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A REVIEW ON THE ROLE OF ASROCYTE ELEVATED GENE-1 IN CANCER

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ABSTRACT: AEG-1 expression is known to elevate in diverse cancers, where it plays a primary role in activating multiple signaling pathways that drives copious oncogenic properties. The versatile role of AEG-1 in mediating oncogenesis was found to be cognate with numerous signaling cascades such as the activation of NF-κB/p65, Ha-Ras, PI3K/Akt, ERK/MAPK, Wnt/β-catenin, AURKA and RNAi pathways. In addition, recent clinical studies reveal that AEG-1 interaction with SND1/AGO2 in RISC may stimulate oncogenic transformation. The defeat of AEG-1 leads to PARP cleavage catalyzed by caspase-3, a key process in mediating apoptosis in AEG-1 expressed cancer cells. Moreover, AEG-1 confers chemo-résistance of cancer cells by inducing autophagy. In recent past, there are several studies reveal that AEG-1 down regulation inhibits chemo-resistance and oncogenic properties of various cancers. With this background, this review will address the multifaceted role of AEG-1 as oncogene and stipulating its potential to become a new therapeutic target and prognostic biomarker for the treatment of cancer.

INTRODUCTION: Astrocyte Elevated Gene-1(AEG-1), popularly known as Metadherin (MTDH)/Lysine-Rich CEACAM1 Co-Isolated (LYRIC) protein, evolved as a vital mediator of tumor malignancy and a key assemble point of a complex network of oncogenic signaling pathways[1]. AEG-1 has become the pivot of curiosity in an increasing spectrum of tumor indications for its numerous roles in modulating cancer progression and metastasis.

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Innumerable studies have shown that AEG-1 has a pivotal role in the development and progression of tumorigenesis and plays a central role in Ha-ras-mediated oncogenesis over the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [2]. The versatile role of AEG-1 in mediating oncogenesisis found to be cognate with numerous signaling cascades such as, the activation of NF-κB/p65, Ha-Ras, PI3K/Akt, ERK/MAPK, Wnt/β-catenin, AURKA and RNAi signaling pathways [3].

In addition, recent clinical study reveals that AEG-1 interaction with staphylococcal nuclease and Tudor domain involving 1 (SND1)/argonaute (AGO2) in RNA-Induced Silencing Complex (RISC) may promote oncogenic transformation [4]. Moreover, AEG-1 confers chemo résistance of cancer cells by inducing autophagy [5].

Distinctive AEG-1 expression and altered localization has been manifested in a diverse cancer, with elevated expression constantly linked to a poor prognosis. Even though, AEG-1 is ubiquitously expressed, the expression level is meager in normal tissues while its expression gradually increases as the cancer becomes more progressed with the highest expression detected in metastatic and invasive tumors [6].

According to PubMed search, more than hundred research articles are published, that analyze the clinical significance of AEG-1/MTDH/LYRIC over expression in cancers. Actually, many papers are devoted to evaluate AEG-1/MTDH/LYRIC expression profile and its clinic-pathological significance rather than identifying the molecular mechanisms of AEG-1/MTDH/LYRIC. These studies clearly show the importance of AEG-1/MTDH/LYRIC in regulating cancer progression and metastasis, which is reflected in the admittance of AEG-1/MTDH/LYRIC in mamma print. The first FDA-approved individualized metastasis prospect assessment assay for mamma cancer that includes a unique 70-gene signature [7]. Notable thing is that AEG-1/MTDH/LYRIC associates with multiple biological phenomena and upcoming research will absolutely identify a broad spectrum of progresses dovetailed with and potentially regulated with the help of AEG-1/MTDH/LYRIC. Despite the established role of AEG-1/MTDH/LYRIC in tumor progression and potentially in evolution of other diseases, the molecular function of AEG-1/MTDH/LYRIC remains to be identified.

Thus, this review is going to address the current status of AEG-1/MTDH/LYRIC research in detail and to produce the notional basis for new insights into AEG-1/MTDH/LYRIC functions and to address the multifaceted role of AEG-1 as oncogene and stipulating it's potential to become a prognostic biomarker and new therapeutic target for the treatment of cancers.

