mRNA and that CpG islands of the promoter region of this gene were hypermethylated in SNU-1, SNU-601, SNU-620, SNU-638, and SNU-719 cell lines. They also found that *COX-2* was not expressed and was hypermethylated in SNU-601, SNU-620, and SNU-719 cell lines (105). CpG islands of the promoter region of the *RUNX3* gene were found to be hypermethylated in SNU-1 and unmethylated in SNU-5, SNU-16, and SNU-719 cell lines (151). *DLC-1* was completely methylated in SNU-1, SNU-16, SNU-601, and SNU-791 cell lines, and partially methylated in SNU-620 cell line (103). Moreover, *Integrinα4* was found to be unmethylated in SNU-484, partially methylated in SNU-668, and completely methylated in SNU-1, SNU-5, SNU-601, SNU-638, and SNU-719 (104). Choi *et al.* (100) recently reported that *AKAP12A* is completely methylated in SNU-1, SNU-601, and SNU-638 and partially methylated in SNU-16, SNU-620, and SNU-719, and that *AKAP12B* is completely methylated in SNU-1, SNU-484, SNU-620, and SNU-719 and partially methylated in SNU-601.

3) SNU hepatocellular carcinoma cell lines

SNU hepatocellular carcinoma cell lines have proven to be of value in carcinogenic studies associated with hepatocellular carcinogenesis and hepatitis B virus X (43,152,153). Our laboratory has developed and reported upon 12 hepatocellular carcinoma cell lines (SNU-182, SNU-354, SNU-368, SNU-387,

SNU-398, SNU-423, SNU-449, SNU-475, SNU-739, SNU-761, SNU-878, and SNU-886) (3,7). At present, these cell lines have been widely used to investigate HBV expression, IGF expression (153), and methylation status of genes (154,155), and other issues (51,155～166) in hepatocellular carcinogenesis.

Two SNU hepatocellular carcinoma cell lines SNU-354 and SNU-354 have been shown to express hepatitis B virus and HBV X transcripts (3). These cell lines have been used widely in the study of hepatocellular carcinogenesis and hepatitis B virus. SNU-354 and SNU-368 hepatocellular carcinoma cell lines have been found to express high levels of the *MDR1* gene (43).

The hepatocellular carcinoma cell line, SNU-368, has already been shown to express hepatitis B virus X antigen, and Lee *et al* (167) reported that the expression of HBX is induced by hypoxia in SNU-368 cells. These workers also found that HBX stimulates the transcription of vascular endothelial growth factor (*VEGF* mRNA), a potent angiogenic factor in hypoxia, which suggests that HBX may play a critical role in hypoxia induced angiogenesis through the transcriptional activation of *VEGF* during hepatocarcinogenesis.

The integration statuses of the hepatitis B virus (HBV) into the human telomerase reverse transcriptase (*hTERT*) gene in five SNU HBV-positive hepatocellular carcinoma cell lines (SNU-387, SNU-387, SNU-423, SNU-449, and SNU-475) were investigated. In SNU-449, the 1452bp initial RS (restriction site)-PCR product containing the HBV/cellular DNA junction sequence had a HBV sequence of 815bp joined to a 637bp sequence from intron 3 of the *hTERT* gene. An analysis of the sequence of the entire HBV integration with flanking human host sequences revealed a 5bp deletion in *hTERT* intron 3. Moreover, *hTERT* mRNA expression was upregulated in SNU-449 versus benign liver tissue. This work suggests that the sites of oncogenic viral integration are nonrandom and that genes at the sites of viral integration may play important roles in carcinogenesis (168).

Park *et al.* (163) recently found that TGF-β treatment significantly enhances the viability of SNU-354, SNU-475, and SNU-449 cell lines, and they showed that these cell lines retain high endogenous *c-Src* activity. Moreover, SNU-449 cell line demonstrates an elevated *c-Src* activity despite its relatively low *c-Src* protein level. These results indicate the possibility that the responsiveness of hepatocellular carcinoma cells to the growth inhibitory effects of TGF-β1 may be controlled by *c-Src* activity.

