then evaluated. Although age, FIGO stage, grade, and positive CA602 tumor marker, did not correlate with the positive antibody, surprisingly, the microsattelite instability (MSI) status was found to correlate with the positive antibody in patients with endometrial cancer (p=0.001) (Table 2). Among 33 endometrial cancer patients whose MSI status was evaluated, 7 of 13 (53.8%) patients with MSI-H had positive serum CAGE antibody, while none of 20 non-MSI-H patients including one MSI-L and 19 MSS patients had anti-CAGE antibody (Fig 5). Interestingly, 2 colon cancers with positive CAGE antibody were also turned out to be MSI positive cancers developed in patients with HNPCC (hereditary non-polyposis colon cancer).

Abnormal DNA mismatch repair enzymes in MSI positive tumor cells frequently cause frameshift changes by slippage mutation in the repetitive sequence in the protein coding region. We have previously found that the tumor specific C-terminal CDX2 peptide generated by the frameshift mutation in MSI positive colon cancer induced IgG responses specific for both altered C-terminal peptide and N-terminal wild type peptide in the patient (14). Thus, we have evaluated the possibility that altered CAGE peptide might induce IgG response to CAGE by sequencing the region containing 6 thymine repeat in the CAGE protein coding region of tumors obtained from 5 CAGE antibody positive patients with MSI-H endometrial cancer. However, none was found to have frameshift mutation in this particular repetitive sequence. Therefore, the mechanism for induction of IgG response to CAGE in MSI positive patients has not been clear and needs further investigation.

## DISCUSSION

In this study, we attempted isolate cancer testis antigens by screening a testis cDNA library with sera from melanoma patients who were frequently immunized with dendritic cells pulsed with autologous tumor lysates, because mRNA for cancer-testis antigens are often expressed at higher level in testis and cancer cells, and sera from patients immunized with autologous tumor constituents may contain higher titer of antibody specific for immunogenic tumor antigens. We also attempted to isolated endometrial cancer antigens by screening a cDNA library made from endometrial cancer cell lines with sera from patients with endometrial cancer, since SEREX has not previously applied for endometrial cancer. Endometrial cancer is the most common invasive neoplasia of female genital tract and the fourth frequently diagnosed cancer in the United States. Worldwide, approximately 150,000 cases are diagnosed each year, making endometrial cancer the fifth most common cancer in women(18). Since radiation and chemotherapy are not so effective, development of alternative therapeutic strategy such as immunotherapy is required for patients with advanced endometrial cancer.

From these independently performed SEREX studies, a cancer testis antigen CAGE was isolated. CAGE was originally isolated by Cho et al.(6) by SEREX with sera from a gastric cancer patient. CAGE mapped to X chromosome p22.13 was previously shown to express in normal testis and various cancers, including gastric, cervical, lung, and liver cancers. Although function of CAGE has not yet been known, CAGE has helicase domains and DEAD box, and appears to be one of the

DEAD box families with conserved Asp-Glu-Ala-Asp (DEAD) motif, which have RNA-dependent ATPase activity and RNA helicase activity. The DEAD box family proteins are reported to play important roles in a wide range of cellular regulations including RNA metabolism, embryogenesis, spermatogenesis, and cellular growth (19-21). Some DEAD box family proteins, including rck/p54(22), DDX1(23), and HAGE are over-expressed in various cancer cell lines, and the expression of DDX1 are correlated with poor prognosis in patients with neuroblastoma(24). Mutations in helicases involved in DNA repair mechanisms were found in cancer-prone syndromes such as xeroderma pigmentosum, Bloom's syndrome, Werner's disease, X-linked mental retardation associated with α-thalassemia, and Cockayne's syndrome. About the immunogenicity of DEAD box protein, a mutated murine DEAD box protein, named p68, was found to encode an antigens recognized by CTL on a UV-induced sarcoma(25). A mutated peptide of MUM-3 homologous to RNA helicases with a DExH motif, was isolated with HLA-A28 restricted autologous melanoma specific CTL(26).

