Annals of Colorectal Cancer Research

Review Article
Published: 11 Nov, 2019

Expression of Oncogenes *ELK1* and *ELK3* in Cancer

Akhlaq Ahmad and Asif Hayat*

College of Chemistry, Fuzhou University, China

Abstract

Cancer is the uncontrolled growth of abnormal cells anywhere in a body, *ELK1* and *ELK3* is a member of the Ets-domain transcription factor family and the TCF (Ternary Complex Factor) subfamily. Proteins in this subfamily regulate transcription when recruited by SRF (Serum Response Factor) to bind to serum response elements. *ELK1* and *ELK3* transcription factors are known as oncogenes. Both transcription factors are proliferated in a different of type of cancer. Herein, we summarized the expression of transcription factor *ELK1* and *ELK3* in cancer cells.

Keywords: ETS; *ELK1*; *ELK3*; Transcription factor; Cancer

Introduction

The ETS, a transcription factor of E twenty-six family based on a dominant ETS amino acids that integrated with a ~10-basepair element arrange in highly mid core sequence 5′-GGA(A/T)-3′ [1-2]. The secular family alter enormous 28/29 members which has been assigned in human and mouse and similarly the family description are further sub-divided into nine sub-families according to their homology and domain factor [3]. More importantly, one of the subfamily members such as ELK (*ETS*-like) adequate an N-terminal ETS DNA-binding domain along with a B-box domain that transmit the response of serum factor upon the formation of ternary complex and therefore manifested as ternary complex factors [4]. Further the ELK sub-divided into *Elk1*, *Elk3* (Net, Erp or Sap2) and *Elk4* (Sap1) proteins [3,4], which simulated varied proportional of potential protein-protein interactions [4,5]. Similarly the ELK can pronounce to a Mitogen-Activated Protein (MAP) kinas signaling in different pathways [4,5], and as such the *Elk1* and *Elk4* are blended as similar but different DNA-binding site respectively [6,7]. Herein, we summarized the expression of transcription factor *ELK1* and *ELK3* in cancer cells. Cancer is a second leading cause of death worldwide, accounting for 8.2 million deaths in 2012 [8]. Breast cancer is the progression of a malignant tumor that developed from cell in the breast.

Breast cancer current statistics

Globally Breast Cancer (BC) accounted for 23% of all cancer cases, lung (1.82 million), breast (1.67 million), and colorectal (1.36 million) [9]. All women are at risk of breast cancer regardless of their racial, ethnic origin or heritage [10]. Unfortunately Pakistan has high rate of breast cancer cases among South Asian countries. One in every nine Pakistani women suffers from breast cancer which is one of the highest incidence rates in Asia [11]. The data generated from various oncology and radiation therapy institutes and hospitals in Pakistan is used to estimate the penetrance of cancer in our population due to unavailability of cancer registry records. Though several risk factors influence the penetrance of breast cancer in Pakistani population but a detailed analysis of their association is yet an area requiring further research. What exactly is responsible for the cause of such an alarming incidence of breast cancer is still unknown, but dietary factors, obesity, use of oral contraceptives, old age and family history are the most common factors.

Breast cancer types

Each breast has large 15 to 20 sections called lobes and many smaller sections called lobules. The lobes and lobules are attached by thin tubes, called ducts (Figure 1). The most common type of breast cancer is ductal cancer which is found in the cells of the ducts. Cancer in lobes or lobules is called lobular cancer. Lobular cancer mostly affects both breasts. Cancers are of two types non-invasive (*in situ*) and invasive (infiltrating). The term *in situ* refers to cancer that confined to the area where it initially developed. Invasive breast cancer has a tendency to affect (metastasize) other tissues of the breast and/or other regions of the body. A less common type of breast cancer is inflammatory breast cancer characterized by general inflammation of the breast. Other rare types of breast cancer are medullary carcinoma (an invasive breast cancer that forms a distinct boundary between tumor tissue and normal tissue), mucinous carcinoma (mucus producing cancer cells), tubular carcinoma, etc.

OPEN ACCESS

Correspondence:
Asif Hayat, College of Chemistry, Fuzhou University, Fuzhou, 350100, China,
E-mail: asifncp11@yahoo.com

Received Date: *27 Sep 2019*
Accepted Date: *06 Nov 2019*
Published Date: *11 Nov 2019*

Citation:
Ahmad A, Hayat A. Expression of Oncogenes ELK1 and ELK3 in Cancer. Ann Colorectal Cancer Res. 2019; 1(1): 1001.