Emergence, cloning, structure and inracellular localization of AEG-1: Transcriptome analysis yields a resilient method for developing gene discovery in the past twenty years. The evolution of inventive technologies and methodologies, in conjunction with microarrays and subtraction hybridization has authorized the systematic recognition of differentially expressed sequence tags (ESTs) in both pathogenic and normal conditions, as well as producing tissue-specific profiles. With the help of progress that has made in diverse genome projects and entire cDNA cloning projects, transcriptome analysis has developed its extent from searches for ESTs to characterization and useful analysis of these ESTs. AEG-1/MTDH/LYRIC was revealed as a result of novel function-based gene discovery tools, which include Rapid Subtraction Hybridization (RaSH), in vivo phage display screening [2, 8] and gene-trap screening of localization-specific genes. In 2002, many research groups has identified the gene under various laboratory settings, initially named as astrocyte elevated gene-1 (AEG-1), recently posses the symbol as MTDH in GenBank, which stands for Metadherin.

In an attempt to locate molecules involved in mediating HIV-related degeneration of neuron, Fisher's group, found AEG-1 as an unique transcript induced by HIV-1 infection or treatment with TNF-α or gp120 by using subtraction hybridization [9]. Subsequently, entire cDNA of AEG-1 was cloned by four autonomous groups. In 2004, Brown and Ruoslahti demonstrated the phage display strategy to locate a lung-homing peptide which was employed in a mouse model of breast cancer metastasis, which clearly showed that a gene identical to AEG-1 was highly expressed in relation to breast cancer metastasis, and the identified gene was named MTDH (Metadherin) after its schemed role in stimulating homing of breast cancer cells to the lungs [3]. Britt *et al*. and Heidi *et al*. individually, identified the similar molecule that also encodes the Lyric (lysine-rich CEACAM-1 co-isolated protein) that co-localizesalong with the tight junction protein ZO-1 in polarized prostate epithelial cells [10], and as a peculiar transmembrane protein that occurs in the cytoplasm, perinuclear regions, endoplasmic reticulum and nucleolus.

Association of AEG-1/MTDH/LYRIC with the tumor phenotype was conspicuous from its foremost characterization wherein AEG-1/MTDH/LYRIC was found to be highly expressed in diverse types of cancerous cell lines and an intermediary of metastasis of murine breast cancer cells to the lungs [3].

AEG-1/MTDH/LYRIC expression is raised in almost all cancers and has been shown to increase survival, proliferation and metastatic ability of cancer cells through numerous mechanisms [4]. Thus, AEG-1/ MTDH/LYRIC proved it as a diagnostic/ prognostic biomarker for cancer (**Table 1**).

TABLE 1: AEG-1/MTDH /LYRIC AS A DIAGNOSTIC/PROGNOSTIC MARKER FOR MULTIPLE CANCER

Types of cancer	No. of cases	Reference
Breast cancer	225	11
	170	12
Non-small cell lung cancer	105	13
Gastric cancer	30	14
Hepatocellular carcinoma	109	1
	323	15
	73	16
	180	17
	520	18
Colorectal cancer	206	19
	196	20
Gallbladder carcinoma	41	21
Ovarian cancer	157(epithelial)	22
	101(serous)	22
Endometrial Cancer	174	23
Prostate cancer	143	24
Renal cell carcinoma	102	25
Bladder cancer	60	26
Glioblastoma Multiform	296	27
Brain Cancer	98	28
Neuroblastoma	32	27
Salivary gland carcinoma	141	29
Head and neck squamous carcinoma	20	30
Osteosarcoma	62	31
Diffuse large B- cell lymphoma	30	32