CAGE was previously reported to express frequently in gastric cancer, cervical cancer, lung cancer, and liver cancer through hypomethylation of promoter region(27). However, expression in other cancers including endometrial cancer and melanoma, has not previously been evaluated. In addition, its immunological recognition has so far been shown only with serum of a single gastric cancer patient. Therefore, we performed further analysis of the protein expression and immunogenicity of CAGE isolated by our 2 independent SEREX experiments using sera from patients with endometrial cancer and melanoma. In addition to the previously reported cancers, we

found that CAGE was also expressed in other types of cancers, including endometrial cancer, melanoma, breast cancer, bladder cancer, pancreatic cancer, renal cell cancer, and leukemia, and in particular it was expressed frequently (7 of 10 patients) in endometrial cancer tissues. Cancer testis antigen frequently expressed in various cancers, MAGE-A4 or NY-ESO-I, was previously reported to be expressed only in 12% or 19% of endometrial cancers, respectively(28). CAGE was also expressed in 1 of 3 atypical endometrial hyperplasia tissues, but not in normal endometrium either proliferation or secretory phase, although cell cycle dependent expression of CAGE was suggested(6). Hypomethylation of the CAGE promoter was reported not only in cancer cells, but also in precancerous states including chronic gastritis and liver cirrhosis, suggesting that CAGE expression may occur in relatively early stage of cancer development.

We next examined immunogenicity of CAGE in patients with various cancers, and found that anti-CAGE IgG antibody were present in sera of patients with various cancers, including endometrial cancers, melanoma, and colon cancer. Since we have been working on immune responses in patients with MSI positive cancers, and subpopulation of endometrial cancer and colon cancer is known to be MSI positive through either mutation of DNA mismatch repair enzyme genes such as MLH1 or silencing of promoters for the repair enzyme genes by methylation, we have evaluated correlation between CAGE antibody positive and MSI status. Particularly, endometrial cancer was reported to be frequently MSI positive due to HNPCC or silencing of the MLH1 promoter by methylation(29). Nine to thirty percent of sporadic endometrial cancers were reported to be MSI positive. Surprisingly, anti-CAGE antibody was detected in sera from 7 of 13 (53.8%) patients with MSI-H, but not in sera

from 20 non MSI-H patients including one MSI-L and 19 MSS patients. Interestingly, 2 colon cancer patients with positive CAGE antibody had also MSI positive cancers developed in patients with HNPCC (hereditary non-polyposis colon cancer). Two melanoma patients with positive CAGE antibody may suggest possible MSI in melanoma, although not evaluated because of unavailability of tumor samples.

Defective DNA mismatch repair frequently causes frameshift changed, unique C-terminal peptides particularly by slippage mutation in the repetitive sequence in the protein coding region. We have previously reported that the CDX2 C-terminal peptide generated by the frameshift mutation induced IgG responses specific for both altered C-terminal peptide and N-terminal wild type peptide in a HNPCC patient(14). Anti-p53 antibody which recognizes wild type p53 was known to be induced through conformational changes of mutated p53. Since CAGE has 6 repeated thymine sequence in the protein coding region, we sequenced this region of genomic DNA obtained from tumor samples of 5 MSI-H endometrial cancer patients, but could not find any alteration in this region. Thus, the mechanism of induction of IgG response to CAGE in MSI positive patients is still unclear. Mutations in other regions of CAGE or other molecules generated by MSI may be involved in modification of the antigen processing and induction of T cells and B cells specific for CAGE.

Since cancer testis antigens are often expressed in HLA negative cells in immunological priviledge sites such as spermatogonia and spermatocytes in tests, they are not recognized by specific T cells, indicating some of the cancer testis antigens may be tumor specific common antigens and one

of the promising targets for cancer immunotherapy. Immunization trials have been in progress for MAGE and NY-ESO-1(30). The recognition by IgG Ab suggests that the same antigen activated CD4+ helper T cells in the patients, meaning that the antigens are immunogenic in cancer patients. In addition, many SEREX defined antigens including MAGE and NY-ESO-1, have been shown to also induce CD8+ cytotoxic T cells (CTL). Positive correlation was observed between positive serum IgG antibody and induction of CD8+ CTL against a cancer-testis antigen NY-ESO-1(31). Patients with MSI positive colon cancer have relatively good prognosis despite of poor histology. Since predominant infiltration of T cells, particularly CD8+ T cells, is observed in MSI positive colon cancer tissues, immune responses to frameshift antigens may contribute to the maintenance of tumor free status after treatment. We have previously demonstrated the immune response to both frameshift mutated and wild type peptides of CDX2 in MSI positive colon cancer patients(14), and T cell response to the frameshift mutated TGFβ-RII frequently detected in MSI positive colon cancer was also reported(32). Although prognosis of MSI positive endometrial cancer is still controversial, there are reports showing better prognosis of patients with MSI positive endometrial cancer(33). If immune response is involved in the good prognosis, CAGE may be one of the target antigens besides the frameshift antigens. Therefore, CAGE may be a good candidate antigen for immunotherapy, at least as CD4+ T cell antigens, particularly for MSI positive endometrial cancer patients with positive CAGE serum antibody.