4) SNU uterine cervical carcinoma cell lines

We have developed and reported upon 12 uterine cervical carcinoma cell lines (SNU-17, SNU-487, SNU-523, SNU-682, SNU-703, SNU-778, SNU-902, SNU-1000, SNU-1005, SNU-1160, SNU-1245, and SNU-1299) (8). These 12 carcinoma cell lines of the human uterine cervix were established from 5 keratinizing and 5 nonkeratinizing squamous-cell carcinomas, and 2 small-cell carcinomas. Ten of these cell lines grow as adherent cells and 2 as floating aggregates. All 12 SNU uterine cervical carcinoma cell lines are infected by human papilloma virus (HPV), seven by HPV-16, three by HPV-18, one by HPV-31, and one by HPV-33. Interestingly, 6 of the 7 cell lines containing HPV-16-type DNA harbor the same alteration of E7 at nucleotide position 647 (amino acid 29, AAT→AGT, Asn→Ser), whereas the 3 HPV-18-positive lines do not. Theses 3 cell lines have been proven to contain intact E1/E2 of HPV, suggesting the presence of episomally replicating HPV DNA as well as the integrated form, whereas the other 9 lines have been shown to have integrated HPV. Most of the HPVs are integrated into the genome of the cells. Episomally replicating HPV infected uterine cervical carcinoma cell lines are rare, but the SNU-1000 cell line contains the episomal form and the non-episomal form of HPV. These SNU uterine carcinoma cell lines have also been used in carcinogenesis studies associated with cervical carcinogenesis and human papilloma virus.

BPV1 E2 was expressed in SNU-17, SNU-902, and SNU-1299 cell lines after the acute infection of an SV40-BPV1 recombinant virus. EPV1 E2 expression caused a significant decrease in E6/E7 transcription in these cell lines, which was accompanied by an increase in the level and activity of p53 protein and a decrease in the expression of Cdc25A, a Cdk2-activating phosphatase; moreover, E2F1 activity and cellular DNA synthesis capacity were significantly reduced. These results indicate that the inhibition of E6/E7 gene expression in HPV16-positive cervical carcinoma cells suppresses cell proliferation by activating the growth inhibitory factors p53 and Rb, and also by downregulating the cell cycle stimulatory factor Cdc25A (169).

5) SNU ovarian carcinoma cell lines

In 1997, we reported upon five human ovarian carcinoma cell lines (SNU-8, SNU-119, SNU-251, SNU-563 and SNU-840) (10). Of these, SNU-251 harbors mutations in p53, *BRCA1,* and *hMLH1*. Of these five cell lines, we consider that SNU-251 is both unique and valuable. This cell line has a nonsense mutation in the *BRCA1* gene at codon 1815 in exon 23, which results in a truncated protein. It is the only reported ovarian carcinoma cell line with a nonsense mutation in this gene. SNU-251 has proven valuable in studies of the function of *BRCA1* (170～174).

The role of *BRCA1* in the development of ovarian cancer is poorly understood, partially owing to a lack of ovarian cancer cell lines with defective *BRCA1*. Zhou *et al.* (171) recently further characterized the SNU-251 cell line to determine the role of *BRCA1* in resistance to both ionizing radiation and paclitaxel. The *BRCA1* mutation in the SNU-251 cell line is predicted to cause the loss of the C-terminal 49 amino acids of *BRCA1* protein, which contains the second half of BRCT (the BRCA1 C-terminal) repeat. Western blot analysis detected a 210-KDa *BRCA1* protein and a high mutant p53 protein expression level in SNU-251 cell line. This mutation of *BRCA1* caused a loss of the transcriptional activation of the endogenous p21 gene, and prevented sustained arrest in the G2/M phase of the cell cycle. Moreover, the *BRCA1* mutation inhibited *BRCA1* subnuclear assembly for DNA-damage repair and increased cellular sensitivity to ionizing radiation and paclitaxel. These results suggest that the deletion of the C-terminal 49 amino acids of *BRCA1* results in a loss of *BRCA1* function in SNU-251. Therefore, SNU-251 may be a useful model for studying the molecular mechanisms of *BRCA1* with respect to the resistance of ovarian cancer to ionizing radiation and chemotherapy, and for studying the development of hereditary human ovarian cancer.

