

# GADD45A

Subjects: Genetics & Heredity | Oncology

Contributor: Sylwia Pietrasik, Gabriela Zajac, Jan Morawiec, Mirosław Soszynski, Michał Fila, Janusz Blasiak

The growth arrest and DNA damage-inducible 45 alpha (GADD45A) gene encodes a 165 aa protein localized in the nucleus, whose level is highest in the G1 phase of the cell cycle, with a substantial reduction in S. The involvement of GADD45A in the cell cycle regulation and interaction with other proteins underline its function in the cellular DNA damage response and maintaining genomic stability, which, in turn, determines its high potential in cancer transformation. The protective role of GADD45A in DNA damage-induced tumorigenesis is the main biological function of this protein, but exact mechanism of it is not known. Emerging evidence suggests that GADD45A may be important in breast cancer and several molecular pathways were reported to underline this importance, including Ras, mitogen-activated protein kinase 8 (MAPK8), JNK (c-Jun N-terminal kinase) and p38. GADD45A may play a tumor-suppressor role by induction of senescence and apoptosis in cancer cells. However, it was also shown that GADD45A may promote tumorigenesis via the GSK3  $\beta$  (glycogen synthase kinase 3 beta)/ $\beta$ -catenin signaling. Therefore, GADD45A may function as either a tumor promotor or suppressor, depending on the kind of oncogenic stress, and these two functions are mediated by different signaling pathways.

Keywords: GADD45 ; breast cancer ; DNA damage response ; tumor suppressor ; tumor promotor

---

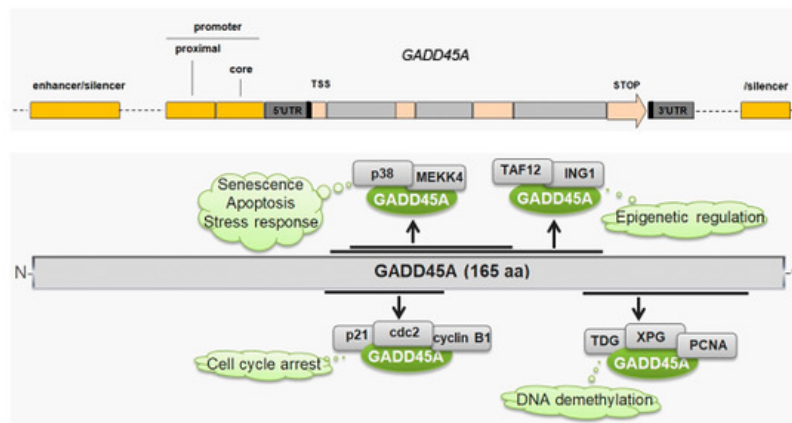
## 1. Introduction

The growth arrest and DNA damage-inducible 45 alpha (GADD45A) gene plays a role in the regulation of the cellular reaction to stress as its transcript levels increase in response to stressful growth arrest conditions and DNA-damaging agents. The protein encoded by this gene responds to environmental stresses by mediating activation of the p38/JNK (c-Jun N-terminal kinase) pathway via the MTK1 (methylthioribose kinase 1)/MEKK4 (MEK kinase 4) kinase. Alternatively spliced transcript variants encoding distinct isoforms have been found for this gene <sup>[1]</sup>.

The *GADD45A* gene codes for a 165 aa protein, the GADD45A protein, localized in the nucleus and ubiquitous in normal tissues. The level of GADD45A is related to the cell cycle and is highest in the G1 phase, with a substantial reduction in S <sup>[2][3]</sup>. It is degraded in the proteasome on ubiquitination and the activation of PKCdelta (protein kinase delta) may result in GADD45A deubiquitination, protecting it from degradation <sup>[4]</sup>.

## 2. GADD45A and Its Role in Breast Cancer

GADD45A plays several important functions in the cell, including cell growth suppression; mediating cell cycle arrest at G2/M; apoptosis induction; and interaction with p53, CDK1 (cyclin dependent kinase 1, Cdc2), and cyclin B1 (Figure 1, reviewed in <sup>[5]</sup>). These functions underline an important role of GADD45A in maintaining genomic stability, DNA damage response (DDR), and cancer transformation. In fact, the protective role of GADD45A in DNA damage-induced tumorigenesis is a main biological function of this protein that has been demonstrated so far <sup>[6][7][8]</sup>. However, molecular pathways underlying this protective role of GADD45A in cancer are not completely known.