Serum anti-CAGE antibody may be utilized as a tumor marker. We often observed disappearance of serum antibody to the SEREX defined antigens after curative treatment in patients

with various cancers(13, 14). Use of serum antibodies against p53(34), Cyclin B1(35), hTERT(36, 37) and survivin(37), were recently reported. Positive rate of 15% for anti-p53 antibody in colon cancers and that of 21.6% or 7.8% for anti-survivin antibody in lung or in colon cancer patients were reported. Positive rate of anti-CAGE antibody in 7 of 13 (53.8%) of MSI positive endometrial cancer patients and 1 of 3 of ATH patients indicated possible use of anti-CAGE serum antibody for prognostic or early diagnosis for patients with MSI positive endometrial cancers. Further analysis with a larger numbers of patients is necessary for confirmation and usefulness of this possibility. CA602, a part of CA125 antigen, is one of the most commonly used tumor markers for endometrial cancers. No correlation was observed between anti-CAGE antibody and CA602 in this study. Although CA602 produced by tumor cells correlates with tumor volume, the induction of antibody was defined by immune response of patients through antigen processing and immune response of T cells and B cells. Therefore, these tumor markers can be independently utilized for diagnosis of endometrial cancer.

In summary, we have demonstrated that CAGE is expressed in various cancers including endometrial cancers and melanoma, and frequent detection of specific serum IgG antibody in patients with MSI-H endometrial cancers, indicating that highly immunogenic nature of CAGE in MSI positive endometrial cancers. These results suggest that CAGE may be useful not only for immunotherapy of various cancers, but also for diagnosis of some cancers, particularly MSI positive endometrial cancers.

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***Table 1*** Anti-CAGE antibodies was detected in various cancer patients sera by Western blotting analysis

| Healthy controls | Endometrial cancer | Ovarian cancer | Melanoma | Colon cancer | Renal cell cancer | Prostate cancer | Pancreas cancer |
|---|---|---|---|---|---|---|---|
| 0/40 | 5/45 | 0/10 | 2/24 | 2/33 | 0/20 | 0/18 | 0/12 |

*Table 2* The correlation of anti-CAGE antibodies and clinicopathological features

| | | | Anti-CAGE Abs (OD 450nm) | | |
|---|---|---|---|---|---|
| | | n | ≦0.058 | >0.058 | P value[a] |
| Age | | | | | |
| | ≦60 | 28 | 20 | 8 | |
| | >60 | 17 | 13 | 4 | 0.98 |
| FIGOstage | | | | | |
| | I+II | 32 | 24 | 8 | |
| | III+IV | 13 | 9 | 4 | 0.98 |
| Grade | | | | | |
| | G1+G2 | 35 | 28 | 7 | |
| | G3 | 10 | 5 | 5 | 0.14 |
| MSI | | | | | |
| | MSI-H | 13 | 6 | 7 | |
| | MSL+MSS | 20 | 20 | 0 | 0.001 |
| | not examined | 12 | | | |
| CA602 value | | | | | |
| | ≦63 | 31 | 24 | 7 | |
| | >63 | 14 | 9 | 5 | 0.58 |

[a] P value was calculated by $\chi^2$ test.

**Figure legends**

**Fig. 1.** Expression of CAGE in various cancers and normal testis evaluated by RT-PCR analysis.

(A) CAGE was expressed only in testis among normal tissues.

(B) CAGE was expressed in 4 of 7 melanoma, 1 of 3 lung cancer, 2 of 4 renal cell cancer, 2 of 3 endometrial cancer, one pancreatic cancer, one bladder cancer, one breast cancer, and 1 of 3 chronic myelogenous leukemia cell lines.