While the initial discovery of AEG-1 left with an profusion of debatable understanding of its biochemical characteristics and biological functions, which remains difficult to find to date, a few features of AEG-1 have been identified with certain consensus AEG-1/MTDH/LYRIC cDNAs encode 579, 581 and 582 amino acid proteins with a calculated molecular weights ~64 kDa and pI~9.3 in human, rat and mouse properly [10] and the amino acid sequences are extremely conserved across vertebrates, but are not located in invertebrates. The AEG 1/MTDH gene contains 11 introns and 12 exons, as identified using genomic BLAST search and is located at 8q22 where cytogenetic investigation of human gliomas suggests repetitive amplification [33]. MTDH/AEG1 is rich in both serine (11.6%) and lysine (12.3%) and residues that are targets for post-translational modifications for instance acetylation and ubiquitination of lysines [6, 34] and phosphorylation of threonine and serine. However, the mechanism by which, the post-transcriptional and post-translational modifications of AEG-1 influence its function and localization is remains unrevealed. Immuno-histochemical and Immuno-fluorescence analysis of MTDH/AEG-1 usually showed cytoplasmic and perinuclear staining as well as few nuclear rim, nucleolar and general nuclear diffuse staining in variegated cell types [10]. Cytoplasmic membrane localization of AEG-1 has also been located by immunostaining of non-permeabilized mouse 4T1 breast cancer cells and by FACS. TNF-α treatment, which enhances AEG-1 expression, as well as ectopic overexpression of AEG-1, has been shown to promote nuclear localization of AEG -1 in HeLa cells [33].

Biological functions and molecular hallmarks of AEG-1: Interest in the biological functions and molecular hallmarks of AEG-1 is arising as a pivotal role in the branch of oncology. Several recent studies have revealed the importance of AEG-1 in diverse human cancers. Prostate cancer, glioma, and Breast cancer, were among the foremost tumor types in which up-regulation of AEG-1/MTDH/LYRIC was documented.

AEG-1/MTDH localizes in the nucleus, endoplasmic reticulum, cytoplasm and cell membrane and assign to a group of signaling pathways, such as NF-κB/p65, PI3K/Akt, Ha-Ras, Wnt/β-catenin, ERK/MAPK, AURKA and RNAi pathways and altering gene expression changes (**Fig. 1**). AEG-1 contributes to diverse hallmarks of cancers, including abnormal proliferation, increased migration, invasiveness, metastasis and survival under traumatic conditions such as serum deprivation and chemotherapy [35].