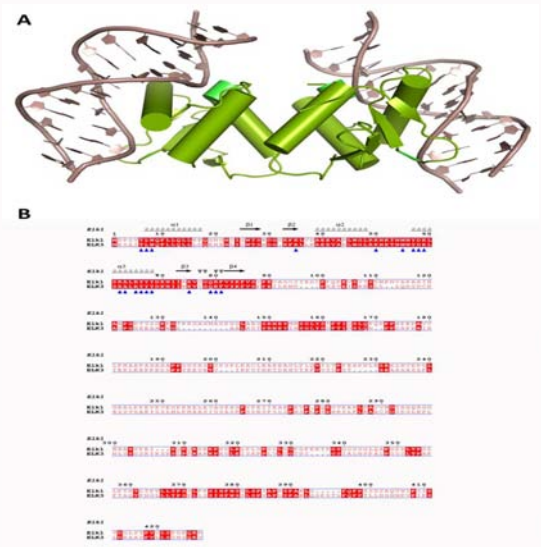

Figure 1: A) The 3D structure of the Elk1- ETS domain interact with DNA PDB (1DUX) α-Helices are represented by cylindrical and β-strands by arrows. B) Amino acid sequences of *ELK1* compare to *ELK3*.

[12]. The ETS (E26 transformation-specific also called as E-Twenty-six) is a largest family of a transcription factor that play important role in cell proliferation, differentiation and apoptosis [13]. The transcription factor *ELK1* and *ELK3* also termed as (NET, SAP-2 or ERP) are the member of ETS family and ternary complex factor TCF subfamily. The TCFS as a result of binding trigger serum response elements with Serum Response Factor (SRF) and by the help of TCF-SRF complexes control many genes such as *c-fos* gene [14].

ELK1 (NCBI ID: BAA36617.1) and *ELK3* (NCBI ID: CAG47047.1) are protein bind to specific DNA sequences in the genome, regulate gene transcription [15]. According to PDB data base *ELK1* contain N domain while in case of domain of *ELK3* no 3D found was found (Figure 1). *ELK1* and *ELK3* are ~38.5% similarity. The *ELK1* protein has 428 amino acids with a molecular weight of 44915.02 with 39 negatively charged residues and 37 positively charged residues. The *ELK3* protein contains 407 amino acids with a molecular weight of 44167.58 with include 35 negatively charged residues and 42 positively charged residues. The central identical region locus at the N domain, ETS (Erythroblast Transformation Specific) domain exists at the N domain that control interaction with DNA. MR-analysis of the structure of the ETS domains shows that it has three alpha-helixes (1-3) and four-stranded beta-sheets (1-4) organized in the order alpha$_1$-beta$_1$-beta$_2$-alpha$_2$-alpha$_3$-beta$_3$-beta$_4$ forming a winged Helix-Turn-Helix (wHTH) topology [13]. Different members of the ETS family proteins display distinct DNA binding specificities. The ETS domains and the adjoining amino acid sequences of the proteins affect the binding affinity, and the changes in a single amino acid in the ETS domain can alter its DNA binding specificities [4].

The secondary structural elements present above the sequences α-Helices are represented by winding and β-strands by bold arrows. Residues conserved in the *Elk-1* and *Elk-3* highlight by red. Residues involved in DNA interaction indicated with blue triangle.

The Figure 2 shows interaction of *ELK1* and *ELK3* with Cyclin-Dependent Kinases (CDKs) in the M phase. While *ELK1* interact with Chromosome segregation process in the M phase as well as meiotic spindle between G_2 and M phase. The expression level of *ELK1* protein in the end stage of G_1 phase elevated. While in the middle stage of G_1 phase and at the end of S phase it almost disappears. However *ELK3* protein expression level in the middle stage of G_2 and G_1 phase became very high. While almost disappear in the middle stage of S phase. *ELK3* are high in the four stages of cell cycle.

The ETS gene play a key role in development, differentiation, transformation and cellular proliferation, their structures are conserved [13,16]. Based on common DNA binding domains, most of the transcription factors are grouped together leading to a similar DNA sequence preference [17,18].

