**Gene Section**

**Review**

**AURKA (aurora kinase A)**

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**Identity**

Other names: Aurora A; ARK1; AURA; Aurora2; BTAK; MGC34538; STK15; STK6; STK7

HGNC (Hugo): AURKA

Location: 20q13.31

**DNA/RNA**

**Description**

The gene encompasses 22.8 kb of DNA; 9 Exons.

**Transcription**

2253 bp mRNA.

**Protein**

**Description**

403 amino acids, 46kDa protein. At the amino terminal domain, three putative conserved Aurora boxes (A-boxI, A-boxII and A-boxIII) can be identified. The functional significance of these boxes is not yet clearly known and there is suggestive evidence in the literature that these may be involved in subcellular localization or substrate recognition for the proteins. One of the serine residues in the A-boxII of Aurora-A kinase has recently been shown to be involved in the degradation of the protein. One activation motif and a destruction box in C-terminal. AURKA is regulated by phosphorylation in a cell cycle dependent manner. This phosphorylation occurs on a conserved residue, threonine 288, within the activation loop of the catalytic domain of the kinase and results in a significant increase in the enzymatic activity. AURKA protein is able to physically associate with multiple important cellular proteins such as p53, BRCA1 and TACC1. The interactions of AURKA with those critical molecules have been shown to disrupt/alter their physiological functions and may play roles in tumorigenesis.

**Expression**

Widely expressed, AURKA mRNA and protein expression levels are low during G1 and S phase and peak during the G2/M phase of the cell cycle. Kinase activity of the protein is also cell cycle regulated and the highest activity coincides with the most elevated expression level of the protein during mitosis.

**Localisation**

AURKA localizes next to the centrosome late in the G1 phase and early in the S phase. As the cell cycle progresses, concentration of AURKA increases and the kinase associates with the mitotic poles and the adjacent spindle microtubules. AURKA remains associated with the spindles through telophase.
**Function**

Serine/threonine kinase identified as key regulator of the mitotic cell division process. Known to be involved in the regulation of centrosome function, bipolar spindle assembly and chromosome segregation processes. AURKA is critical for proper formation of mitotic spindle. It is required for the recruitment of several different proteins important to the spindle formation. Among these target proteins are TACC, a microtubule-associated protein that stabilizes centrosomal microtubules and Kinesin 5, a motor protein involved in the formation of the bipolar mitotic spindle. Two upstream regulators of AURKA, Ajuba and targeting protein for Xklp2 (TPX2) are known. TPX2 is a MT-binding protein involved in spindle pole formation and is the best characterized RanGTP-dependent spindle activator. TPX2 is required for AURKA binding to spindle MTs and its binding to AURKA holds the latter in an active conformation. Ajuba and AURKA interact in mitotic cells and become phosphorylated. In vitro analyses revealed that Ajuba induces the autophosphorylation and consequent activation of AURKA. Depletion of Ajuba prevented activation of AURKA at centrosomes in late G2 phase and inhibited mitotic entry.

AURKA induces p53 degradation by phosphorylation of Ser-315. It was demonstrated that DNA binding and transactivation activity of p53 was abrogated by AURKA. AURKA phosphorylates p53 at Ser-215 in vitro and in vivo. The inhibition of p53 DNA binding and transactivation activity by AURKA depends on phosphorylation of Ser-215 but not Ser-315. Further, AURKA phosphorylation of Ser-215 of p53 is associated with AURKA-regulated cell cycle progression, cell survival, and transformation. The p53 is a physiological substrate of AURKA and that AURKA exerts its function through phosphorylation of Ser-215 of p53.

**Homology**

Aurora related kinases, AURKA and AURKB are present in Drosophila, C.elegans and X. laevis. Among mammals, three members of the family, AURKA, -B and -C have so far been identified. The three members of the mammalian kinases of varying peptide lengths share similar catalytic domains located in the carboxyl terminus but their amino terminal extensions are of variable length and display little or no similarity. By examination of the AURKA cDNA sequence the threonine at residue 288 in the catalytic domain was found to be highly conserved in all Aurora family members as well as in various other serine/threonine kinases.