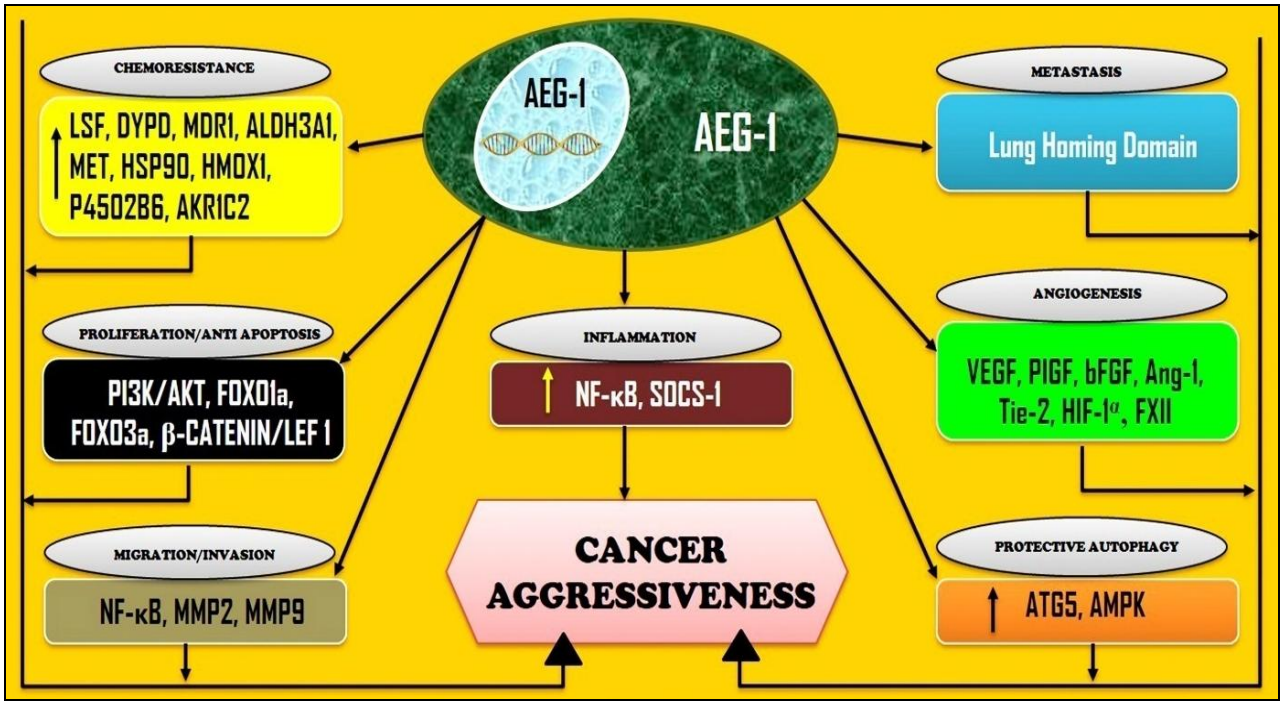

FIG. 1: VARIOUS BIOLOGICAL FUNCTIONS AND POTENTIAL LEAD MOLECULES OF AEG-1/MTDH/LYRIC

Beginning research in AEG-1, evidenced that hoisted expressing AEG-1 subjected breast cancer cells to lung homing which was then later confirmed by *in vivo* experiments. Moreover, AEG-1 was revealed to endorse invasion and migration of cancer cells. Emdad *et al*. first proclaimed that the NFκB pathway was required to promote invasion of Hela cells induced by AEG-1. NF-κB is the initial signaling pathway showing activation by AEG-1/MTDH/LYRIC [15]. AEG-1/ MTDH/ LYRIC trigger the NF-κB pathway by accelerating IκB degradation and by elevating binding of the transcriptional activator p50/p65 convoluted in the nucleus. NF-κB complex transcriptionally modulates diverse genes involved in invasion, adhesion, metastasis, and angiogenesis [36].

Simultaneously, Liu *et al*. found that AEG-1 promoted the invasion of glioma cells in an *in situ* xeno-transplantation glioma model in mouse through targeting directly and trans-activating the promoter of MMP-9 gene, a molecule globally accepted to be a primary metalloproteinase needed for extracellular matrix degradation and activation of cytokine of invading cells during the time of tumor invasion and metastasis, as well as other patho-physiological conditions [37].

The second prime signaling pathway activated by AEG-1/MTDH/LYRIC is the PI3K/Akt pathway. Lee *et al* first indicate that AEG-1/MTDH/LYRIC is a downstream object gene of Ha-ras, and this induction was impaired by treatment with over expression of LY294002 or PTEN, indicating that activation of the PI3K signaling pathway regulates Ha-ras-mediated AEG-1/ MTDH/ LYRIC inauguration [3]. In neuroblastoma cells, elevated expression of AEG-1/MTDH/LYRIC activates the PI3K/Akt pathways and stabilizes N-myc. Inhibition of AEG-1/MTDH/LYRIC by knockdown approach was shown to trigger apoptosis over the up-regulation of FOXO3a activity in prostate cancer cells [38-40] and FOXO1 activity in breast cancer cells via Akt signaling, respectively.

PI3K/Akt pathway activates by AEG-1/ MTDH/LYRIC led to an increase in multidrug resistance gene 1 (MDR1) levels by hoisted association of MDR1 mRNA to polysomes in drug-resistant human Hepatocellular carcinoma cells (HCC) [39- 41]. Hu *et al*. showed the elevated expression of AEG-1 in breast cancer enables tumor cells to escape cell death induced by doxorubicin, paclitaxel or cisplatin. In their research, chemo-resistance induced by AEG-1 was thought to be arbitrated by survival-promoting genes, more specifically c-MET and ALDH3A1. Moreover, in the same study, hydrogen peroxide-mediated oxidative stress could also be relieved by HOMOX1, an AEG-1 downstream gene.

Microarray analysis of breast cancer cells demonstrated that MTDH/AEG-1 knockdown led to reduced expression of chemo-resistance genes ALDH3A1, HSP90, HMOX1 and MET and elevated expression of pro-apoptotic genes BNIP3 and TRAIL. Among these genes, ALDH3A1 and MET were legalized to partially contribute to the chemo-resistance role of MTDH/AEG-1 in MDA-MB-231 breast cancer cells [3]. Pie *et al.* aimed to establish key regulators of 5-FU resistance gene evidenced that AEG-1 enhanced the expression of dihydropyrimidine dehydrogenase (DPYD), the rate-limiting enzyme of 5-FU degradation. AEG-1 could activate protective autophagy, a common mechanism employed by cancer cells to cope with metabolic stress. Bhutia *et al*. reveals the increased autophagy may be due to activation of AMPK which leads to elevate autophagy regulator ATG5 [42]. Several studies revealed that AEG-1 has been evidently linked to down-regulation of cell cycle inhibitors, leading to accelerated cell proliferation and in some studies AEG-1 has been found to be enough to prevent apoptosis through via PI3K/Akt signaling pathway [38, 39].

