ANG (angiogenin, ribonuclease, RNase A family, 5)
Shouji Shimoyama
Gastrointestinal Unit, Settlement Clinic, 4-20-7, Towa, Adachi-ku, Tokyo, 120-0003, Japan (SS)

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Identity
Other names: ALS9; HEL168; MGC22466; MGC71966; RNASE4; RNASE5
HGNC (Hugo): ANG
Location: 14q11.2

DNA/RNA
2152336  NT_026437.12  2162345
5'       coding lesion       3'
Starts at 2152336 and ends at 2162345 in NCBI reference sequence NT_026437.12. Gene map locus is available at NCBI Nucleotide. Total length of ANG DNA is 10010 nucleotides. The coding region starts at 2162723 and ends at 2162166 including stop codon TAA.

Protein
Description
The amino acid sequence is available at NCBI protein locus AAA51678. It consists of a signal peptide from amino acid 1 to 24 and a mature peptide from amino acid 25 to 147.
ANG is a basic, single chain potent blood-vessel inducing protein with a molecular weight of 14 kDa which was originally discovered in conditioned media of a human colon carcinoma cell line HT-29. ANG belongs to the RNase superfamily, being 35% identical and 68% homologous to the pancreatic RNase A sequence. The overall crystal structure of ANG shows a similarity to, but the biological actions of ANG differ distinctly from those of RNase A. ANG possesses two distinct regions: a ribonucleolytic and a noncatalytic site, both being critical for angiogenic activity. Besides the ribonucleolytic activity, ANG differs from RNase A in noncatalytic activities such as interactions with endothelial and smooth muscle cells and subsequent cellular responses in the events of neovascularization, including basement membrane degradation, signal transduction, and nuclear translocation.

Expression
ANG mRNA is expressed in a wide spectrum of cells including neoplastic cells as well as normal epithelial cells, fibroblasts, peripheral blood cells, and vascular endothelial cells.

Localisation
Strikingly, ANG localizes freely in the circulation, and is translocated into the nucleus. Nuclear translocation of ANG triggers subsequent cell proliferation. However, the precise mechanisms for why serum ANG is inactive and continuous angiogenesis does not take place remain unknown.

Function
1. Ribonuclease activity
The catalytic activity of ANG is several orders of magnitude weaker than that of RNase A, this being partly due to the partial occupation of the pyrimidine-binding pocket of RNase A by glutamine-117 residue so that the substrate binding is compromised. Key amino acids for the ribo-
nucleolytic activity of ANG are His13, Lys40, or His114 of ANG, a catalytic triad, but mutations of these amino acids also reduce ANG induced angiogenesis, suggesting that the ribonucleolytic activity of ANG, although weak, is necessary for the angiogenic activity of ANG. Furthermore, several arginines are essential for ribonucleolytic and angiogenic activities.

II. Angiogenic activity

In addition to the catalytic activity, cell binding sites which encompass residues 60-68 of the surface loop as well as asparagine-109 are necessary for angiogenesis. The variants undergoing alterations of these residues lack any angiogenic activity while the enzymatic activity remains intact. Inversely, replacing the surface loop in RNAse A (residues 59-73) with the corresponding region of ANG (residue 57-70) bestows a neovascularization activity to the RNAse A.

1) Basement membrane degradation

Amino acid residues from Lys60 to Asn68 of the ANG constitute a cell surface receptor binding site. Accordingly, a 42 kDa endothelial cell surface protein was identified as an ANG binding protein, which was later found to be a smooth muscle type alpha-actin. The ANG-actin complex dissociates from the cell surface and activates a tissue type plasminogen activator, thus accelerating degradation of the basement membrane and extracellular matrix that allows endothelial cells to penetrate or migrate through the extracellular matrix more easily, an initial step of neovascularization. Furthermore, fibulin-1, an important molecule for stabilization of the blood vessel wall, binds to ANG, suggesting that the ANG-fibulin-1 complex modulates new blood vessel formation and stabilization.

2) Signal transduction

Besides the 42 kDa ANG receptor, a 170 kDa molecule later found on the endothelial surface is responsible for signal transduction, an important process leading to cell proliferation. ANG activates several secondary message cascades such as extracellular signal related kinase 1/2 (ERK1 and ERK2), protein kinase B/Akt, and stress-associated protein kinase/c-Jun N-terminal kinase (SAPK/JNK).