**Figure 1.** GADD45A (growth arrest and DNA damage-inducible 45 alpha) gene and protein. The *GADD45A* gene is located in 1p31.3 and contains four exons. The GADD45 protein interacts with many proteins to perform many functions in stress signaling, DNA repair, cell survival, cell cycle arrest, senescence, or apoptosis (clouds). TSS—transcription start site, UTR—untranslated region, MEKK4—mitogen-activated protein kinase 4, TAF12—TATA-box binding protein associated factor 12, ING1—inhibitor of growth family member 1, cdc2—cyclin dependent kinase 2, TDG—thymine DNA glycosylase, XPG—xeroderma pigmentosum group, G—complementary protein, and PCNA—proliferating cell nuclear antigen. Dotted lines represent DNA fragments non-essential for the *GADD45A* gene.

The important role of GADD45A in cancer transformation was also confirmed in breast cancer. A higher expression of GADD45A was observed in breast cancer samples compared with adjacent non-cancerous tissues [9]. Tront et al. observed that the loss of GADD45A accelerated mammary tumor formation driven by Ras activation in mice and that these tumors showed an increasing growth rate and were characterized by a more aggressive phenotype [10]. Moreover, they observed a decrease of apoptosis that was associated with the activation of mitogen-activated protein kinase 8 (MAPK8), as well as a decrease in Ras-induced senescence that was correlated with a decreased activation of p38. These authors presented the tumor-suppressive role of GADD45 in Ras-driven breast carcinogenesis through the induction of stress-sensitive JNK and p38 kinases. However, in their next work, Tront et al. showed that GADD45A promoted Myc-driven breast carcinogenesis by a negative regulation of MMP10 via GSK3  $\beta$ / $\beta$ -catenin signaling that resulted in enhanced tumor vascularization and growth [11]. These two works suggest that GADD45A may function as either a tumor promotor or suppressor, depending on the kind of oncogenic stress, and these two functions are mediated by different signaling pathways. Some associations between variability of the *GADD45A* gene and the occurrence of breast cancer with no BRCA1/2 mutation (sporadic and familial) were found in a large cohort study performed in a Chinese population [12]. Similar results were also obtained in nearly 100 French Canadian families without BRCA1/2 mutations [13].

Tront et al. correlated GADD45A expression with the hormone receptor status in breast cancer samples and normal tissues [14]. They observed that normal breast tissue was characterized by low levels of GADD45A, but high levels of this protein were observed in luminal A and B types of breast cancer. Triple negative breast cancer was associated with low levels of GADD45 or its absence. Therefore, the expression of GADD45A may be a prognostic marker in breast cancer and GADD45A may thus be considered a target in breast cancer therapy.

It was shown that 5-azaC induced the expression of GADD45 in breast cancer cell lines, with little or no expression in cell lines derived from normal breast epithelium [15]. Therefore, *GADD45* can be considered a methylation-sensitive gene in breast cancer.

## References

1. Zhang, Y.; Bhatia, D.; Xia, H.; Castranova, V.; Shi, X.; Chen, F.; Nucleolin links to arsenic-induced stabilization of GADD45alpha mRNA. *Nucleic Acids Res* **2006**, *34*, 485-495., [10.1093/nar/gkj459](https://doi.org/10.1093/nar/gkj459).
2. J M Kearsey; Philip J Coates; A R Prescott; E Warbrick; P A Hall; Gadd45 is a nuclear cell cycle regulated protein which interacts with p21Cip1.. *Oncogene* **1995**, *11*, .
3. M Vairapandi; A G Balliet; A J Fornace; B Hoffman; D A Liebermann; The differentiation primary response gene MyD118, related to GADD45, encodes for a nuclear protein which interacts with PCNA and p21WAF1/CIP1.. *Oncogene* **1996**, *12*, .