6) SNU uterine malignant mixed mllerian tumor

We have also reported on the establishment and characterization of three cell lines (SNU-539, SNU-685, and SNU-1077) derived from uterine malignant mixed Müllerian tumor (MMMT). SNU-539 and SNU-1077 cells stain positively for both epithelial and mesenchymal antigens, whereas SNU-685 cells only stain positively for mesenchymal antigens. One missense mutation from AAC to GAC at codon 239 of exon 7 in the p53 gene was identified in SNU-539. These permanent uterine MMMT cell lines should be considered as a valuable resource for a multitude of in vitro investigations, and could be used for clarifying the obscure histogenetic origin and the biologic behavior of this aggressive tumor (11).

7) SNU B-lymphoblastoid cell lines from cancer patients

Seventeen lymphoblastoid cell lines (SNU-9, SNU-20, SNU-99, SNU-247, SNU-265, SNU-285, SNU-291, SNU-299, SNU-315, SNU-374, SNU-445, SNU-447, SNU-538, SNU-817, SNU-889, and SNU-1103) have also been established from cancer tissues obtained from Korean patients. During the establishment of tumor cell lines from cancer tissues, outgrowths of lymphoblasts growing as cell clumps in suspension were noted, in the absence of tumor cells growth. These lymphoblastoid cells were EBV-transformed cells, and arose from EBV-infected B cells present in the incubated cancer tissues. The presence of latently-infectious EBV in these cell lines was verified by the detection of the EBNA1gene and EBV-encoded nuclear antigens (EBNA1 and -2), and by the inducibility of an EBV early antigen (9). These cell lines have been found to be useful for studies on the role of EBV in carcinogenesis (149,175～178).

8) SNU laryngeal squamous cell carcinoma cell lines

A total of six human laryngeal squamous cell carcinoma cell lines (SNU-46, SNU-585, SNU-899, SNU-1066, SNU-1076, and SNU-1214) established from Korean patients have been described (12). All cell lines grew as adherent cells; five lines as monolayers and one line (SNU-585) as stratified colonies. p53 mutations were found in SNU-46 (Gly 245 Cys), SNU-585 (Arg 273 Leu), and in SNU-1066 (a deletion of 46bp from nucleotides 514 to 559 resulting in a premature stop codon at 62bp down stream. *p16* mutations were observed in five cell lines, including a one base deletion resulting in a premature stop codon in SNU-1066 and a stop codon in SNU-1214 cell lines. Two mutations in *TGF-βRII* were found in two lines: SNU-46 cell line has a frameshift mutation in exon 3, and SNU-1066 has a missense mutation (Ser 409 Phe) in the kinase domain. These laryngeal squamous cell carcinoma cell lines have been found useful by those investigating the biologic characteristics of laryngeal cancer (179～183). SNU-1041 cell line derived from pharyngeal cancer was also established in our laboratory. In addition, these cell lines were used to study the effect of nitric oxide on *COX-2* overexpression, and the inhibitory effect of *p27KIP1* gene transfer in head and neck squamous cell carcinoma (179).

9) SNU renal cell carcinoma cell lines

The establishment and characterization of a total of 7 SNU renal cell carcinoma cell lines were reported in 2000 (13). Five of these cell lines were derived from clear cells (SNU-228, SNU-267, SNU-328, SNU-349, and SNU-1272), one from granular cells (SNU-482), and one from a mixed clear and granular cell type (SNU-333). Mutations of the *VHL* gene were found in SNU-349 (a frameshift mutation at codon 108 resulting in a premature truncating protein) and in SNU-1272 (His 186 Gln), and in their tumor tissues. The SNU-267 line has a frameshift mutation (at codon 219 resulting in a prematurely truncated protein) in the *p53* gene. A missense mutation (Cys 121 Arg) of the *TGF-βRII* gene was detected in the SNU-1272 line and in the corresponding tissue. Analysis of the repeat sequences of the *TGF-βRII* gene showed one cell line (SNU-349) to have MSI (microsatellite instability) and the other 6 microsatellite stability. As MSI is a hallmark of the inactivation of mismatch repair genes, the presence of *hMSH2* and *hMLH1* mutations was investigated in all 7 cell lines. An inactivating homozygous single base-pair deletion of the *hMLH1* gene (a frameshift mutation at codon 711 resulting in a premature truncating protein) was found only in SNU-349 cell line and in corresponding tissue. Moreover, a frameshift mutation within an 8-bp polyadenine repeat present in the *hMSH3* coding region was found only in the MSI cell line and tumour tissue. These well characterized renal cell carcinoma cell lines should provide a useful in vitro model for studies related to human renal cell carcinoma.