The ETS transcription factor in human is encoded by 28 genes. *ELK1* and *ELK3* are Ternary Complex Factors (TCFs) that belong to the sub-family of Erythroblast Transformation Specific (ETS) domain proteins which bind to a DNA specific sequence through a purine-rich GGA core sequence, transcription factors control the expression of various genes i.e. proto oncogenes [19]. The Elk subfamily consists of three different types of proteins *ELK1*, *ELK3* and *ELK4* (Net, Erp or Sap2 and Sap1), which have diverse possible protein-protein interaction [3-5,20-22]. The sequence of ETS gene family was identified in 1983, E26 which induce leukemia's in chickens. Moreover, the ETS factor orthologous consequently identified in mouse (26), *Caenorhabditis elegans* (10) and *Drosophila melanogaster* (8) displays extraordinary sequence homology with human ETS factors [23-26].

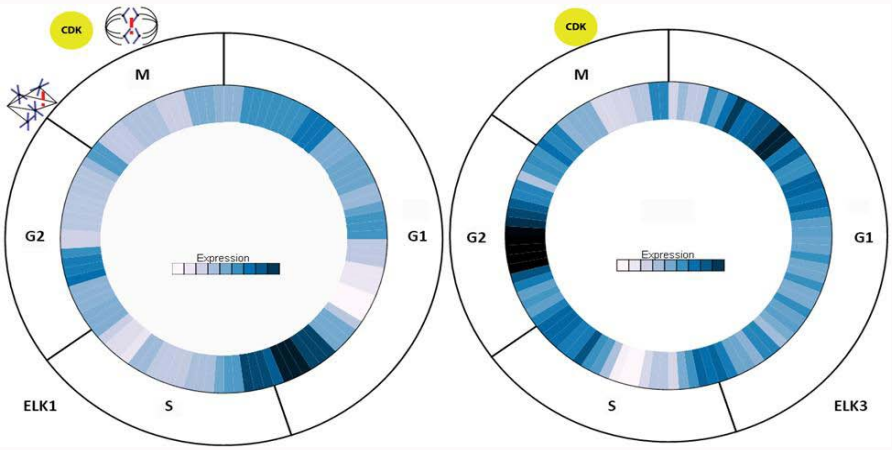

Figure 2: *ELK1* and *ELK3* protein expression level in four stage of cell cycle model.