In addition, AEG-1 has been shown to promote tumor-induced angiogenesis. Angiogenic markers such as Ang-1, CD31 and HIF1 alpha are correlated with AEG-1 up-regulation in tumors formed by AEG-1- transduced rat embryo fibroblasts. Nikpour *et al.* showed the over-expression of AEG-1 in bladder cancer and they reported AEG-1 protects apoptosis and defects in apoptosis are familiar to contribute substantially to chemoresistance of bladder cancer, the protein may constitute a valid target for overcoming therapy resistance [43].

The sensitivity of breast cancer cells can be enhanced by the Knockdown of AEG-1/MTDH/LYRIC to a novel ATP-noncompetitive inhibitor of MAP/ERK kinase by regulating FOXO3 activity and expression [3]. Liu *et al.* shows that knockdown of AEG-1 could lessen EMT in cervical cancer cells. In addition, they found that knockdown of AEG-1 weakened stem-like property of HeLa cells, in the process of exhibited by reduced cell migration and invasion, reduced colony formation and enlarged susceptibility to cancer drugs [44]. Kim *et al*. showed AEG-1 was reduced after TBK1 (TANK-binding kinases1) knockdown. TBK1 reportedly intervenes pro-survival signaling by activating NF-κB and AKT. They establish that loss of MTDH leads to PARP cleavage and diminished cell viability. In addition, they performed shRNA-mediated knockdown of MTDH, TBK1, and KRAS in 14 lung cancer cell lines with detail EGFR and KRAS mutation status [45].

Santarpia *et al.* contribute a better understanding role of metastatic NSCLC and has identified the combination of BRCA1 and AEG-1 expression as an efficient model which can determine prognosis to platinum-based chemotherapy in patients along with wild-type EGFR and to Erlotinib treatment in patients with EGFR mutations [46]. As a relatively novel gene, MTDH/AEG-1 has raised as a potent regulator in multiple aspects of cancer evolution and progression. Clinical and functional analyses have prevails this multifaceted gene as a potentially valuable target in cancer treatments.

Potential role of AEG-1 in activating oncogenic signal cascades: During this decade, several research have witnessed increased interest on AEG-1/MTDH/LYRIC functions firmly connecting key cellular signaling cascades might be associated with the ability of AEG-1/MTDH/LYRIC to execute various biological processes in multiple disease conditions. As a multifaceted protein, AEG-1/MTDH/LYRIC awfully modulates a various arrangements of signaling networks and lead molecules involved in tumor development [47] (**Fig. 2**).

