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Mini Review

# SMG-1 as a Promising Tumor Suppressor in the Management of Cancer

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## Introduction

SMG-1 (Suppressor of Morphogenesis in Genitalia-1) is an evolutionally conserved serine/threonine-protein kinase and belongs Phosphatidylinositol-3-Kinase (PI3K) related kinases (PIKKs) that include Ataxia Telangiectasia Mutated (ATM), ATM and Rad3 Related (ATR), Mammalian Target of Rapamycin (mTOR), DNA-Dependent Protein Kinase Catalytic Subunit (DNA-PKcs) and Transformation/Transcription Domain-Associated Protein (TRRAP) [1]. The deduced 3,521-amino acid protein has a calculated molecular mass of 410kD [2]. PIKKs have diverse functions. For example, ATM, ATR and DNA-PKcs are involved in the response to DNA damage. ATM and DNA-PKcs respond to DNA Double Strand Breaks (DSBs) and ATR to DNA replication blockers or formation of long stretches of single strand DNA [3]. mTOR is a nutrient-regulated kinase that controls a wide variety of pathways involved in metabolism and cell growth [4]. TRRAP functions as part of a multiprotein co-activator complex which is involved with the transcriptional activity of c-Myc and other transcriptional factors [5]. SMG-1 is a part of the mRNA surveillance complex that regulates Nonsense-Mediated mRNA Decay (NMD) [6]. SMG-1 was firstly reported as a member of the informational suppression in *Caenorhabditis elegans* (*C. elegans*) which affected several mRNA processes in 1989 [7]. Pulak et al. reported that loss of function mutations affecting seven *C. elegans* smg genes eliminates NMD [8] and later demonstrated that smg-1 kinase activity was essential for NMD [9]. In 2001, Deming et al. reported a partial sequence of human SMG-1 as *C. elegans* SMG-1 related protein [10]. Yamashita et al. also reported the full-length sequence for human smg-1 which encoded a 3657 aa protein that was a novel PIKK and showed the involvement of SMG1 in mammalian NMD [11]. In 2004, Brumbaugh et al. reported the activation of SMG-1 by DNA damage and involvement of SMG-1 in genotoxic stress-induced phosphorylation of P53 [2]. Besides NMD, SMG-1 roles as a protective agency in genotoxic stress such as radiation, tumor proliferation, and apoptosis. I will briefly summarize the roles of SMG-1 related with NMD and others in this paper.

## SMG-1 as a Player in NMD

NMD is a cellular defense mechanism eliminating mRNA that harbors Premature Translation Termination Codons (PTCs) and encode nonfunctional or potentially harmful polypeptides [6,12,13]. NMD pathway involves a cascade of fine-coordinated events. A SURF complex (SMG-1, SMG-8, SMG-9, UPF1 and the eukaryotic release factors 1 and 3 (eRF1 and 3) is formed on a ribosome which encounters a PTC [14,15]. Interaction of UPF1 with UPF2 and UPF3B bound to the downstream EJC triggers UPF1 phosphorylation by the SMG-1 and remodels the SURF complex to form the decay-inducing complex [16-19]. The primary structure of PIKKs contains a conserved C terminus preceded by a long stretch of helical, mostly HEAT (huntington, elongation factor 3, a subunit of PP2A and TOR1) repeats which are units of two anti-parallel α-helices connected by flexible loops and large superhelical frequently twisted structures [20]. A bent arm comprising a long region of HEAT repeats at the N-terminus of SMG-1 functions as a scaffold for SMG-8 and SMG-9, and projects from C-terminal core containing PI3K domain, which modulates NMD [21,22]. Resultant NMD processes decrease the production of potentially harmful polypeptides and enhances the accuracy of gene expression. SMG-1 is one of the essential players triggering an NMD response, because it is the kinase that phosphorylates the UPF1 protein. SMG-1 functions in NMD by selective degrading PTCs mRNAs which can be generated by gene mutations, splicing or transcription errors and by phosphorylating specific serine residues in UPF1 helicase which is a crucial regulator of NMD [23]. Phosphorylated UPF1 leads the releases of eRF1 and eRF3 and recruits NMD factors such as SMG-5~7 [24]. They recognize its phosphorylation by inducing the remodeling of the mRNA surveillance complex which discriminates the PTC-containing mRNA from the normal mRNA as an essential step in NMD [11,14]. Recently, González-Huici et al. declared that SMG-1 kinase activity could be activated following DNA damage to phosphorylate specific DNA repair proteins and/or NMD inactivation may lead to aberrant mRNAs leading to synthesis of malfunctioning DNA repair proteins [25]. Consequently, SMG-1 play viral roles in the regulation of cell growth, proliferation, survival, and cellular responses to stresses as a member of PIKKs.