4. Leung, C.H.; Lam, W.; Zhuang, W.J.; Wong, N.S.; Yang, M.S.; Fong, W.F.; PKCdelta-dependent deubiquitination and stabilization of Gadd45 in A431 cells overexposed to EGF. *Biochemical and biophysical research communications* **2001**, *285*, 283-288., [10.1006/bbrc.2001.5164](https://doi.org/10.1006/bbrc.2001.5164).
5. Jesús M. Salvador; Joshua D. Brown-Clay; Albert J. Fornace; Gadd45 in Stress Signaling, Cell Cycle Control, and Apoptosis. *Advances in Experimental Medicine and Biology* **2013**, *793*, 1-19, [10.1007/978-1-4614-8289-5\\_1](https://doi.org/10.1007/978-1-4614-8289-5_1).
6. Jeffrey Hildesheim; D V Bulavin; Miriam R Anver; W Gregory Alvord; M Christine Hollander; Lilit Vardanian; Albert J. Fornace; Gadd45a protects against UV irradiation-induced skin tumors, and promotes apoptosis and stress signaling via MAPK and p53.. *Cancer Research* **2002**, *62*, , .
7. M C Hollander; O Kovalsky; J M Salvador; K E Kim; A D Patterson; D C Haines; A J Fornace; Dimethylbenzanthracene carcinogenesis in Gadd45a-null mice is associated with decreased DNA repair and increased mutation frequency.. *Cancer Research* **2001**, *61*, , .
8. Gowdhaman Et Al. Gowdhaman Et Al.; Tjprc; Sourabh Jain Et Al. Sourabh Jain Et Al.; Test 1. *International Journal of Agricultural Science and Research* **2018**, *8*, 1-15, [10.24247/ijdrdjun20186](https://doi.org/10.24247/ijdrdjun20186).
9. Junnan Wang; Yiran Wang; Fei Long; Fengshang Yan; Ning Wang; Yajie Wang; The expression and clinical significance of GADD45A in breast cancer patients. *PeerJ* **2018**, *6*, e5344, [10.7717/peerj.5344](https://doi.org/10.7717/peerj.5344).
10. Jennifer S. Tront; Barbara Hoffman; Dan A. Liebermann; Gadd45a Suppresses Ras-Driven Mammary Tumorigenesis by Activation of c-Jun NH2-Terminal Kinase and p38 Stress Signaling Resulting in Apoptosis and Senescence. *Cancer Research* **2006**, *66*, 8448-8454, [10.1158/0008-5472.can-06-2013](https://doi.org/10.1158/0008-5472.can-06-2013).
11. Jennifer S. Tront; Yajue Huang; Albert J. Fornace; Barbara Hoffman; Dan A. Liebermann; Yajue Huang; Gadd45a functions as a promoter or suppressor of breast cancer dependent on the oncogenic stress.. *Cancer Research* **2010**, *70*, 9671-9681, [10.1158/0008-5472.CAN-10-2177](https://doi.org/10.1158/0008-5472.CAN-10-2177).
12. Ke-Da Yu; Gen-Hong Di; Wen-Feng Li; Nan-Yan Rao; Lei Fan; Wen-Tao Yuan; Zhen Hu; Jiong Wu; Zhen-Zhou Shen; Wei Huang; et al. Genetic contribution of GADD45A to susceptibility to sporadic and non-BRCA1/2 familial breast cancers: a systematic evaluation in Chinese populations. *Breast Cancer Research and Treatment* **2009**, *121*, 157-167, [10.1007/s10549-009-0516-9](https://doi.org/10.1007/s10549-009-0516-9).
13. Sylvie Desjardins; Inherit Brcas; Genevieve Ouellette; Yvan Labrie; Jacques Simard; Francine Durocher; Analysis of GADD45A sequence variations in French Canadian families with high risk of breast cancer. *Journal of Human Genetics* **2008**, *53*, 490-498, [10.1007/s10038-008-0276-0](https://doi.org/10.1007/s10038-008-0276-0).
14. Jennifer S Tront; Alliric I. Willis; Yajue Huang; Barbara Hoffman; Dan A. Liebermann; Gadd45a levels in human breast cancer are hormone receptor dependent. *Journal of Translational Medicine* **2013**, *11*, 131-131, [10.1186/1479-5876-11-131](https://doi.org/10.1186/1479-5876-11-131).
15. Wei Wang; Gudrun Huper; Yueqi Guo; Susan K. Murphy; John A Olson; J R Marks; Analysis of methylation-sensitive transcriptome identifies GADD45a as a frequently methylated gene in breast cancer. *Oncogene* **2005**, *24*, 2705-2714, [10.1038/sj.onc.1208464](https://doi.org/10.1038/sj.onc.1208464).