**Fig. 2.** Expression of CAGE in endometrial cancer tissues, but not in normal endometrial tissues

(A) CAGE was expressed in none of 8 normal endometrium tissues (4 in the proliferation phase and 4 in the secretory phase).

(B) 7 of 10 endometrial cancer tissues (4 in G1, 4 in G2, and 2 in G3) and 1 of 3 AEH tissues expressed CAGE. G1, G2 and G3 are the differentiation grades, grade1, grade2, and grade3, respectively. NC ; negative control, PC : positive control.

**Fig. 3.** Expression of the CAGE protein in various cancer cell lines

The specific CAGE band was detected in lysates from 2 endometrial cancer cell lines, Hec-Ib and Ishikawa, and one melanoma cell line 888mel, those are CAGE positive by RT-PCR analysis, but was not shown in lysate from PCR negative cultured melanocytes. NIH-3T3 cells transfected with pcDNA-CAGE was positive control and untransfected NIH-3T3 cells was negatine control.

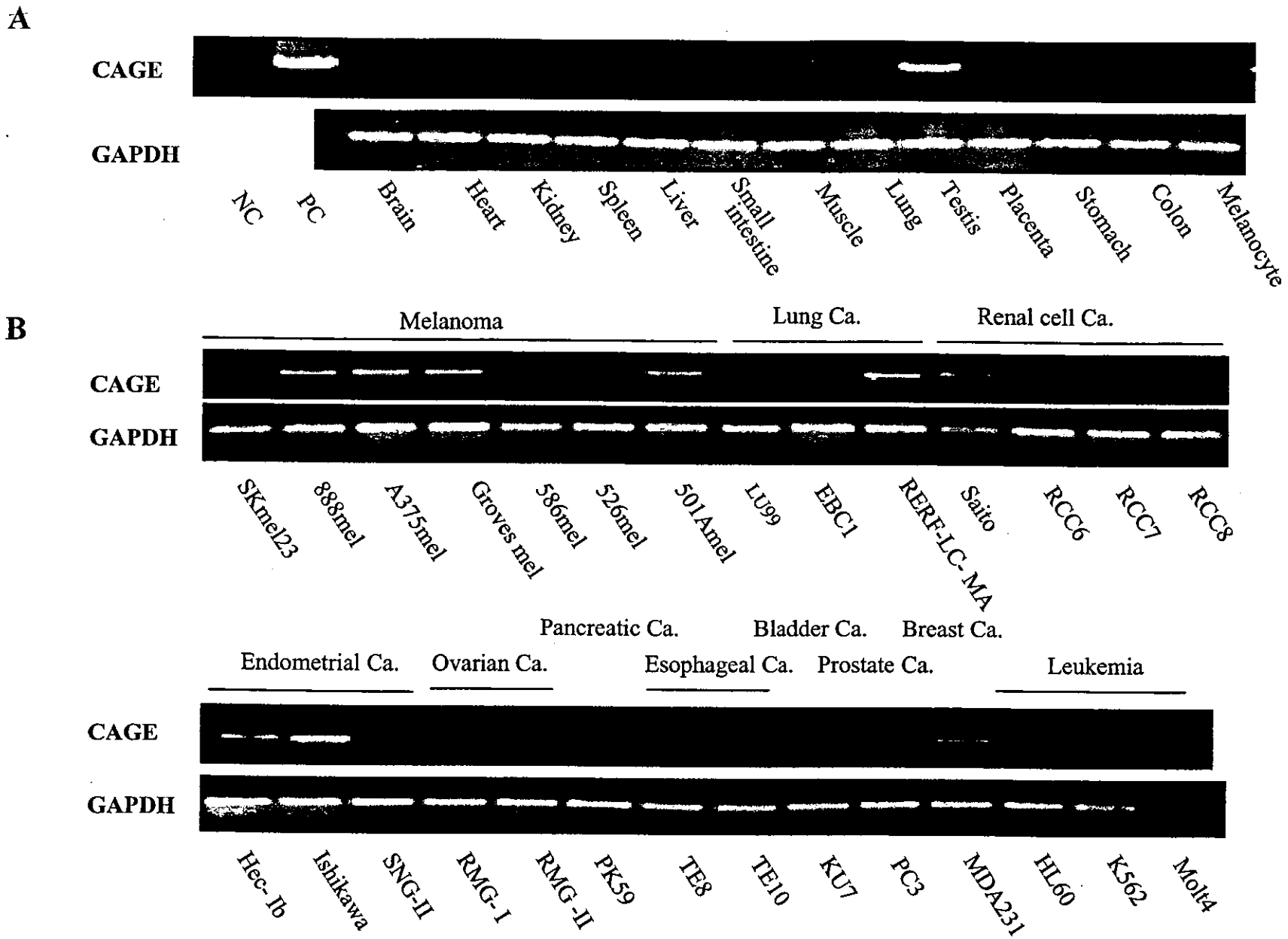
**Fig. 4.** Presence of anti-CAGE IgG antibodies in sera from various cancer patients detected by Western blot analysis with bacterial recombinant CAGE protein