**Mutations**

**Germinial**

No germline mutations have been reported.

**Somatic**

Recent studies have demonstrated the overexpression and amplification of AURKA in many malignant human cancers and cell lines including breast, ovarian, colon, prostate, and neuroblastoma cancer cell lines. AURKA overexpression induces supernumerary centrosomes aneuploidy and cells transformation. It has been also reported that ectopic overexpression of AURKA in NIH3T3 and immortalized Rat1 induces cells transformation that generates tumor when implanted in nude mice. Elevated AURKA expression overcomes the checkpoint mechanism that monitors mitotic spindle assembly, inducing resistance to the chemotherapeutic agent paclitaxel. Cells overexpressing Aurora-A inappropriately enter anaphase despite defective spindle formation, and the persistence of MAD2 at the kinetochores, marking continued activation of the spindle assembly checkpoint. These findings suggest that enhanced AURKA expression causes resistance to apoptosis induced by mitotic inhibitors in human cancer cells.

**Implicated in**

**Breast cancer**

**Disease**

Breast cancer is the most common cause of cancer in women and the second most common cause of cancer death in women. Some of the patients are hereditary, with a large proportion characterized by mutation in BRCA1 and/or BRCA2 genes.

**Oncogenesis**

The protein level of AURKA is increased at the G2 to M phase transition in normal cells, where AURKA is specifically localised at centrosomes and mitotic spindles. By contrast, analysis of tumour cells of the breast for AURKA expression patterns shows that overexpression of AURKA was present in 94% of the cases, regardless of their cell-cycle phases, and is diffusely detected in the cytoplasm. Amplification of AURKA has been detected at higher frequency in tumors from BRCA1 and BRCA2 mutation carriers than in sporadic breast tumors, suggesting that overexpression of AURKA and inactivation of BRCA1 and BRCA2 cooperate during tumor development and progression. The F31I polymorphism in AURKA has been associated with...
breast cancer risk in the homozygous state in prior studies. Studies have demonstrated that AURKA overexpression contributes to genetic instability and tumourigenesis by disrupting the proper assembly of the mitotic checkpoint complex and occurs in a high proportion of breast cancers.

**Pancreatic cancer**

**Disease**

Pancreatic ductal adenocarcinoma is one of the most fatal malignancies. Intensive investigation of molecular pathogenesis might lead to identifying useful molecules for diagnosis and treatment of the disease.

**Oncogenesis**

Pancreatic ductal adenocarcinoma harbors complicated aberrations of alleles including losses of 1p, 6q, 9p, 12q, 17p, 18q, and 21q, and gains of 8q and 20q. Pancreatic cancer is usually initiated by mutation of KRAS and aberrant expression of SHH. Overexpression of AURKA mapping on 20q13.2 may significantly enhance overt tumorigenecity. AURKA was a direct downstream target of MAPK1, suggesting that the overexpression of AURKA without gene amplification may be induced by constitutive activation of MAPK1 in cancer cells. The constitutive activation of MAPK1 is frequently observed in pancreatic cancer.

**Ovarian cancer**

**Disease**

Ovarian cancer is the most lethal gynecologic malignancy in developed countries. The exact cause is usually unknown. The risk of developing ovarian cancer appears to be affected by several factors.

**Oncogenesis**

Recent studies have shown that DNA gains of the chromosomal region 20q13 and overexpression of the centrosomal kinase AURKA, the gene of which is found within the 20q13 region, are hallmarks of ovarian cancer. Amplification of AURKA has been reported in ovarian tumors, suggesting a role in ovarian cancer pathlogy. AURKA is polymorphic with two single nucleotide substitutions (449t/a and 527g/a) in evolutionarily conserved regions causing amino acid changes (F31I and V57I). Two other nucleotide substitutions (287c/g and 1891g/c) of unknown significance are in 5' and 3' untranslated regions (UTR), respectively. AURKA overexpression represented a survival factor for tumor cells and a negative prognostic molecular marker.