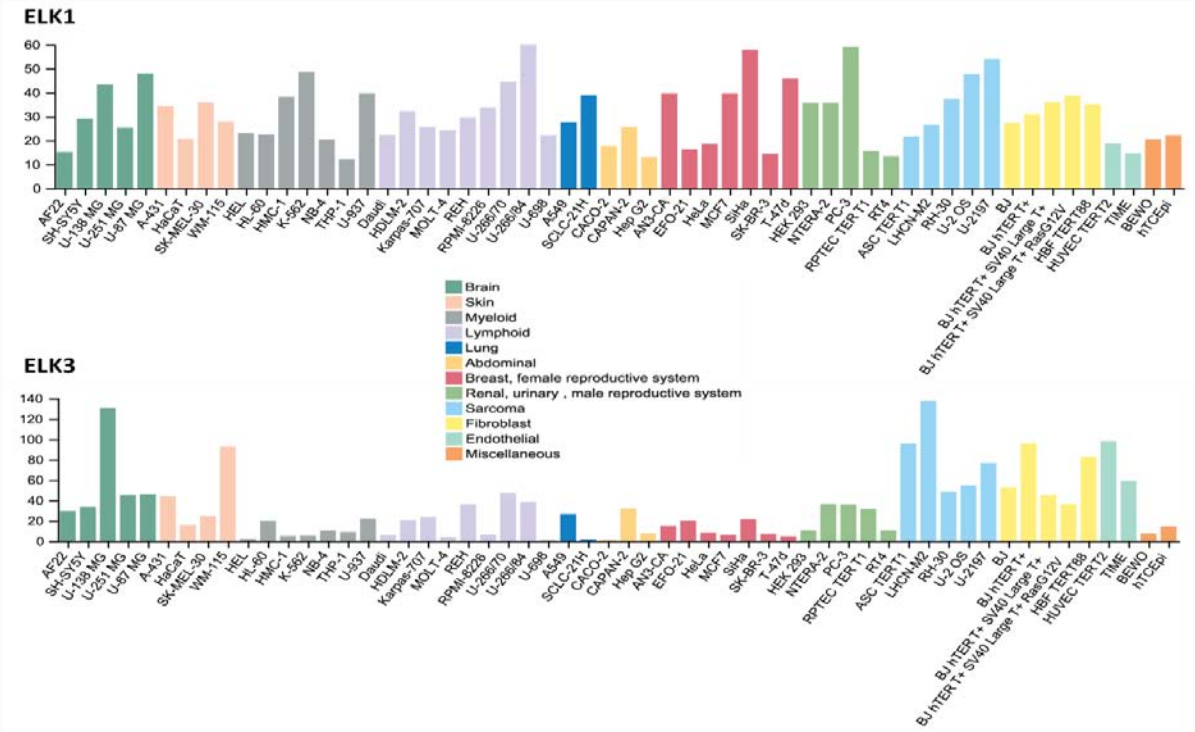

Figure 3: RNA expression level.

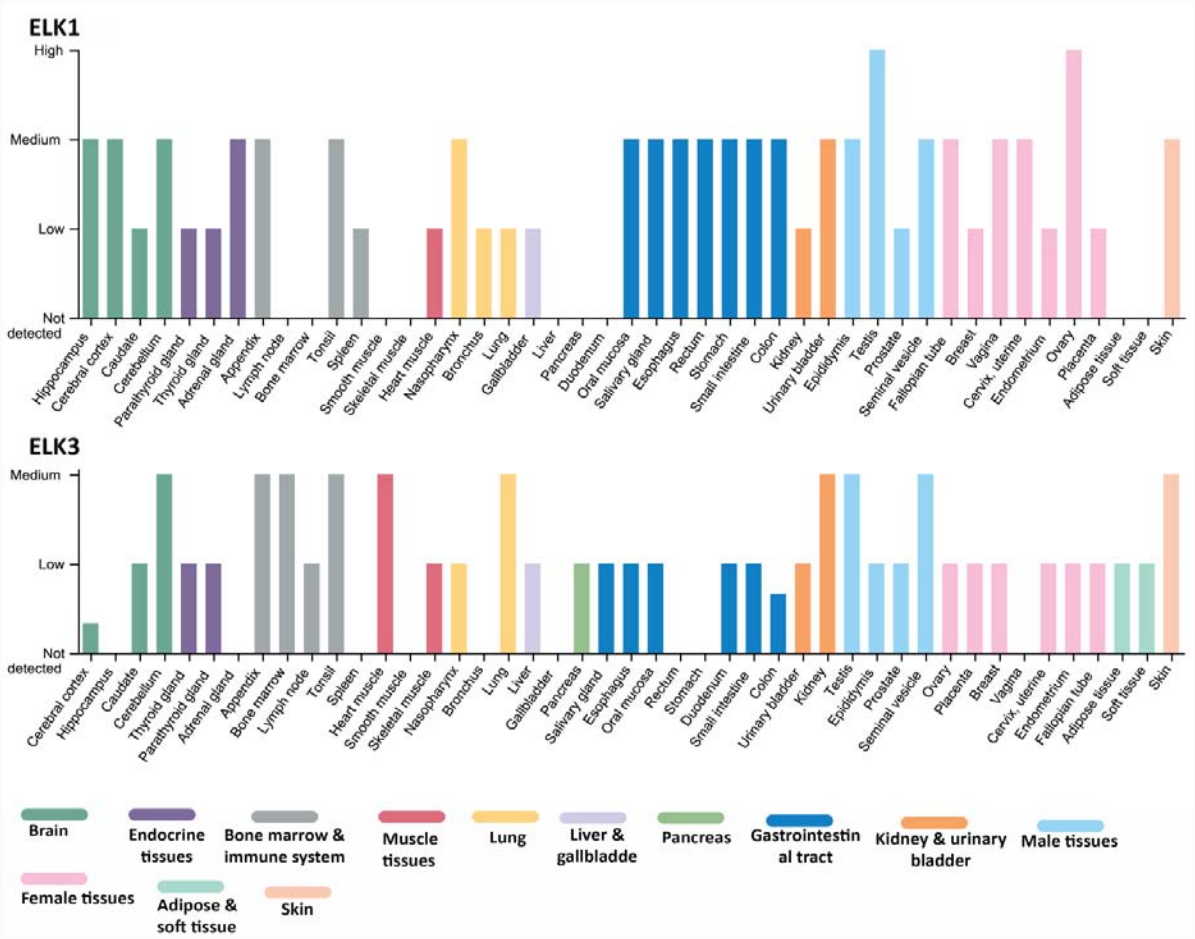

Figure 4: Protein expression level.

