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ASPP2, a New Regulator of the Mevalonate Pathway in Cancer

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Tumor is the abnormal growth tissue, which needs adequate energy and abundant material to meet requirement for growth. Cholesterol is an essential lipid to maintain intracellular homeostasis. It is an important part of the cell membrane and a primer precursor of steroids and vitamin D. The mevalonate (MVA) pathway is a metabolic pathway for the synthesis of isoprene pyrophosphate and daily pyrophosphate from acetyl-CoA, which regulates the biosynthesis of cholesterol and non-sterol isoprene. Isoprene is used to synthesize important biomolecules in vivo, such as dodecyl, heme A, ubiquinone, coenzyme Q, and hydrophobic long chains, the last one can anchor proteins such as Ras and Rho to the cell membrane for signal transduction. Therefore, mevalonate pathway is related to a variety of cell processes, involved in cell proliferation, differentiation, tumorigenesis, metastasis, and immune escape[1].

In recent years, a large number of studies have shown that the metabolites of MVA pathway are beneficial to the survival of tumor cells, and a variety of key enzymes of MVA pathway are essential for the survival of tumor cells[2-4]. Tumor cells need sufficient cholesterol and intermediates of the cholesterol biosynthesis to maintain their high levels of proliferation.

Transcriptional Regulation of the Mevalonate Pathway

Transcriptional activation of key enzymes in MVA pathway, like 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1), 3-hydroxy-3- methylglutaryl-CoA reductase (HMGCR) are controlled by sterol regulated element binding protein-2 (SREBP-2). SREBP2, a member of SREBPs family, which is synthesized as an inactive precursor locating on endoplasmic reticulum (ER) membrane[5]. The activation of SREBP2 is normally regulated by cholesterol level in ER, upon cholesterol level decrease SREBP-2 is translocated from ER to the Golgi apparatus, leading to subsequent proteolytic cleavage to its active mature form[6]. Mature SREBP-2 translocates to nucleus and binds with sterol regulatory elements (SREs) in the promoters of its target genes to regulate MVA pathway and cholesterol synthesis[7].

Recent studies have shown that the transcriptional activity of SREBP-2 can be regulated by several tumor suppressor genes or oncogenes[8]. Tumor suppressor gene p53 plays an important regulatory role in the tumors progression. Studies have confirmed that the MVA pathway is a new way for p53 to inhibit tumor growth. P53 blocks the activation of SREBP-2 by inducing the expression of ABCA1, a member of ATP-binding cassette (ABC) transporters which regulate cholesterol transport across membrane. Derepression of
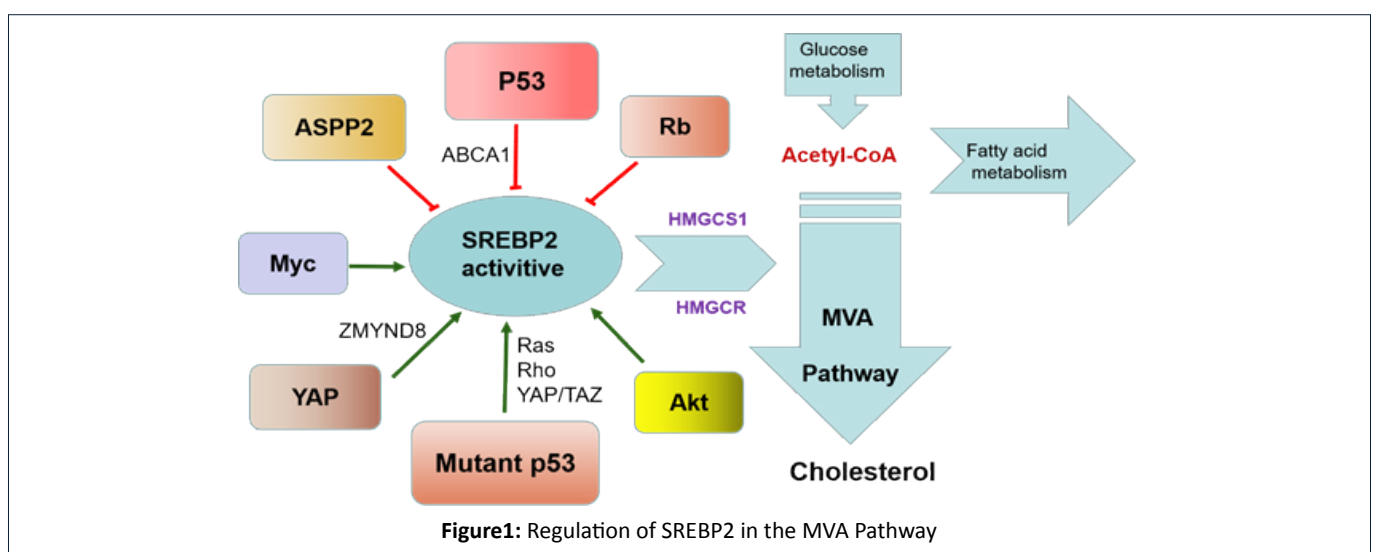
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the MVA pathway is essential for tumorigenesis caused by p53 loss in Myc induced mouse liver cancer[9]. Mutant TP53 (TP53R273H and TP53R280K) can bind to SREBP-2 and increase the transcription of MVA pathway genes, which contributes to mutant p53 induced disruption of normal breast acinar morph[10]. Mutant p53 can also up-regulate the activity of MVA pathway-related oncogene (such as RAS, Rho, YAP/TAZ), thus promoting tumor progression[11].Rb prevents SREBP-2 from being associated with the target gene promoter and acts as a negative regulator of MVA metabolism[12]. Data from the Encyclopedia of DNA Elements (ENCODE) project has shown that MYC binds to promoters of MVA pathway genes in close proximity to SREBP-2, which may contribute to Myc-induced hepatocarcinogenesis[12]. YAP target gene ZMYND8 interacts with SERBP2 to up-regulate the MVA pathway[13]. HSP90 and the MVA pathway promote STAT3 phosphorylation mediated by mutant p53 in glioblastoma and pancreatic cancer cells[14]. PI3K/AKT signaling activates the MVA pathway through increasing the expression of SREBPs[15]. Schematic representation summarizes the most important regulation of SREBP2 in the MVA Pathway (Fig. 1).