Table 8. SNU cell lines deposited in ATCC

Gastric carcinoma cell lines
SNU-1 (CRL-5971), SNU-5 (CRL-5973),
SNU-16 (CRL-5974)
Colorectal carcinoma cell lines
SNU-C1 (CRL-5972), SNU-C2A (CCL-250.1),
SNU-C2B (CCL-250)
Hepatocellular carcinoma cell lines
SNU-182 (CRL-2235), SNU-387 (CRL-2237),
SNU-398 (CRL-2233), SNU-449 (CRL-2234),
SNU-475 (CRL-2236)

10) SNU brain tumor cell lines

In 2001, we reported on the characteristics of newly-established human brain tumor cell lines including six glioblastoma (SNU-201, SNU-444, SNU-466, SNU-489, SNU-626, and SNU-1105), two oligodendroglioma (SNU-738 and SNU-791), and one primitive neuroectodermal tumor (PNET) (SNU-1118) (14). All were established from pathologically proven brain tumors. In terms of *p53* mutations the following were found; a point mutation at a splice acceptor of intron 4 in SNU-201, a missense mutation (Cys 275 Tyr) in SNU-444, a missense mutation (Pro 77 Arg) in SNU-626, and a one base C deletion at codon 157 resulting in a premature truncating protein in SNU-1118. In terms of *PTEN* mutations, a missense mutation (Arg 130 Gln) in SNU-626 and a genomic deletion from exons 49 in SNU-1105 were identified. The mRNA of *PTEN* in SNU-1105 was also absent. Homozygous deletion of the *p15* gene was observed in the SNU-201, SNU-444, SNU-466, and

SNU-1105 cell lines. And, the homozygous deletion of the *p16* gene wholly or in part, was observed in SNU-201, SNU-444, SNU-466, SNU-738, and SNU-1105. This suggests that alterations of both or either of the *p16* and *p15* genes are common genetic alterations in human brain cancer cell lines. *DCC* expression was absent in seven cell lines (SNU-201, SNU-466, SNU-489, SNU-626, SNU-738, SNU-791, and SNU-1119). Alterations in BAT-25, BAT-26, and BAT-40 were observed in all cell lines, indicating that all have microsatellite stability. It is hoped that these cell lines will be found useful tools by those investigating the biological characteristics of human brain tumors (184).

11) SNU biliary tract cancer cell lines

Human cell lines established from biliary tract cancers are rare; only 5 have been reported previously. We recently described the characterization of six new biliary tract cancer cell lines (designated SNU-245, SNU-308, SNU-478, SNU-869, SNU-1079, and SNU-1196), which were established from primary tumor samples taken from Korean patients (15). These cell lines were isolated from two extrahepatic bile duct cancers [one adenocarcinoma of common bile duct (SNU-245), one hilar bile duct cancer (SNU-1196), two adenocarcinomas of ampulla of Vater (SNU-468 and SNU-869), one intrahepatic bile duct cancer (cholangiocarcinoma) (SNU-1079), and one adenocarcinoma of the gall bladder (SNU-308). *p53* mutations were found in SNU-478 (266～267insT), SNU-869 (Asp 48 Gly), and SNU-1196 (Arg 273 Cys) and homozygous deletions of both *p16* and *p15* genes were found in 3 lines (SNU-478, SNU-1079, and SNU-1196). The SNU-478 cell line was found to have a heterozygous missense mutation (Asp3 85 Val) in *hMLH1*, and the *E-cadherin* gene was found to be hypermethylated in two lines (SNU-478 and SNU-1079). These newly established and well characterized biliary tract cancer cell lines are likely to be found highly useful for studying the biology of biliary tract cancers. Of these cell lines, SNU-245, SNU-308, and SNU-1079 were subjected to oligonucleotide microarray analysis to identify novel cellular targets in biliary tract cancer (185). These cell lines were also used to validate differentially up-regulated genes by semi-quantitative RT-PCR.