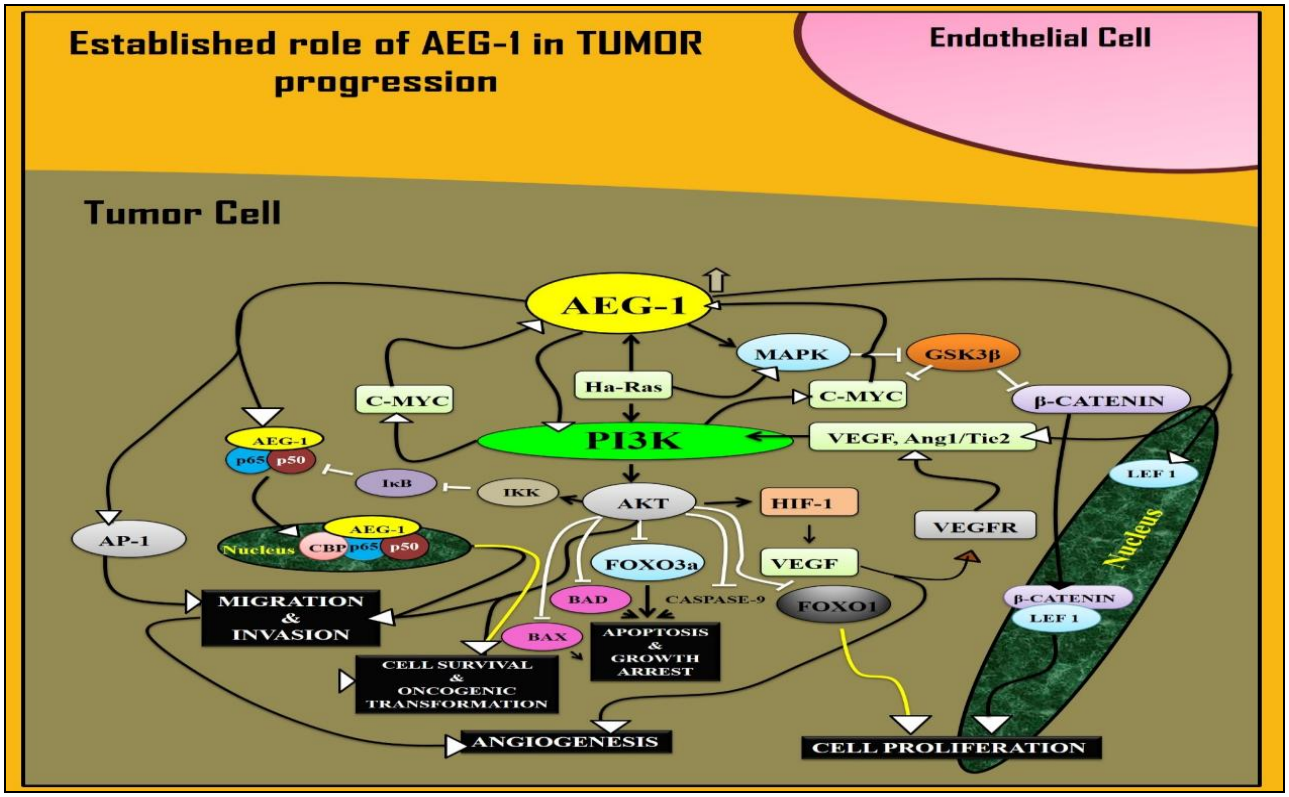

FIG. 2: ESTABLISHED ROLE OF AEG-1 IN TUMOR PROGRESSION

Nuclear factor-kB: The NF-κB transcription factor family is a renowned crucial mediator of the inflammatory process and a major contributor in adaptive and innate immune responses [48]. Several deep-rooted oncogenes, such as Rac, Ras and constitutive activation of NF-κB has been seen in a various human cancers, including but not restricted to breast, colon, gastric, hepatocellular, head and neck carcinomas, Hodgkin's disease, melanoma, leukemias, lymphomas, pancreatic and ovarian [40]. The first signaling pathway reported to be activated by AEG-1 was NF-κB pathway, through physical interaction with the p65 subunit of NF-κB complex, with further evidence stating that transcriptional activation might be due to recruitment of acetyltransferase CBP to p65 as a result of binding of AEG-1 to p65.

A gene array analysis disclosed that ectopic expression of AEG-1/MTDH/LYRIC by Ad.AEG-1 infection showed marked upregulation of NF-κB responsive cell adhesion molecules (ICAM-2 ICAM-3, selectin E, selectin L, and selectin P ligand), FOS, JUN, TLR4, TLR5, and IL-8 [40]. These proteins plays a major role in mediating NF-κB-induced inflammation, proliferation, and angiogenesis inflammation, all needed for the carcinogenic process, showing that activation of NF-κB also revealed multiple aspects of AEG-1/MTDH/LYRIC function. Treatment of HeLa cells and human malignant glioma cells with TNF-α resulted in AEG-1/MTDH/LYRIC translocation into the nucleus where it interacts with the p65 subunit of NF-kB and increased NF-κB-induced gene expression [9, 36]. Inhibition of NF-κB pathway using an IkB super-repressor (Ad.IkBα-mt32) significantly regress AEG-1/ MTDH/LYRIC-induced agar cloning efficiency and invasion in human glioma cells.