Table 1: *ELK1* and *ELK3* expression at protein and mRNA level.

	ELK1	*ELK3*
Cellular Component	axon terminus	nucleoplasm
	nucleus	nucleus
	mitochondrion	intracellular membrane-bounded organelle
	nucleoplasm	mitochondrion
	Dendrite	
	neuronal cell body	
Molecular Function	sequence-specific DNA binding transcription factor activity	purine-rich negative regulatory element binding sequence-specific DNA binding transcription factor activity
	RNA polymerase II core promoter proximal region sequence-specific DNA binding transcription factor activity involved in positive regulation of transcription	transcription corepressor activity
	core promoter binding	RNA polymerase II core promoter proximal region sequence-specific DNA binding transcription factor activity involved in positive regulation of transcription
	double-stranded DNA binding	DNA binding
	chromatin binding	RNA polymerase II core promoter proximal region sequence-specific DNA binding
	RNA polymerase II core promoter proximal region sequence-specific DNA binding	sequence-specific DNA binding RNA polymerase II transcription factor activity
Biological Process	toll-like receptor 3 signaling pathway	cell differentiation
	cellular response to gamma radiation	wound healing
	toll-like receptor 2 signaling pathway	regulation of transcription, DNA-templated
	cell differentiation	regulation of transcription from RNA polymerase II promoter
	toll-like receptor TLR1:TLR2 signaling pathway	positive regulation of transcription from RNA polymerase II promoter
	response to light stimulus	transcription from RNA polymerase II promoter
	toll-like receptor TLR6:TLR2 signaling pathway	negative regulation of transcription, DNA-templated angiogenesis
	transcription from RNA polymerase II promoter	
	toll-like receptor signaling pathway	
	neurotrophin TRK receptor signaling pathway	
	innate immune response	
	cellular response to testosterone stimulus	
	toll-like receptor 9 signaling pathway	
	TRIF-dependent toll-like receptor signaling pathway	
	toll-like receptor 5 signaling pathway	
	stress-activated MAPK cascade	
	toll-like receptor 10 signaling pathway	
	positive regulation of transcription, DNA-templated	
	toll-like receptor 4 signaling pathway	
	positive regulation of neuron death	
	MyD88-dependent toll-like receptor signaling pathway	
	MyD88-independent toll-like receptor signaling pathway	
	positive regulation of transcription from RNA polymerase II promoter	

The ETS transcription factors are involved in different types of cancer *via* their association in chromosomal translation or over expression in cancer and also have the ability to mediate the signaling cascades [16]. In our study, we found that miR-135a regulated *ELK1* and *ELK3* expression at protein and mRNA level in MCF-7 and T47D cells (Figures 3 and 4, Table 1), suggesting the key role of a miR-135 a dysregulation in the pathogenesis of BC. *Elk-1*, a *c-Fos* proto-oncogene regulator, plays an important role in the induction of immediate early gene expression in response to a variety of extracellular signals, member of ETS-domain family of transcriptional factors. Both "*BRCA1*a and *BRCA1*b" splice variants act as growth suppressors of BC. Chai et al. [27] demonstrated for the first time *Elk-1* association with *BRCA1* splice variants "*BRCA1*a and *BRCA1*b" through "GST-pull down assays, co-imunoprecipitations/ Western blot analysis of cell extracts from breast cancer cells and mammalian two-hybrid assays" [28]. They confined the *BRCA1* interaction domain of *Elk-1* protein to the conserved ETS domain, a motif involved in DNA binding and protein-protein interactions. They also observed binding of *BRCA1* proteins to other ETS-domain transcription factors "SAP1, ETS-1, ERG-2 and Fli-1 but not with *Elk-1* splice variant Delta *Elk-1* and *c-Fos* proto-oncogene". Interestingly, their studies revealed that although both *Elk-1* and SAP-1 are also

