

**Supplementary table S1: bona fide tumor suppressor genes methylated or deleted in melanoma**

TSG	Protein	Location	Protein role	Pathway	Hallmark of cancer	First author	Year	Sample type	Method
PTEN	Phosphatase and tensin homolog	10q23.31	Multifunctional phosphatase, regulating apoptosis, regulating secretion of MMPs and IGFs and expression of VEGF	PTEN → PI3K↓ → AKT↓ → apoptosis	Apoptosis ↓	Mirmohammadsadegh A.	2006	Cell lines (Serum) (Tissue)	AKT kinase assay: 5-Aza → phosphorylation GSK3↓
					Tumor growth ↑ Metastasis ↑	Hwang P. H.	2001	Cell line Nude mice	1.PTEN-vector in cell line → colony formation↓ + no difference in proliferation 2.The above cell line in mice → tumor volume↓ + number of metastasis↓
					Tumor growth ↑	Inoue-Narita T.	2008	Mice	1. Mice with PTEN-deficient melanocytes → no spontaneous melanoma + larger melanocytes 2. The above mice + DMBA/TPA → large nevi and invasive spindle cell melanoma ↑
BRMS1	Breast cancer metastasis suppressor 1	11q13.2	Regulation of transcription, angiogenesis and other metastasis-related genes	/	Invasion ↑ Metastasis ↑	Shevde L. A.	2002	Cell lines	1. BRMS1 in cell lines without it → invasion↓ + no difference in cell morphology and primary tumor growth 2. The above cell lines in mice → metastasis↓
				BRMS1 → (ING4) → NF-κB (p50/65 subunits)↓ → IL-6↓ → angiogenesis↓	Angiogenesis ↑	Li J. (2 articles)	2010	Cell lines Nude mice	1. BRMS1/ING4 in cell lines → human umbilical vein endothelial cell growth↓ + tubular structures↓ 2. BRMS1/ING4 knockdown in cell lines → human umbilical

									vein endothelial cell growth↑ + tubular structures↑ 3. The first cell lines in mice → angiogenesis↓
FERMT3 KIND3	Kindlin-3	11q13.1	Integrin activating protein	Kindlin-3 → Talin → integrins β1/3/5 → cell attachment	Migration↑ Invasion↑ Proliferation↑ Cell/tumor growth↑ Metastasis↑	Djaafri I.	2014	Cell lines Nude mice (Tissue)	1. FERMT3 overexpression in cell lines → migration↓ + invasion↓ 2. FERMT3 knockdown in cell lines → migration↑ + invasion↑ + proliferation↑ + anchorage-independent growth↑ 3. FERMT3 KO mice → tumor growth↑ + lung metastases↑
AKAP12 SSeCKS	A-kinase anchoring protein 12	6q25.1	Controlling the secretion of tumor chemo-attractants	AKAP12 → CXCL9/10↓ → metastatic chemotaxis↓	Metastasis↑	Muramatsu M.	2017	Cell lines in transgenic mice	AKAP12 KO mice → peritoneal, liver and lung metastases↑ + no difference in primary tumor growth
CDKN2A	p16INK4a p14Arf	9p21.3	1. p16INK4A: cell cycle regulation, oncogenic signaling, DNA damage, physiologic aging, inhibition of proliferation, senescence. 2. p14ARF: induction of ROS generation, cell cycle regulation	1. p16INK4 → CDK4/6↓ → cyclin D1 complex formation↓ → pRB1↓ → tumor growth through unlimited cell cycle progression↓ 2. p16INK4 → CDK4/6↓ → cyclin D1 complex formation↓ → pRB1↓ → E2F1↓ → BRN2↓ → invasion↓ 3. p14ARF → ROS generation → p53 activation → tumor cell growth/proliferation↓ 4. p14ARF → complex with MDM2 → p53 degradation↓	Proliferation↑ Tumor growth↑ Apoptosis↓ Migration↑ Invasion↑	Bai M.	2016	Cell line Nude mice (Tissue)	1. CDKN2A (P16INK4A or p14ARF) overexpression in cell line without it → proliferation↓ + cells in G0/G1↑ + apoptosis↑ + migration↓ + invasion↓ 2. The above cell line in nude mice → tumor growth↓
					Proliferation	Zeng H.	2018	Cell lines	1. CDKN2A null NHMs:

					↑ Invasion ↑ Motility ↑ Migration ↑ Metastasis ↑			Nude mice	proliferation↑ + motility↑(independent of driver mutation and proliferation) + migration↑ + invasion↑ 2. Cell lines in nude mice → metastasis↑ in CDKN2A knockdown cell line + metastasis↓ in p16INK4a expressing cell line (without correlation with proliferation)
					Proliferation ↑ Tumor growth↑ Senescence ↓	Regneri J.	2019	Xiphophor us melanoma cell line  Medaka fish	1. Cdkn2ab (fish ortholog) overexpression in cell line → proliferation↓ + senescence-like phenotype 2. In vivo co- expression of Xiphophorus cdkn2ab in medaka with oncogene and its promotor → melanoma development↓ 3. In vivo CDKN2A KO medaka with oncogene and its promotor → tumor growth↑
APAF-1	Apoptotic peptidase activating factor 1	12q23.1	Mediating p53- dependent apoptosis	p53 → Bax ↑ → cytochrome c ↑ → Apaf-1/Casp9 death effector complex	Apoptosis ↓	Soengas M. S.	2001	Cell lines (Tissue)	Retroviral APAF-1 transfer/5-Aza in cell lines → apoptosis↑ + adriamycin (p53 activator) sensitivity↑
MTAP	Methylthio- adenosine	9p21.3	Catalyzation of the phos- phorylation of	MTAP↓ → MTA accumulates (inhibition of methyltransferases) →	Invasion ↑	Behrmann I.	2003	Cell lines (Tissue)	MTAP re-expression in cell line → invasion↓ + no

	phosphoryla se		methyl- thioadenosine (MTA)	methylation of arg31 in STAT1 by PRMT1↓ → binding PIAS to STAT1 → inhibition of STAT1 DNA binding activity → interferon- $\alpha$ and - $\beta$ signaling pathway↓ → IFN-treatment response↓					change in proliferation
MEN1	Menin 1	11q13.1	Role in transcription, cell cycle regulation and proliferation, oncogene induced senescence in melanocytes, maintenance of genome integrity.	DNA damage → ATM/ATR →MEN1 phosphorylation (stabilization) → MEN1 + MLL → ESR1 → BRCA1, RAD51, RAD51AP1 → H3K4me3↑ → transcription of target genes (HOX, CDKI)	DNA repair ↓ Cell growth ↑	Fang M.	2013	Cell lines	<ol style="list-style-type: none"> <li>1. MEN1 overexpression in cell line → growth ↓</li> <li>2. MEN1 knockdown in cell line → double-stranded DNA breaks ↑ + homologous recombination repair ↓ + nonhomologous end-joining repair ↑</li> </ol>