## SMG-1 as a Player in Tumor Suppression

SMG-1 has been suggested as a tumor suppressor, though its role as an NMD effector has been precisely documented. In the planarians study, the planarian mTORC1 signaling compounds and SMG-1 performed as a key regulator of regeneration and growth antagonistically. Rapamycin as an inhibitor of mTORC1 increased the survival rate of smg-1 animals by decreasing cell proliferation. They showed the possibility of the tumor suppressor function of SMG-1 [26]. Gubanova et al. reported that in Human Papillomavirus (HPV)-positive head and neck squamous cell carcinoma, SMG-1 was underexpressed and exhibited tumor suppressive activity [27]. They also reported that SMG-1 suppresses CKD2 and tumor growth by regulating both the p53 and Cdc25A signaling pathways in 2013. They showed that SMG-1 regulates the G 1/S checkpoint




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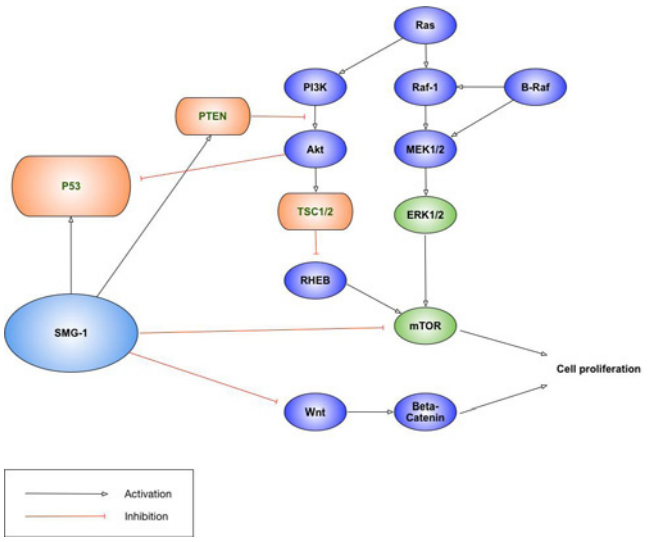


**Figure 1:** SMG-1 as a tumor suppressor.

through both a p53-dependent, and a p53-independent pathway and depletion of SMG-1 increased tumor growth [28]. In 2014, Nam et al. declared that SMG-1 as a promising modulator of sorafenib resistance by using an unbiased genome-wide massive genetic screen method. They showed that the inhibition of SMG-1 reduced sorafenib sensitivity in the several hepatocellular carcinoma cell lines and could be an agent to reverse sorafenib resistance [29]. The results suggested the possibility of SMG-1 as a potent tumor suppressor (Figure 1). At a similar time, Han et al. demonstrated that expression of SMG-1 was significantly lower in the HCC tissue than that in the normal tissues and declared that SMG-1 expression was an independent prognostic marker for overall survival [30]. A novel AKT inhibitor inhibited phosphorylation of AKT downstream molecules and activated phosphorylation of mTOR and SMG-1 in the several liver cancer cell lines [31]. This report suggested the promising possibility of usage as anti-cancer regimen of SMG-1. Recently, Zhang et al. reported that SMG-1 was suppressed by miR-192 and -215 and functioned as a tumor suppressor in gastric cancer by inactive Wnt signaling and suppressing epithelial-mesenchymal transition [32].

## Conclusion

SMG-1 is involved in NMD as an active effector and tumorigenesis as a tumor suppressor. Moreover, SMG-1 may be a promising interrupter during the cancer proliferation mechanisms for development of anti-cancer agent and represent a biomarker for predicting the prognosis of cancer. SMG-1 may warrant investigation to defeat cancer in the future. Therefore, more well-coordinated studies are needed to elucidate the overall precise mechanisms of SMG-1 involving NMD and cancer development processes.

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