3) Nuclear translocation

The nuclear mechanisms underlying the function of ANG remain elusive. Internalization could involve cell surface ANG binding to proteins as well as to other molecules such as proteoglycans, followed by endocytosis. In this event, ANG interacts directly with intracellular protein alpha-actinin-2 followed by translocation into the nucleus through the nuclear pore in a passive manner. After nuclear retention, ANG binds to carrier proteins through a sequence 29-IMRRRGL-35 (nuclear localization signal) of ANG and to the ANG-binding element of ribosomal DNA (CTCT repeats) and subsequently, stimulates ribosomal RNA transcription. Nuclear translocation is essential for cell proliferation since it is considered a third messenger and promotes gene activation and transcription events, and inhibition of the nuclear translocation of angiogenin abolishes ANG-induced angiogenesis. Interestingly, the expression of cell surface receptors responsible for internalization as well as for the nuclear translocation of ANG also depends on the cell density.
III. Roles of ANG in physiological angiogenesis

The above biological events, which are distinct from those of RNase A, are regulated tightly by the cell density-dependent expression of ANG receptors. The discovery of the uniquely regulated expression of ANG receptors provides us with the following conceivable mechanisms for ANG related angiogenesis. In the region where neovascularization is required, ANG binds to the endothelial surface 42 kDa receptor, and the ANG-42 kDa receptor complex dissociates from the cell surface and stimulates proteolytic activity, thus facilitating the penetration of endothelial cells through the extracellular matrix. After the leading cells migrate away, the endothelial cell density in the vicinity of migrating cells might be sparse, and such cell sparsity triggers the endothelial proliferation machinery that includes signal transduction, ANG internalization, and nuclear translocation. A 170 kDa receptor is one of the receptors responsible for this orchestrated process. Once the microenvironment is filled up with the sufficient amount of endothelial cells and the vascular network is established, such cell proliferating events diminish. Therefore, the above cell density dependent biological events are intelligent mechanisms where the proliferation machinery and subsequent angiogenic switch are on when neovascularization is needed while they are off to prevent unwanted angiogenesis.

Homology

Of the 123 amino acids of human ANG, 43 (35%) and 25 are respectively identical to human pancreatic RNAse or to other RNases, and 16 are conservative replacements, constituting an overall homology of 68%.

Implicated in

Various cancers

Note

There is growing evidence that increased ANG expression in tissue and/or in sera is correlated with tumor aggressiveness. These facts are explained at least in part by the hypothesis that ANG in malignancy plays roles in the proliferation and migration of malignant cells, mimicking endothelial cell behavior during physiological angiogenesis. As described earlier, ANG could activate proteolytic activity, so that ANG-expressing malignant cells are allowed to invade through the extracellular matrix and enter into the bloodstream. In addition, the continuous translocation of ANG to the nucleus of HeLa cells in a cell density-independent manner suggests that cancer cells are also targets for ANG, and that ANG per se is a contributing factor for sustained cell growth and the constant supply of ribosomes, a characteristic of malignant cells.

Several ANG antagonists have been introduced and some have proved to be effective inhibitors for the establishment or metastasis of human tumors in athymic mice. These compounds include a monoclonal antibody, antisense oligonucleotides complementary to the AUG translational start site region of ANG, translocation blocker, enzymatic inhibitor targeting ANG enzymatic active site, ANG binding polypeptide complementary to the receptor binding site of ANG, and internalization pathway blocker.

Female breast cancer

Disease

Female breast cancer is globally the most common cancer with an annual incidence of 1,15 million worldwide. It is also the leading cause of death, with a mortality rate of 133 per million. Breast cancer incidence rates have increased in most geographic regions.

Prognosis

The ANG level in sera and the roles of ANG in breast cancer patients seem to be conflicting. Some studies found significantly increased serum ANG in breast cancer patients in comparison with normal controls while other studies failed to find such a difference. The serum ANG level is significantly decreased after breast cancer resection, suggesting that the source of ANG is at least in part the breast cancer cells. However, there is conflicting evidence concerning the role of ANG. The correlation between ANG expression in tissue or in sera and patient survival was inverse, neutral, or even positive. The absence of any increase in serum ANG levels in early stage breast cancer patients suggests that ANG may have clinical implications when breast cancer progresses to the advanced stage.

