Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

GADD45A (growth arrest and DNA-damage-inducible, alpha)

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Published in Atlas Database: June 2014

Online updated version : http://AtlasGeneticsOncology.org/Genes/GADD45AID339ch1p31.html
DOI: 10.4267/2042/56405

Abstract

Growth Arrest and DNA-damage-inducible, alpha (GADD45α) is a member of the GADD family proteins that also include GADD45β and GADD45γ.
The highly conserved GADD45 proteins are small (18 kDa) and primarily localized in the nucleus. The GADD45 proteins acting as sensors of environmental and physiological stress interact with and/or modulate the activities of partner proteins involved in cell cycle, cell survival, apoptosis, maintenance of genomic stability and DNA repair. GADD45 proteins also act as sensors of oncogenic stress in the initiation of tumors and in tumor responses to different therapeutics.
The expression of GADD45α in response to DNA damage is mediated by p53-dependent and p53-independent mechanisms, the latter which involves Wilms tumor 1 (WT1) protein. GADD45α subsequently inhibits G2/M transition of cell cycle and induces apoptosis. GADD45α also has a role in DNA-demethylation to promote genome stability. In many malignancies, GADD45α levels are down-regulated, likely allowing tumor cells to escape from senescence and apoptosis.
Novel approaches are therefore being developed to regulate GADD45α levels to combat malignancies.

Keywords
GADD45α, DDIT1, DNA damage, cell cycle

Identity

Other names: DDIT1, GADD45

HGNC (Hugo): GADD45A

Location: 1p31.3

DNA/RNA

Description

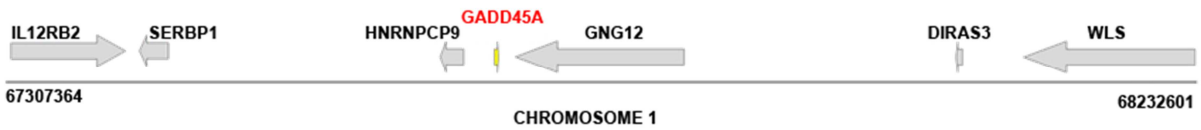
The human GADD45α is localized on chromosome 1 and comprises four exons (NCBI, 2014).

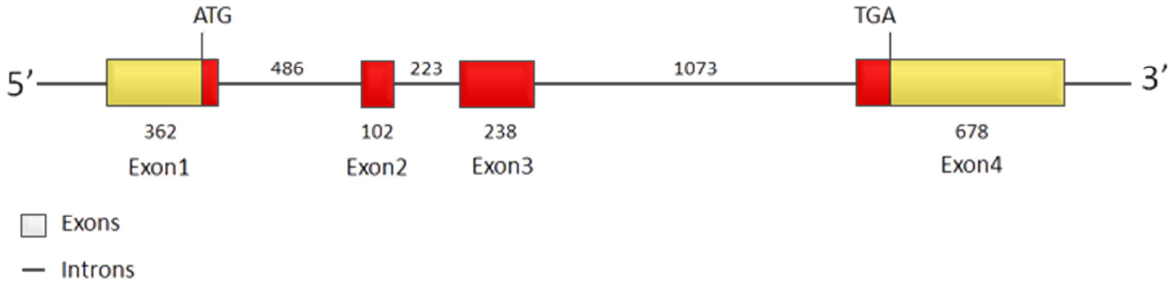
Transcription

Depending on the splicing of the GADD45α pre-mRNA, there are three mRNA variants.

Pseudogene

Homologous sequence on chromosome 12q may be a retro-pseudogene (Papathanasiou et al., 1991).





Human GADD45α located on chromosome 1 is on the forward strand. It consists of four exons represented as boxes and introns shown as lines. Darker grey boxes indicate the open reading frame (ORF) of 498 base pairs (bp). The first methionine (ATG) and the stop codon (TGA) of ORF are marked. The length of each exon and intron is shown in base pairs.

Protein

Note

Based on mRNA sequences, it is predicted that there are three isoforms of GADD45α protein (NCBI, 2014). While the isoform 1 utilizes 498 bp ORF encoding 165 amino acids (aa)-long protein (protein ID: NP_001915.1), the absence of the second in-frame exon in the isoform 2 results in a 396 bp ORF giving rise to a 131 aa-long protein (protein ID: NP_001186670.1). In the isoform 3, the second and third exons partially exist forming a 183 bp mRNA that encodes a 60 aa-long protein (protein ID: NP_001186671.1).

Description

GADD45α protein is a member of the GADD family that includes GADD45β and GADD45γ. Forming a homodimer as well as heterodimers with other family members, GADD45α is involved in the maintenance of genomic integrity, growth arrest and apoptosis (Rosemary Siafakas and Richardson, 2009; Sytnikova et al., 2011) through interactions with various proteins including Cdc2 protein kinase, Waf1/Cip1 ID: 139> protein, core histone proteins, proliferating cell nuclear antigen (PCNA) and MTK/MEKK4 (Zerbini and Libermann, 2005; Zhan, 2005; Rosemary Siafakas and Richardson, 2009; Johnson et al., 2013). GADD45α also acts as an RNA binding protein (Sytnikova et al., 2011). Ubiquitination appears to be involved in the turnover of GADD45α (Leung et al., 2001).