AEG-1/MTDH/LYRIC also develops EMT in breast cancer cells in an NF-κB-dependent manner [49]. Khuda *et al*. showed first time, that AEG-1 is a LPS-responsive gene and plays an potential role in LPS-induced TNF-α and PGE2 production via NF-κB activation. These results suggested that AEG-1 might be a target molecule for the therapy of LPS-related diseases, such as septic shock, sepsis and systemic inflammatory response syndrome. In inclusion to pathogen-stimulated inflammation, many other disease states for instance burns, severe trauma, and surgery, induce the NF-κB-dependent production of pro-inflammatory mediators [50].

PI3K/Akt pathway: Next to NF-κB, the signaling pathway which is activated by AEG-1/MTDH/ LYRIC is the PI3K/Akt pathway. Lee *et al*. first declare that AEG-1 is a downstream target gene of Ha-ras, and this induction was impaired by treatment with PTEN or LY294002 over-expression, specifying that activation of the PI3K signaling pathway modulates Ha-ras-mediated AEG-1 induction. In a study, to reveal the molecular mechanism that promotes the expression of AEG-1, the PI3K/AKT was described to be required for Ras-induced AEG-1 expression. The PI3K/Akt signaling pathway is a decisive regulator of physiological cell processes, which include apoptosis, differentiation, proliferation, metabolism, motility, and autophagy [51]. The PI3K/Akt signaling is largely up-regulated in numerous cancers where it negatively influences prognosis. The arousal of PI3K produces the second messenger phosphatidylinositol-3,4,5-trisphosphate from phosphatidylinositol 4,5-bisphosphate. Activated Akt translocates to the cytoplasm and nucleus and triggers downstream targets involved in various stages of cancer [52]. Akt phosphorylates and suppress Bad, a pro-apoptotic member of the Bcl-2 family, thereby enhancing survival. Akt suppresses the catalytic function of caspase-9 by phosphorylation and truncates its pro-apoptotic potential [53].

Forkhead group of transcription factors (FOXO) is well-established substrates of Akt which stimulate the expression of pro-apoptotic factors including Fas ligand [54]. Akt also phosphorylates IKK, which in turn decays IκB. Glycogen synthase kinase-3 (GSK3), insulin receptor substrate-1, mTOR (mammalian target of rapamycin), FKHR, a Forkhead family member, cyclin-dependent kinase (CDK) inhibitors p27KIP1 and p21Cip1/Waf-1/mda-6; and may be, Raf1 are all Akt targets involved in glycogen metabolism, protein synthesis and cell cycle regulation. Akt phosphorylates the CDK inhibitors, p27 and p21, and inactivates their anti-proliferative effects [55].

In addition, phosphorylation of MDM2 by Akt promotes the inactivation of p53, leading to increased cell cycle activity in the G1/S phase [56]. Interestingly, in a study demonstrated by Lee et al. found that AKT was also a downstream mediator of the diverse functions of AEG-1, as over-expression or silencing of AEG-1 consummation in elevation or depletion, respectively, of the phosphorylation status of AKT. Activation of AKT by AEG-1 led to phosphorylation of GSK3β and suppression of FOXO1/3 activity, resulting in increased cell viability and proliferation [39].

In hepatocellular carcinoma, AEG-1 has been reported to enhance phosphorylation of MAPK molecules, which includesp38 and ERK1/2, which finally promotes Wnt/β-catenin signaling and consequently leads to enhanced tumor angiogenesis. It was clarified that knockdown of AEG-1 by AEG-1 shRNA inactivates PI3k/Akt pathway. They revealed that maximum inhibitory effect on the P13K/Akt pathway occurred while AEG-1 shRNA plus 100μg/mL HP (Huaier polysaccharide) was used as treatment. In neuroblastoma cells, elevated expression of AEG-1 activates the PI3K/Akt pathways and stabilizes N-myc.

MTDH/AEG-1 knockdown promotes apoptosis of breast cancer cells and prostate cancer cells through the reduction of Akt activity and up-regulation of FOXO1 and FOXO3a activity [39]. In esophageal cancer cells, activation of Akt by AEG-1 leads to down-regulation of p27 and up-regulation of cyclin D1.In NSCLC, AEG- 1 significantly hoisted the levels of PI3K, Akt and p110, phosphorylation and inhibited apoptosis by regulating caspase-3 and Bcl-2 [57]. The PI3K/Akt pathway also regulates AEG-1 induced angiogenesis. Additionally, Noch *et al*. demonstrated that AEG-1 was induced by hypoxia via the PI3K/Akt pathway and then AEG-1 feeds back to activate PI3K and create a positive feedback loop [40]. Thus, MTDH/AEG-1 is both a downstream target of Akt and a crucial activator of the PI3K-Akt pathway.