Pancreas cancer

Disease

The pancreas is composed of exocrine (acinar glands and pancreas duct) and endocrine (islets of Langerhans) components. Both can give rise to malignant neoplasms, but adenocarcinoma arising from the pancreatic ducts is representative of all pancreatic cancers.

Prognosis

Pancreatic cancer is one of the most aggressive diseases with most cancers already in later stages at presentation, the 5-year survival rate being around 5% both in USA and in Europe. Investigations concerning ANG expression in pancreatic cancer are scarce. ANG in sera is elevated in pancreatic cancer patients as compared with healthy volunteers, and increased ANG mRNA in tissue or increased ANG in sera has been correlated with cancer aggressiveness. In addition, the involvement of ANG in the cancer microenvironment has been suggested by findings of the ANG expression in chronic pancreatitis adjacent to pancreatic cancer but not in pure chronic pancreatitis. Cancer derived fibroblasts also express ANG.
**Gastric cancer**

**Disease**
Gastric cancer, the third most common cancer and the second leading cause of cancer death among men, arises in an estimated one million new cases in both sexes worldwide. Gastric cancer is anatomically classified as noncardia and cardia cancers, and the former incidence has declined while the latter incidence has increased. Helicobacter pylori infection is one of the risk factors for noncardia cancer. Adenocarcinomas account for a large majority of gastric cancer histologic diagnoses.

**Prognosis**
The 5-year survival rate of gastric cancer in Japan is double that of the United States and Europe. The better treatment outcomes are ascribed partly to the social screening program that attempts to capitalize on the benefit of early detection, and partly to systematic lymph node dissection. ANG in sera is increased in gastric cancer patients and is decreased by resection, suggesting gastric cancer to be a source of ANG. Increased mRNA expression in gastric cancer tissues or increased serum ANG levels is correlated with cancer progression, proliferation ability, and poor patient prognosis.

**Colorectal cancer**

**Disease**
Colon cancer is the fourth most commonly diagnosed cancer and fourth most frequent cause of cancer death among men. Colon cancer incidence rates have increased in most parts of the world. Typically, there is a pathologic evolution from benign adenomas to cancer (adenoma-carcinoma sequence), so that colorectal cancer screening aims to detect lesions at the adenoma stage and interrupt the adenoma carcinoma sequence, ultimately reducing colorectal cancer incidence and mortality.

**Prognosis**
Colorectal cancer exhibits increased serum ANG concentration, and the degree of elevation is correlated with cancer progression. ANG message expression in colorectal cancer tissue has also been correlated with poor patient survival.

**Cytogenetics**
Overexpression of the 14q11.1-14q11.2 product was observed in a colon adenocarcinoma cell line.

**Lung cancer**

**Disease**
Lung cancer is the most frequently diagnosed cancer among men. The mortality rate is the highest among men and the second highest among women worldwide. Cigarette smoking is the most important risk factor for lung cancer. The main histologic types of lung cancer are adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell carcinoma. The stage of the disease is a strong predictor of survival, suggesting that early detection is needed for improvement in treatment outcomes.

**Prognosis**
Immunoreactivity in lung cancer tissue is correlated with tumor size and positive nodal involvement. Recently, the detection of ANG in exhaled breath condensate has been achieved, and breath based ANG may help in the early detection of lung cancer.

**Cytogenetics**
DNA damage in 14q11.2 was found in asbestos-exposed lung cancer patients.

**Liver cancer**

**Disease**
The global incidence and mortality rate of liver cancer is ranked among top 5 (in men) and top 10 (in women) cancer types. The hepatitis B virus and hepatitis C virus are the most important risk factors for liver cancer. Histologic classification separates hepatocellular carcinoma (HCC) (liver cell origin) from cholangiocarcinoma, which arises from intrahepatic bile ducts. HCC is the most common histology of liver cancer which is characterized by vigorous neovascularization.

**Prognosis**
The serum ANG is increased in hypervascular hepatocellular carcinoma. The serum ANG level decreases after therapy but again increases at recurrence, suggesting the usefulness of serum ANG measurement for monitoring the disease and prediction of patient survival. However, other investigators found a neutral correlation between serum ANG and survival. The ANG immunoreactivity is correlated with poorer histological differentiation.

**Cytogenetics**
14q11.2 is found to be highly amplified in hepatoblastoma.

**Prostate cancer**

**Disease**
Prostate cancer is the second most frequently diagnosed cancer among men. Prognosis is excellent for early stage disease while it is poor for those diagnosed with advanced cases, pointing to the benefit of earlier diagnosis. Measurement of prostate specific antigen helps to detect biologically indolent prostate cancer.