ASPP2, a New Regulator of SREBP2 and the MVA Pathway

ASPP2 (Apoptosis-stimulating protein of p53) is a member of the ASPP family. ASPP2 is identified as an activator of the p53 family, which can promote apoptosis[16]. In human cancer, ASPP2 expression is down-regulated epigenetically by DNA methylation or histone deacetylation[17,18]. As we know, a large number of studies have confirmed that ASPP2 can regulate a series of biological process by cooperating with specific targets, such as p73, Bcl-2, NF-kB, Yes-Association Protein-1, RAS, Par3, β-catenin, and Beclin-1. Most of the previous studies suggest that ASPP2 is mainly expressed in tumor cytoplasm or cell membrane. ASPP2 expressed on the cell membrane can bind to PAR3 through its N-terminal to maintain the integrity of cell polarization[19,20], and can bind to β-catenin-E-cadherin complex to regulate epithelial plasticity[21]. In the cytoplasm, ASPP2 binds to RAS to regulate RAS signaling pathway[22,23] and interacts with ATG5 and Beclin-1 to regulate autophagy[24,25]. However, nucleic ASPP2 is important for it to execute its proapoptotic effect. In the nucleus, ASPP2 binds to p53 and p73 through its C-terminal[26] and function as a transcription cofactor to regulate p53 target apoptotic genes. Whether ASPP2 also plays a role in the MVA pathway? That attracted us more interests in recent years. In our previous study, we found ASPP2 interacted with SREBP-2 in the nucleus and negatively regulated SREBP-2 transcriptional activity and its target MVA pathway genes[27]. HCC tissues with nucleic ASPP2 staining were more prone to have low HMGCR expression than HCC tissue with cytoplasmic ASPP2 staining, further supporting a negative effect of nuclear ASPP2 on the MVA pathway. Given that p53 and RAS are essential regulators in MVApathway, whether the interactions between ASPP2 and p53, ASPP2 and RAS, crosstalk in MVA pathway still need further investigation. The key role of ASPP2 in regulating MVA metabolism and its importance in tumor growth may provide a new strategy for the treatment of cancer (Fig. 2).