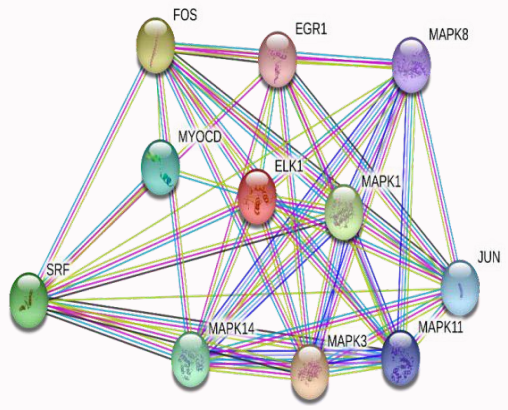

Figure 5: *ELK1* and *ELK3* Pathway.

called ternary complex factors, only *Elk-1* but not *SAP-1* boosted the growth suppressive function of *BRCA1*a/1b proteins in breast cancer cells. Thus *Elk-1* could be a potential downstream target of *BRCA1* in its growth control pathway. Furthermore, they observed inhibition of *c-Fos* promoter activity in *BRCA1*a transfected stable breast cancer cells and over expression of *BRCA1*a/1b reduced MEK-induced SRE activation *in vivo*. These results validated an association between the growth suppressive function of *BRCA1*a/1b proteins and signal transduction pathway involving *Elk-1* protein. All these results together recommended that one of the mechanisms by which . *BRCA1*a/1b proteins function as growth/tumor suppressors is by inhibition of the expression of *Elk-1* target genes like *c-Fos via* the *Elk-1* SRE-SRF ternary complex on the c-Fos promoter, or *via* competing for a common factor(s) [28]. Although we have focused on the role of ETS proteins, it is clear that AP-1 can also have regulatory functions at ETS/AP-1 sites. RAS/ERK signaling results in up regulation of both JUN and FOS expression levels [29]. This may change the subunit composition of AP-1 at ETS/AP-1 binding sequences in favor of proteins that are stronger transcriptional activators. JUN is also a target of JNK phosphorylation, and this pathway increases transcriptional activation by AP-1 [30]. Thus, it will be interesting to discover how the JNK pathway integrates with the RAS/ERK pathway to regulate genes through ETS/AP-1 sequences.

In addition to ETS and AP-1, other transcription factors likely play important roles in the regulation of this RAS/ERK gene expression program. The PEA2 site of the polyoma virus enhancer, which is bound by a RUNX transcription factor, is critical for enhancer function. Interestingly, ETS/RUNX composite sites have been identified in genomic regions bound by *ETS1* in T cells [31]. Binding sites for TCF/LEF1, transcription factors activated by WNT signaling have been shown to cooperate with ETS, AP-1, and RUNX sequences at various regulatory elements, including the MMP7 enhancer [32-34]. Over expression of ETS oncogenes has been reported to activate WNT signaling in prostate cells indicating collaboration with this pathway [35].

In conclusion, the RAS/ERK gene expression program that is regulated, in part, by ETS/AP-1 sequences is an important pathway for the motility and invasion of cancer cells. The regulation of even this simple ETS/AP-1 element can be highly complex and depends on the expression levels of multiple transcription factors and the status of multiple signaling pathways. It is fitting that the ETS transcription factor originally named for the PEA3 sequence element (now renamed ETV4) and the ETS subfamily that inherited the same name play a key role in the biology of this long-studied regulatory sequence (Figure 5) [36].

miRNAs, a family of small non-coding RNAs first discovered by Lee et al. [37] that regulate a wide array of biological processes including carcinogenesis. In cancer cells, miRNAs have been found to be heavily dysregulated. Recently, miRNAs have been shown to involve in differentiation states of various human malignancies, including BC. In particular, comparison of normal and malignant breast tissue has revealed that a small subset of deregulated miRNAs including "mir-125b, mir-145, mir-21, and mir-155" can be identified that obviously differentiate normal from malignant breast tissue [37]. The techniques of the TNM system of clinical stages classification were developed in 1943-1952 by Denoix [38], based on dissemination of cancer according to the feature of primary tumor localization, size, and extension to the surrounding structure.