The MAP kinase: The MAP Kinase network involves in transmits and amplifies signals for cell multiplication and cell death process. In breast cancer, ERk-1 and 2 are mostly elevated among three major MAP kinase pathways. Recent research is shown that highly proportion of cells activated form of MAP Kinase. The up-regulation MAP Kinase activity does not depend or represent Ras genomic mutations [58]. The knockdown of AEG-1 can enhance the sensitivity of breast cancer cells to AZD6244.

This is an ATP-noncompetitive inhibitor of MAP/ERK kinase by action expression and activity of FOXO3a [59]. MTDH/AEG-1 expression has been found to be involved in multiple signaling pathways, such as: NF-κB, PI3K/Akt, MAPK and Wnt/ß-catenin [60]. The MAP kinase activation is frequently observed in cancer, usually activated by growth factors, hormones and chemokines [3]. Emdad et al. gave a statement that specific inhibitor for MAPK pathways are can lead the abolishment of the oncogeneis activity of AEG-1. Those activities are invasion and anchorage-independent growth.

Ha-Ras: MTDH/AEG-1 is a downstream target gene for oncogenic Ha-ras, and MTDH/AEG-1 activated at transcriptional level by Ha-ras [61]. The AEG-1 is the one of target gene of Oncogenic Ha-Ras in breast cancer. The oncogenic Ha-ras could give up-regulate the AEG-1 expression by binding of C-Myc to the AEG-1 promoter region thereby promoting AEG-1 transcription [62]. Kang DC *et al*, confirmed that elevated levels AEG-1 in subsets of Breast cancer, melanoma and glioblastoma and determine the ectopic over-expression of AEG-1. It can promote anchorage-independent colony-forming competence of immortalized melanoma cells synergistically with oncogenic Ha-ras [63]. AEG-1expression markedly induced by Ha-ras, which is transcriptionally mediated by PI3K signaling pathway [64, 65]. The E-box elements in the AEG-1 promote PI3K/Akt/GSK3ß/c-Myc pathway can lead Ha-ras mediated oncogenesis [64]. AEG-1 expression was significantly induced by the Ha-ras, which was arbitrated by tanscriptionaly through via of PI3K signaling pathway [62]. The AEG-1 and it can be used as downstream target molecule of Ha-ras and C-Myc mediated tumor-promoting effects [66]. Ha-ras and c-Myc genes are co-operatively involves and promote the transformation, tumor development, progression and metastasis.

CONCLUSION: AEG-1/MTDH has a pivotal role in the process of tumorigenesis in multiple models, as resolved by *in vitro* and *in vivo* studies and expression analysis. AEG-1/MTDH is an extremely crucial molecule for the regulation of a variety of pathological and physiological processes by inflects the transcription and translation of factors convoluted in the signaling pathways.

AEG-1/MTDH is a crucial regulator in various aspects of cancer development and progression. The Clinical and functional analyses propose that the multifunctional gene, AEG-1/MTDH, is a probably valuable target in cancer treatment. The anti-AEG-1 autoantibody evaluation may be a diagnostic biomarker for cancer patients with AEG-1-positive expression, and a feasible inducer, with substantial immunity across AEG-1 by immunization sustain with AEG-1 vaccines. The therapeutic model of AEG-1/MTDH vaccine elevated the chemo-sensitivity to doxorubicin and inhibited breast cancer. The numerous functions of AEG-1/MTDH features of several important clinical implications. AEG-1/MTDH, as a prevalent biomarker for aggressive tumors, may be used for the conventional screening of patients. The AEG-1/MTDH vaccine in unification with chemotherapy may offer unique approach for the treatment of cancer metastasis. AEG-1/MTDH is a useful diagnostic or prognostic biomarker established on its over-expression and correlations with disease execute and outcome throughout a wide range of cancer.

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