**Prognosis**
The immunoreactivity of ANG is more evident according to prostate epithelial cells evolution from a benign to an invasive phenotype. In vitro analyses using prostate cancer cell line have elucidated that ANG is one of the elements responsible for tumorigenicity and tumor growth. Furthermore, serum ANG is more increased in hormone-refractory patients than in healthy controls.
Leukemia

Disease
Leukemias are malignancies that affect blood-forming stem cells in the bone marrow. Leukemia, a heterogeneous group of malignancies, is classified into several subtypes according to the major cell type such as acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), etc. Acute types refer to cancers arising in immature stem cells while chronic types refer to cancers arising in mature stem cells.

Prognosis
The ANG level in sera was increased in AML and CML, although other investigators failed to find such correlation. In sharp contrast to the clinical significance of serum ANG in other solid tumors, elevated serum ANG in AML and CML is correlated with better patient survival.

Cytogenetics
14q11.2 is one of the risk foci for ALL.

Hodgkin and non-hodgkin lymphomas

Disease
Lymphomas, malignancies of the lymphoid cells, are divided on the basis of their pathologic features into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL almost always develops in a lymph node or other lymphoid structure and spread to nearby nodes. HL is characterized by the presence of Hodgkin Reed Sternberg cells. It is one of the most common cancers diagnosed in younger persons. The proportions of patients being diagnosed below 50 years old accounts for 60%. NHL occurs in more elderly patients in the context of HIV-related immunosuppression. NHL with HIV shows extensively poorer survivals than those without HIV.

Prognosis
In sharp contrast to the other solid malignancies, serum ANG concentrations in patients with HL or NHL are less than or the same as those in healthy controls. Increased serum ANG renders no or an inverse impact on survival in NHL patients.

Cytogenetics
One subtype of NHL experiences multiple translocations at 14q11.2.

Kidney and bladder cancer

Disease
Kidney and bladder cancers are placed among the top ten cancer types in both sexes. Cancer of the urinary bladder most commonly originates in the urothelium, the epithelium that lines the bladder. Bladder cancer incidence is significantly higher in males than in females. There are three major histologic types of bladder cancer: transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma, the former being overwhelmingly the most common. The majority of cancers of the kidney are renal cell carcinomas, which arise from renal tubules. On the other hand, cancer of the renal pelvis designated as transitional cell carcinoma comprises the minority.

Prognosis
The serum level of ANG is increased in renal cell carcinoma and bladder cancer; however, the increase in serum ANG level does not correlate with patient survival for renal cell carcinoma. On the other hand, increased serum ANG or ANG message in urothelial cancer correlates with poor patient survival or cancer progression. Recently, ANG in the urine has been found to be increased in bladder cancer patients.

Melanoma

Disease
Melanoma is placed as the leading cause of skin cancer death and its incidence has dramatically increased over the last ten years. It is characterized as having a notorious resistance to currently available therapies so that early detection and intervention is needed.

Prognosis
Survival clearly worsens with increasing tumor thickness. Thin lesions exhibit excellent survival outcomes while the MST of patients with advance cases is around 8 months. The ANG in sera is increased in melanoma patients, and increased serum ANG correlates with malignancy potential, accordingly, ANG contributes directly to A375 melanoma cell proliferation. However, other investigators failed to find such a correlation.

Gynecological cancers

Disease
Cancers of the uterus and ovary are respectively the second and the sixth most frequently diagnosed cancer among women. Cancer of the uterus is further classified as cancer of the cervix and corpus, and cancer of the cervix uteri shows the highest incidence among the three gynecological malignancies. Cancer of the cervix uteri can be attributed to persistent infection with carcinogenic genotypes of human papilloma virus. The three most common histological types of cancer of the cervix uteri are squamous, adenosquamous, and adenocarcinoma. Adenocarcinoma is the most common histology of cancer of the corpus uteri and ovary. Women with ovarian cancer have poorer survival rates than those with other gynecological cancers.

Prognosis
Serum ANG is significantly increased in ovarian cancer patients, while other studies failed to find such a difference. Increased serum ANG concentration is correlated with cancer progression in ovary and cervix uteri.

Cytogenetics
Gains on 14q11.2 are associated with chemoresistant ovarian cancer.
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