The ETS transcription factor in humans is encoded by 28 genes. *ELK1* and *ELK3* are Ternary Complex Factors (TCFs) that belong to the sub-family of Erythroblast Transformation Specific (ETS) domain proteins which bind to a DNA specific sequence through a purine-rich GGA core sequence, both of the transcription factors regulate the expression of a variety of genes including proto oncogenes [19]. The Elk subfamily is consisted of three different type of proteins *ELK1*, *ELK3* and *ELK4* (Net, Erp or Sap2 and Sap1), which have diverse possible protein-protein interaction [3-5,20-22]. The sequence of ETS gene family was identified in 1983, E26 which have the function to induces leukemia's in chickens. Moreover the ETS factor orthologous consequently identified in mouse (26), *Caenorhabditis elegans* (10) and *Drosophila melanogaster* (8) displays extraordinary sequence homology with human ETS factors [23-26].

References

1. Tada-Oikawa S, Hiraku Y, Kawanishi M, Kawanishi S. Mechanism for generation of hydrogen peroxide and change of mitochondrial membrane potential during rotenone-induced apoptosis. Life Sci. 2003;73(25):3277-88.
2. Whitmarsh AJ, Shore P, Sharrocks AD, Davis RJ. Integration of MAP kinase signal transduction pathways at the serum response element. Science. 1995;269(5222):403-7.
3. Kobberup S, Nyeng P, Juhl K, Hutton J, Jensen J. ETS-family genes in pancreatic development. Dev Dyn. 2007;236(11):3100-10.
4. Buchwalter G, Gross C, Wasylyk B. Ets ternary complex transcription factors. Gene. 2004;324:1-14.
5. Ducret C, Maira SM, Lutz Y, Wasylyk B. The ternary complex factor Net contains two distinct elements that mediate different responses to MAP kinase signalling cascades. Oncogene. 2000;19(44):5063-72.
6. Shore P, Sharrocks AD. The MADS-box family of transcription factors. Eur J Biochem. 1995;229(1):1-13.
7. Dalton S, Treisman R. Characterization of SAP-1, a protein recruited by serum response factor to the c-fos serum response element. Cell. 1992;68(3):597-612.
8. Wade TJ, Calderon RL, Brenner KP, Sams E, Beach M, Haugland R, et al. High sensitivity of children to swimming-associated gastrointestinal illness: results using a rapid assay of recreational water quality. Epidemiology. 2008;19(3):375-83.
9. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
10. Markert JM, Medlock MD, Rabkin SD, Gillespie GY, Todo T, Hunter WD, et al. Conditionally replicating herpes simplex virus mutant, G207

for the treatment of malignant glioma: results of a phase I trial. Gene Ther. 2000;7(10):867-74.

11. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Risk factor analysis of permanent pacemaker infection. Clin Infect Dis. 2007;45(2):166-73.

12. Brosius III FC, Waller BF, Roberts WC. Radiation heart disease: Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med. 1981;70(3):519-30.

13. Oikawa T, Yamada T. Molecular biology of the Ets family of transcription factors. Gene. 2003;303:11-34.

14. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. N Engl J Med. 1991;324(17):1149-55.

15. Zinser E, Sperka-Gottlieb CD, Fasch EV, Kohlwein SD, Paltauf F, Daum G. Phospholipid synthesis and lipid composition of subcellular membranes in the unicellular eukaryote Saccharomyces cerevisiae. J Bacteriol. 1991;173(6):2026-34.

16. Sharrocks AD. The ETS-domain transcription factor family. Nat Rev Mol Cell Biol. 2001;2(11):827-37.

17. Messina DN, Glasscock J, Gish W, Lovett M. An ORFeome-based analysis of human transcription factor genes and the construction of a microarray to interrogate their expression. Genome Res. 2004;14(10b):2041-7.

18. Wei GH, Badis G, Berger MF, Kivioja T, Palin K, Enge M, et al. Genome-wide analysis of ETS-family DNA-binding *in vitro* and *in vivo*. EMBO J. 2010;29(13):2147-60.

19. Hipskind RA, Rao VN, Mueller CG, Reddy ES, Nordheim A. Ets-related protein Elk-1 is homologous to the c-fos regulatory factor p62TCF. Nature. 1991;354(6354):531-4.

20. Criqui-Filipe P, Ducret C, Maira SM, Wasylyk B. Net, a negative Ras-switchable TCF, contains a second inhibition domain, the CID that mediates repression through interactions with CtBP and de-acetylation. EMBO J. 1999;18(12):3392-403.