**Human esophageal squamous cell carcinoma**

**Disease**

Human esophageal squamous cell carcinoma (ESCC) is one of the most frequent malignancies worldwide and occurs at a very high frequency in the People's Republic of China, South Africa, France, and Italy. A number of epidemiological investigations have shown that esophageal carcinogenesis and the malignant development of esophageal cancers are complex and associated with multiple etiologic factors, including genetic backgrounds, environmental stimuli, nutritional conditions, and cultural habits.

**Oncogenesis**

Despite some epidemiological observations, the biological mechanism(s) that is involved in ESCC occurrence and progression remains to be elucidated. It has been shown that point mutations of the tumor suppressor gene p53 are detected in 40% of human esophageal cancers. The Rh gene is also frequently mutated in ESCC. Amplification of the cellular protooncogenes Myc, EGFR, HST1, INT2, and cyclin D1 are often found in this malignant disease. A recent demonstration indicates that AURKA polymorphisms are associated with advanced disease status of ESCC, and there is strong evidence that AURKA is overexpressed in human ESCC and may play a role in carcinogenesis and malignancy development of ESCC.

**Human Bladder Cancer**

**Disease**

Bladder tumors are among the most common human cancers, with approximately 55,000 new cases detected each year in the United States. Bladder cancers, which represent a group of tumors with diverse morphologic and clinical behavior, exhibit one of the strongest relationships seen in any cancer between clinical aggressiveness and degree of aneuploidy.

**Oncogenesis**

Bladder cancers arise from at least two distinct, albeit sometimes overlapping, pathways that lead to the development of papillary and solid or nonpapillary tumors. Most superficially growing, low-grade papillary lesions are diploid or near-diploid. Although they often recur, they are unlikely to invade the bladder wall and metastasize. By contrast, virtually all nonpapillary tumors are highly aneuploid and have a strong propensity to invade the stroma and metastasize. Superficial bladder tumors that are aneuploid are also likely to progress to invasive clinically aggressive carcinomas, which may metastasize. AURKA amplification is frequently overexpressed in bladder tumors tested by FISH and the strong association of the gene amplification and overexpression levels with the degree of aneuploidy suggests that AURKA may play an important role in bladder carcinogenesis by contributing to the development of aneuploid cell populations with aggressive phenotypes.

**Human colon cancer**

**Disease**

It is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. Colorectal cancer causes 655,000 deaths worldwide per year, including about 16,000 in the UK, where it is the second most common site (after lung) to cause cancer death. The most common colon cancer cell type is adenocarcinoma which accounts for
95% of cases. Other, rarer types include lymphoma and squamous cell carcinoma. Adenocarcinoma is a malignant epithelial tumor, originating from glandular epithelium of the colorectal mucosa. It invades the wall, infiltrating the muscularis mucosae, the submucosa and thence the muscularis propria.

**Oncogenesis**

Colorectal cancer is a disease originating from the epithelial cells lining the gastrointestinal tract. Hereditary or somatic mutations in specific DNA sequences, among which are included DNA replication or DNA repair genes and also the APC, K-Ras, NOD2 and p53 genes, lead to unrestricted cell division. Furthermore, genetic instability is expressed in colon cancer by an increased rate of a number of different genetic alterations. These different manifestations of genetic instability are classified into two major categories. The first one involves subtle changes in DNA sequences typically represented by microsatellite instability (MIN). The second one is characterized by gains and losses of whole or parts of chromosomes, named chromosomal instability (CIN), and it is considered a driving force for tumourigenesis. MIN occurs in approximately 15% of colon cancers and results from inactivation of the mismatch repair (MMR) system by either MMR gene mutations or hypermethylation of the MLH1 promoter. The mechanisms inducing CIN in cancer and more specifically in colon cancer are only partly understood. At least two possible causes, not mutually exclusive, could be responsible for CIN: mutations in genes encoding mitotic regulators, such as spindle checkpoint proteins, and defects in genes controlling centrosome homeostasis. The presence of mutations of the mitotic checkpoint regulators BUB1 and BUBR1 and amplification of AURKA in a subset of human colon cancers have suggest that CIN results primarily from deregulation of DNA replication and mitotic-spindle checkpoints.