By Western blot analysis, the recombinant His-tagged CAGE protein fragment containing N-terminal 211 amino acids of CAGE (M.W. = 31.1kDa) was recognized by IgG antibodies in sera from some of the patients with various cancers. Lane1: Staining of CAGE with anti-His antibody. Lanes2-12: staining with 1:100 diluted sera. Lanes 2-6 sera from endometrial cancer patients; Lanes 7and 8 sera from melanoma patients; Lane 9 and 10 sera from colon cancer patients; Lane 11 and 1; sera from healthy controls. Only positive cancer samples are shown in this representative experiment. No band was shown in the lanes with sera from 2 healthy individuals. 1μg of recombinant CAGE protein was loaded per lane.

**Fig.5** Frequent detection of anti-CAGE antibodies in sera from patients with MSI-H endometrial cancer evaluated by ELISA

ELISA was performed with the recombinant CAGE protein. The horizontal line indicates the cutoff

value for positivity (OD=0.058: the average absorbance of the healthy individuals plus 2SD). Positive sera were found in 12 of 45 (26.7%) endometrial, 4 of 33 (12.5%) colon cancer, 2 of 20 (10.0%) melanoma patients, and 1 of 40 (2.5%) age matched healthy individuals, but not in 10 ovarian cancer patients. Among 33 endometrial cancer patients whose MSI status was evaluated, 7 of 13 (53.8%) patients with MSI-H had positive serum CAGE antibody, while none of 20 non-MSI-H patients including one MSI-L and 19 MSS patients had anti-CAGE antibody.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Colon
Melanocyte
B
Melanoma
Lung Ca.
Renal cell Ca.
CAGE
GAPDH
SKmel23
888mel
A375mel
Groves mel
586mel
526mel
501Amel
LU99
EBC1
RERF-LC-MA
Saito
RCC6
RCC7
RCC8
Pancreatic Ca.
Bladder Ca.
Breast Ca.
Endometrial Ca.
Ovarian Ca.
Esophageal Ca.
Prostate Ca.
Leukemia
CAGE
GAPDH
Hec-1b
Ishikawa
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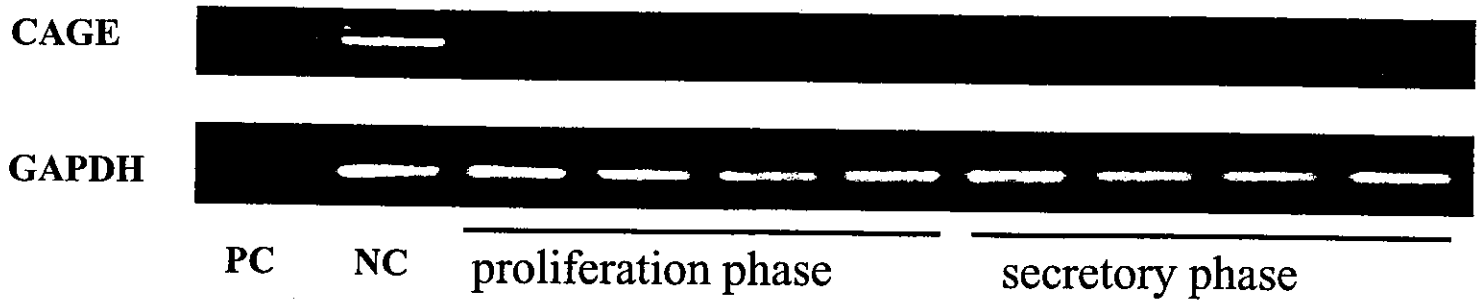
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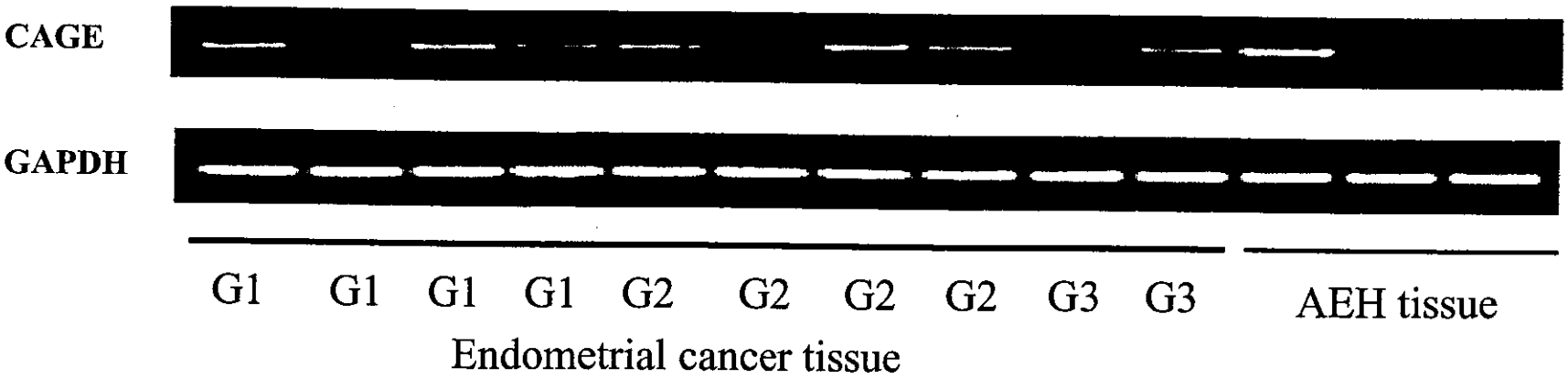
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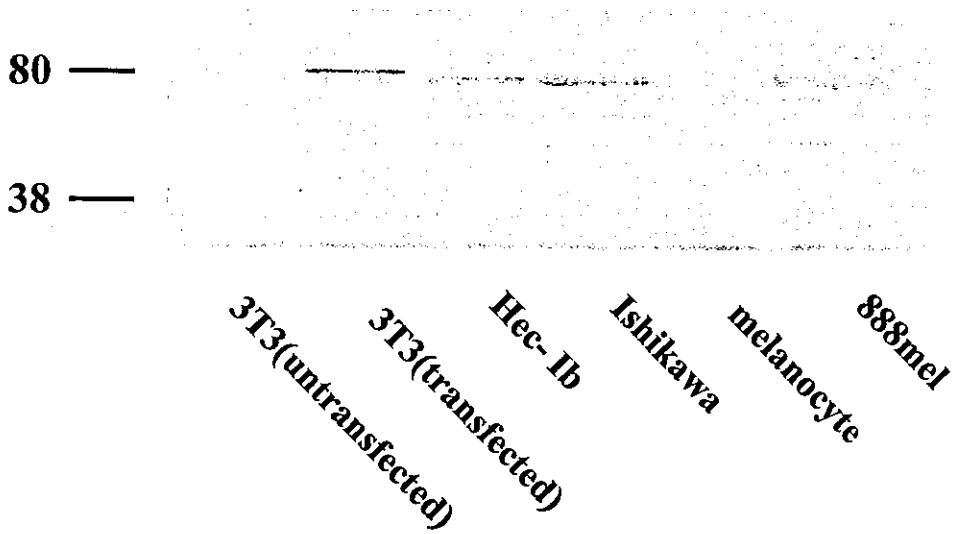
Endometrial cancer tissue


(kDa)
80
38
3T3(untransfected)
3T3(transfected)
Hec-1b
Ishikawa
melanocyte
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