The mechanism by which ASPP2 translocates to nucleus is still unclear. There are Ankyrin repetitive sequences at the C terminal of ASPP2, which may help ASPP2 enter the nucleus through the establishment of RanGDP/Ankyrin binding nuclear input pathway[28]. Phosphorylation of ASPP2 may be necessary for it to enter into nuclear. Phosphorylation of ASPP2 protein at Ser827 by mitogen-activated protein kinase pathway can cause ASPP2 translocation from the cell membrane to the nucleus, which is critical for its proapoptotic effect[22,29]. In a system-wide phosphoproteome study, AMP-activated protein kinase phosphorylates ASPP2 at Ser479 to promote apoptosis in an irradiation-dependent way[30]. In addition, nuclear translocation of

Figure1: Regulation of SREBP2 in the MVA Pathway

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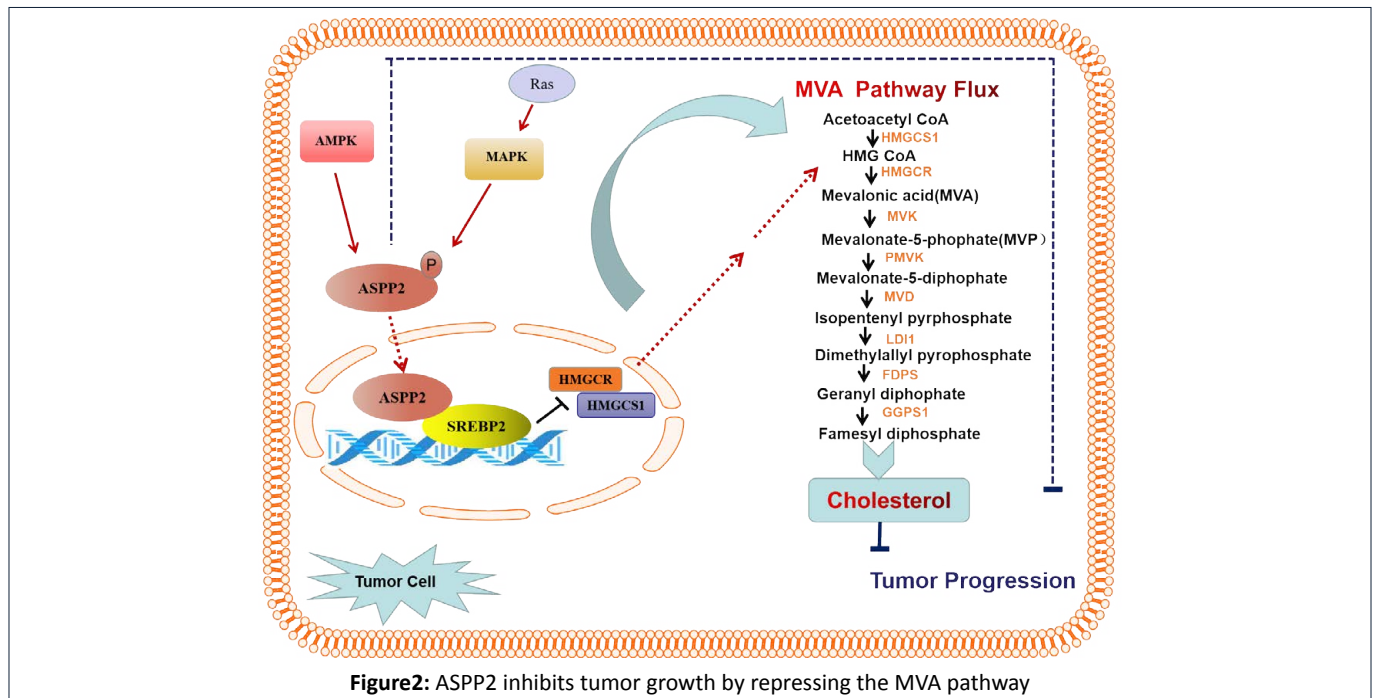Journal of Cancer Treatment and Diagnosis

Figure2: ASPP2 inhibits tumor growth by repressing the MVA pathway

ASPP2 may related to inflammation stimulation in immune cells. The transfer of ASPP2 from the cytoplasm to the nucleus in mouse macrophages is found in the mouse model of maternal inflammation induced by LPS[31].

Conclusions and Future Perspectives

Metabolic reprogramming is a hallmark of tumor cells. The MVA pathway recently has been regarded as an attractive target for tumor therapy. As a haplo-insufficient tumor suppressor, ASPP2 can be expressed in tumor cytoplasm, cell membrane and nuclear. Nucleic ASPP2 has been found to inhibit cholesterol biosynthesis by regulating the MVA pathway. But what stimulates ASPP2 to transfer from cytoplasm to nuclear? Whether nuclear ASPP2 has more functions in tumor progression deserves our further attention.

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