**Human Multiple myeloma**

**Disease**

Multiple myeloma (also known as MM, myeloma, plasma cell myeloma, or as Kahrler’s disease after Otto Kahler) is a type of cancer of plasma cells which are immune system cells in bone marrow that produce antibodies. Myeloma is regarded as incurable, but remissions may be induced with steroids, chemotherapy, thalidomide and stem cell transplants. Myeloma is part of the broad group of diseases called hematological malignancies. Multiple myeloma (MM) is a malignancy characterized by genetic instability, suggesting a disruption of checkpoints that arrest cells at G2M when injury to the mitotic machinery occurs.

**Oncogenesis**

The expression of RHAMM and other centrosome-associated genes are known to correlate with the extent of centrosome amplification in multiple myeloma, and with poor prognosis. RHAMM has a significant interaction with TPX2, a protein which regulates the localization and action of AURKA at the spindle poles. AURKA is expressed ubiquitously in myeloma, to varying degrees. Aurora kinase inhibitor VE-465 also induces apoptosis and death in myeloma cell lines and primary myeloma plasma cells. The combination of VE-465 and dexamethasone improves cell killing compared with the use of either agent alone, even in cells resistant to the single agents.

**Human hepatocellular carcinoma**

**Disease**

Hepatocellular carcinoma (HCC, also called hepatoma) is a primary malignancy (cancer) of the liver. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis). In countries where hepatitis is not endemic, most malignant cancers in the liver are not primary HCC but metastasis (spread) of cancer from elsewhere in the body, e.g. the colon. Treatment options of HCC and prognosis are dependent on many factors but especially on tumor size and staging.

**Oncogenesis**

AURKA is overexpressed frequently in HCC, and correlated with high grade and high stage, indicating that overexpression of AURKA plays a role in the development and progression of HCC. Furthermore in HCC is frequently associated the homozygous deletion of p15E2 (MTS2/INK4b/CDKN2B) and p16E2 (MTS1/INK4a/CDKN2A) with overexpression of AURKA gene, this association may play a role in the oncogenesis and malignant progression of HCC.

**Human Upper gastrointestinal adenocarcinomas**

**Disease**

Upper gastrointestinal adenocarcinomas are the second most common cause of cancer-related death in the world and are characterized by complex molecular changes. Several epidemiological studies have indicated that the incidence of proximal adenocarcinomas of the gastroesophageal junction and lower esophagus is rising faster than ever before in the Western world. The incidence of adenocarcinoma of the cardia, gastroesophageal junction, and lower esophagus has been rapidly rising, 5-fold to 6-fold in the past few decades, especially in patients younger than 50 years of age.

**Oncogenesis**

Overexpression of AURKA is frequent in upper gastrointestinal adenocarcinomas and in recently works it was identified the AURKA/AKT axis as an important mechanism that provides cancer cells with potent antiapoptotic properties through regulating p53-dependent apoptosis. Frequent overexpression of AURKA at the mRNA and protein levels in upper gastrointestinal adenocarcinomas, and interestingly, this overexpression was more prevalent in
gastroesophageal junction adenocarcinomas and lower esophageal, Barrett-related adenocarcinomas (BAs) than in antrum and body gastric adenocarcinomas. There are not an association between AURKA overexpression and histopathological parameters such as tumor grade, TNM classification, and lymph-node metastasis.

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