21. Fitzsimmons D, Hodsdon W, Wheat W, Maira SM, Wasylyk B, Hagman J. Pax-5 (BSAP) recruits Ets proto-oncogene family proteins to form functional ternary complexes on a B-cell-specific promoter. Genes Dev. 1996;10(17):2198-211.

22. Maira SM, Wurtz JM, Wasylyk B. Net (ERP/SAP2) one of the Ras-inducible TCFs, has a novel inhibitory domain with resemblance to the helix-loop-helix motif. EMBO J. 1996;15(21):5849-65.

23. Leprince D, Gegonne A, Coll J, de Taisne C, Schneeberger A, Lagrou C, et al. A putative second cell-derived oncogene of the avian leukaemia retrovirus E26. Nature. 1983;306(5941):395-7.

24. Wasylyk B, Hahn SL, Giovane A. The Ets family of transcription factors. Eur J Biochem. 1993;211(1-2):7-18.

25. Laudet V, Niel C, Duterquecoquillaud M, Leprince D, Stehelin D. Evolution of the ets Gene Family. Biochem Biophys Res Commun. 1993;190(1):8-14.

26. Hsu T, Trojanowska M, Watson DK. Ets proteins in biological control and cancer. J Cell Biochem. 2004;91(5):896-903.

27. Chai Y, Chipitsyna G, Cui J, Liao B, Liu S, Aysola K, et al. c-Fos oncogene regulator Elk-1 interacts with BRCA1 splice variants BRCA1a/1b and enhances BRCA1a/1b-mediated growth suppression in breast cancer cells. Oncogene. 2001;20(11):1357-67.

28. Goyal L. Cell death inhibition: keeping caspases in check. Cell. 2001;104(6):805-8.

29. Hess J, Angel P, Schorpp-Kistner M. AP-1 subunits: quarrel and harmony among siblings. J Cell Sci. 2004;117(Pt 25):5965-73.

30. Dérijard B, Hibi M, Wu IH, Barrett T, Su B, Deng T, et al. JNK1: a protein kinase stimulated by UV light and Ha-Ras that binds and phosphorylates the c-Jun activation domain. Cell. 1994;76(6):1025-37.

31. Hollenhorst PC, Chandler KJ, Poulsen RL, Johnson WE, Speck NA, Graves BJ. DNA specificity determinants associate with distinct transcription factor functions. PLoS Genet. 2009;5(12):e1000778.

32. Crawford HC, Fingleton B, Gustavson MD, Kurpios N, Wagenaar RA, Hassell JA, et al. The PEA3 subfamily of Ets transcription factors synergizes with β-catenin–LEF-1 to activate matrilysin transcription in intestinal tumors. Mol Cell Biol. 2001;21(4):1370-83.

33. El-Tanani M, Platt-Higgins A, Rudland PS, Campbell FC. ETS gene PEA3 cooperates with β-catenin-Lef-1 and c-Jun in regulation of osteopontin transcription. J Biol Chem. 2004;279(20):20794-806.

34. Giese K, Kingsley C, Kirshner JR, Grosschedl R. Assembly and function of a TCR alpha enhancer complex is dependent on LEF-1-induced DNA bending and multiple protein-protein interactions. Genes Dev. 1995;9(8):995-1008.

35. Gupta S, Iljin K, Sara H, Mpindi JP, Mirtti T, Vainio P, et al. FZD4 as a mediator of ERG oncogene–induced WNT signaling and epithelial-to-mesenchymal transition in human prostate cancer cells. Cancer Res. 2010;70(17):6735-45.

36. Xin JH, Cowie A, Lachance P, Hassell JA. Molecular cloning and characterization of PEA3, a new member of the Ets oncogene family that is differentially expressed in mouse embryonic cells. Genes Dev. 1992;6(3):481-96.

37. Lee JM, Hanson JM, Chu WA, Johnson JA. Phosphatidylinositol 3-kinase, not extracellular signal-regulated kinase, regulates activation of the antioxidant-responsive element in IMR-32 human neuroblastoma cells. J Biol Chem. 2001;276(23):20011-6.

38. Denoix P. Tumor, Node and Metastasis (TNM). Bull Inst Nat Hyg (Paris). 1944;1(1):1-69.