Expression

Protein levels of GADD45α varies during the cell cycle, the highest being in G1 phase and the lowest in S phase (Zhan, 2005; Rosemary Siafakas and Richardson, 2009). The expression of GADD45α is regulated by p53-dependent and p53-independent mechanisms. The p53-dependent pathway involves the direct binding of p53 to a cognate response element located on the third intron of GADD45α. Whereas, in the p53-independent signaling route, p53 modulates GADD45α expression by interacting with WT1, a transcription factor and a tumor suppressor, bound on GC-rich motifs of the GADD45α promoter (Zhan, 2005; Johnson et al., 2013). Rapid and transient expression of GADD45α can be induced by DNA damaging agents including UV (p53-independent), ionizing radiation (p53-dependent), methylmethane sulfonate (MMS), nitrogen mustard, melphalan, hydrogen peroxide and hypoxia as well as by the withdrawal of growth factors (Hollander and Fornace, 2002; Zhan, 2005; Rosemary Siafakas and Richardson, 2009). GADD45α expression is also activated by breast cancer 1, early onset, (BRCA1) in various cell lines (Harkin et al., 1999).

Localisation

GADD45α, as other members of GADD family proteins, is predominantly localized in the nucleus (Zhan, 2005; Rosemary Siafakas and Richardson, 2009). In glioblastoma and breast tumors, GADD45α is also observed to localize in the cytoplasm (Reddy et al., 2008; Tront et al., 2013).

Function

The maintenance of genome integrity is essential to prevent the development of cancer, which is associated with genomic instability. GADD45α plays an important role in maintaining genomic integrity by promoting nucleotide-excision repair (NER), cell cycle arrest and apoptosis (Hollander and Fornace, 2002; Barreto et al., 2007; Sytnikova et al., 2011).

GADD45α mediates NER by binding to repair endonuclease xeroderma pigmentosum G (XPG) protein (Hollander and Fornace, 2002; Barreto et al., 2007; Sytnikova et al., 2011). While the disruption of Cdc2/Cyclin B1 interactions by GADD45α is critical for the blockage of G2/M transition (Zhan et al., 1999; Rosemary Siafakas and Richardson, 2009), the activation of c-Jun N-terminal kinase (JNK) as a result of the interaction of GADD45α with mitogen-activated protein three kinase (MTK1) induces apoptosis (Zerbini and Libermann, 2005). GADD45α is also reported to repress cell migration and invasion by suppressing β-catenin signaling through stress-mediated p38 mitogen activated protein kinase (MAPK) pathway (Hildesheim et al., 2004).

Homology

The human GADD45α shows 90% aa identity to GADD45α of other species including rhesus monkey, domestic cat, hamster, mouse and rat (Rosemary Siafakas and Richardson, 2009).
In addition, there is a nearly 50% aa identity among GADD45α and other GADD45 proteins (Rosemary Siafakas and Richardson, 2009).
The RNA-binding domain of GADD45α displays high aa homology to many RNA binding proteins that includes ribosomal proteins L7a, S12 and L30e (Sytnikova et al., 2011; Tian and Locker, 2013).

Implicated in

Colorectal carcinoma

Note

In primary colorectal carcinoma tissue samples grouped according to tumor staging (group 1: restricted to gut; group 2: restricted to gut but signs of malignancy on lymph nodes are present; group 3: in addition to group 2 characteristics, metastasis to distant tissue is present), it was observed that GADD45α expression decreases as staging increases.
Whereas, GADD45α expression in close proximity or distant tissues remains unchanged (Štorcelová et al., 2013).

Breast cancer

Note

Intracellular level of GADD45α assessed by immunocytochemistry is reported to positively correlate with the presence of estrogen and progesterone receptors in primary breast cancer samples (Tront et al., 2013).
It appears that GADD45α levels are higher in Luminal A (ER+, PR+, HER2-) and Luminal B (ER+, PR+, HER2+) subgroups of tumors than HER2+ (HER2+, ER-,PR-) and Triple Negative (ER-, PR-, HER2-) subgroups (Tront et al., 2013).

Gastric cardia adenocarcinoma

Note

Relative mRNA expression evaluated by qPCR of gastric cardia adenocarcinoma (GCA) samples suggests that the expression of GADD45α is repressed compared to that of neighboring normal tissue samples. Based on TNM staging, GADD45α mRNA levels were found to be higher in Stage I and Stage II patient samples than Stage III and Stage IV patient samples. Higher degree of methylation of the GADD45α gene promoter appears to be one reason for the decreased expression of GADD45α in GCA. There were no other correlation between GADD45α mRNA levels and clinicopathological characteristics (Guo et al., 2013).

Glioblastoma

Note

In diffuse-infiltrating astrocytomas, the expression of GADD45α assessed by qPCR shows variations depending on tumor grading. It appears that GADD45α is expressed at higher levels in glioblastoma (GBM; WHO grade IV) compared to astrocytoma (DA; WHO grade II) or to anaplastic astrocytoma (AP; WHO grade III) (Reddy et al., 2008).

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This article should be referenced as such:

User SD, Muyan M. GADD45A (growth arrest and DNA-damage-inducible, alpha). Atlas Genet Cytogenet Oncol Haematol. 2015; 19(3):164-167.