12) SNU pancreatic carcinoma cell lines

We previously reported on the establishment and characterization of four pancreatic carcinoma cell lines (SNU-213, SNU-324, SNU-410, and SNU-494), which were established from histopathologically varied primary (SNU-213, SNU-324, and SNU-494) or liver metastatic (SNU-410) tumor samples from Korean patients (16). Mutations of the *K-ras* gene were identified in SNU-213 (Gly 12 Val), SNU-410 (Gly 12 Val), and in SNU-494 (Gly 12 Val), and p53 mutations were found within the DNA-binding domain of two, SNU-213 (Arg175His) and SNU-494 (Cys 238 Tyr). Homozygous deletions in both *p16* and *p15* genes were found in SNU-410 and SNU-494, and SNU-324 was found to have a missense mutation (Ala22Val). No mutations were found in the *DPC4* gene (deleted in pancreatic cancer). SNU-324 has a -1-bp or +1-bp mutation in 10-bp polydeoxyadenine repeat tracts of the *TGF-βRII* gene, and SNU-410 has a genomic deletion of this gene. SNU-324 contains two heterozygous missense mutations in the *hMLH1* gene (Cys 233 Arg and Val 384 Asp). In addition, this line showed microsatellite instability and harbored frameshift mutations in simple repeated sequences of the coding regions of the *TGF-βRII*, *BAX*, and *hMSH3* genes. These cell lines should be useful in studies of pancreatic carcinoma biology.

KOREAN CELL LINE BANK

1) Role of Korean Cell Line Bank

Korean Cell Line Bank is a non-profit bioscience organization aimed for distributing the essential cell lines to the life science researchers. The major activities of KCLB are as follows; i) establishment, characterization, deposition, collection, storage, and distribution of cell lines; ii) management of database related to cell lines; and iii) education, workshops, and conferences related to cell lines. KCLB is being supported by the Korean Cell Line Research Foundation (KCLRF). On August 31 in 1993, the KCLRF acquired the status of the International Depositary Authority approved by the World Intellectual Property Organization (WIPO) as specified in Article 6 of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The KCLB is currently supported by the Korean Science and Engineering Foundation and the Ministry of Science and Technology of Korean. KCLB distributes cell lines throughout Korean.

2) Patent cell lines and SNU cell lines in ATCC

Korean Cell Line Bank has obtained three patents for the invention of cell lines. i) two hepatocelluluar cell lines (SNU-354 and -368) expressing *MDR1* gene and hepatitis B virus (Korean patent # 118123), ii) uterine cervical carcinoma cell line (SNU-1000) having intact episomal HPV-16 (Korean patent # 0225491), and iii) ovarian carcinoma cell line (SNU-251) having a nonsense mutation of codon 1815 in exon 23 of the *BRCA1* gene (United States patent # 5,948,679). Researchers wishing to obtain these cell lines should contact to the Korean Cell Line Bank and Korean Cell Line Research Foundation (KCLRF). Researchers can also deposit cells for patent application purposes to Korean Cell Line Research Foundation (http://cellbank.snu.ac.kr).

Several gastric, colorectal, and hepatocellular carcinoma cell lines have been deposited in and are also available from the ATCC (American Type Culture Collection, http://www.atcc.org) (Table 8).

3) Distribution of SNU cell lines

All SNU cell lines have been deposited at the KCLB (Korean Cell Line Bank) and are available on request. The KCLB perform quality control on these cell line products, which includes the mycoplasma test, cell viability testing, and DNA fingerprinting analysis.

The order form for SNU cell lines is available from the KCLB website (http://cellbank.snu.ac.kr). To order cell lines from the KCLB, researchers should complete the KCLB order form (MS-Word or PDF if overseas) and fax it to the KCLB. We will on receipt prepare the cell lines and provide information on their characteristics. Cell lines will be delivered in

a frozen or cultured state according to customer request. The average time required for dispatch is two weeks.

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