Supplemental Materials: The Role of AMP-Activated Protein Kinase as a Potential Target of Treatment of Hepatocellular Carcinoma

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Table S1. Regulation of AMPK on HCC.

Actions	Models	Regulation/pathway	Effects	Reference.
Dysregulation of AMPK in HCC	In clinic, cirrhotic liver tissues; In vivo, C57BL/6 mice	Autophagy-related	Negative correlation between AMPK activation and HCC occurrence	[1] (2018)
	In clinic, normal liver tissues obtained from the distal normal liver tissue of patients with liver hemangioma; Formalin-fixed and paraffin-embedded HCC tissues from 273 consecutive patients and fresh-frozen HCC tissues from 19 patients who underwent radical resection	NF-κB and STAT3 signaling	Activation of AMPK inhibited HCC cells growth	[2] (2013)
	In clinic, 378 HCC patients	High percentage of OV6+ tumor-initiating cells (T-ICs) in HCC specimens	High pAMPKα (Thr172) level may serve as a positive predictor of survival in HCC patients undergoing TACE	[3] (2016)
	In vitro, human HepG2, Hep3B, PLC, HEK293 and HEK293T cells; In vivo, nude mice	Ketolysis and autophagy	Nutrition-deprived HCC cells employ ketone bodies for energy supply and cancer progression	[4] (2016)
	In clinic, patients with HCC; In vitro, PLC/PRF/5, HepG2 and Hep3B cells; In vivo, NOC male mice	AMPK-mTOR pathway	Metformin could be a therapeutic drug for HCC in patients with mutated p53, inactivated SIRT1, and AMPK expression	[5] (2015)
	In vitro, Hep3B and PLC/PRF/5(PLC5) cell lines; In vivo, 5-week-old male NCr athymic nude mice	Oncogenic PP5 inhibition	AMPK activation by inhibiting PP5 for anti-HCC therapy	[6] (2017)
	In clinic, 153 primary HCC tumor tissues and a paired normal tissue; In vivo, Hep3B, PLC5, and Huh7 cells	PP5/AMPK axis independent of CDK4/6	Palbociclib induced autophagy and apoptosis in HCC cells	[7] (2017)
	In vitro, HepG2 and SK-Hep1 cells	SIRT1/AMPK	Gallotannin-induced senescence and impaired autophagy leading to cell death in HCC cells	[8] (2017)
	In vitro, the human HCC cell line HCCLM3, HepG2, SK-Hep1, Huh7, and the normal liver cell line L02	PKM2-AMPK-PGC1α signaling	Shikonin exerts antitumor activity by causing mitochondrial dysfunction in HCC	[9] (2018)
	In vitro, HCC cells	AMPK-mTOR-S6 K1 signaling	ATIC suppresses AMPK activation and supports growth and motility activity of HCC cells	[10] (2017)
Regulation on cell proliferation;	In clinic, the human tissue samples; In vitro, the human hepatoma cell lines, PLC/PRF/5 and HepG2; In vivo, BALB/c-nu mice	Metabolism and the cell cycle	AMPK activity inhibits the proliferation of HCC	[11] (2014)

Regulation on cell death	In clinic, liver tumor specimens and adjacent non-tumorous specimens; In vitro, the human hepatoma cell lines HepG2, SK-Hep1, and PLC/PRF/5; In vivo, BALB/c nude mice	AMPK/p27Kip1 axis, CDK/Rb/E2F pathway	PCK1 negatively regulates cell cycle progression and hepatoma cell proliferation	[12] (2019)
	In vitro, HCC cell lines, HepG2 and Hep3B; In vivo, male BALB/c nude mice	Upregulated p21 and p27 by regulating AMPK and STAT3-Skp2 axis	Simvastatin induces G0/G1 arrest	[13] (2017)
	In vitro, the HepG2 cell line	AMPK and the downstream acetyl-CoA carboxylase carboxylase	Fatsioside A induced apoptotic death of HepG2 HCC cells	[14] (2015)
	In vitro, HLF cells	ACC and cyclin D1, CDK4 and CDK6 expression	Fucoidan inhibits proliferation through AMPK-associated suppression of fatty acid synthesis and G1/S transition in HLF cells	[15] (2015)
	In vitro, the cancer cell lines including HepG2, PLC/PRF/5 and Hep3B	mTOR translational pathway	G1 arrest of the cell-cycle and subsequent cell death	[16] (2010)
	In vitro, human liver cancer cell lines HepG2 and Bel-7402	A p53-dependent manner	Exposure of hepatoma cells to low doses of metformin results in the induction of senescence instead of apoptosis	[17] (2013)
	In vitro, HCC cells	AMPKα-mediated inhibition of Sp1 and DNMT1	Ursolic acid inhibits growth of HCC	[18] (2014)
	In vitro, the Hep3B HCC cell line	GSK3β-independent AMPK/β-catenin pathway	Selenium down-regulates the β-catenin survival pathway through activation of AMPK in hepatocellular carcinoma cells and xenograft tumor models	[19] (2016)
	In vitro, human Huh7 and Bel7402 cells; In vivo, male BALB/c nude mice	mitochondria dysfunction and endoplasmic reticulum stress	Physcion had pro-apoptotic role on HCC cells	[20] (2018)
	In vitro, the human HCC cell lines (HepG2, SMMC-7721 and Bel-7402) and the normal liver cell line (HL-7702)	AMPK-mediated caspase-dependent mitochondrial pathway cell apoptosis	AMPK may be involved in the antitumor effect of berberine	[21] (2013)
	In vitro, human SMMC7721 and Bel7402 cell lines; In vivo, male athymic BALB/c nu/nu mice	Activation of PPARγ	PPARγ activation by hispidulin effectively suppressed HCC cell growth and metastasis	[22] (2018)
	In vitro, the human hepatoma cell lines, HepG2 and PLC/PRF/5	Destabilising p53 in a SIRT1-dependent manner	Inactivation of AMPK promotes hepatocarcinogenesis	[23] (2012)
	In vitro, the human hepatoma cell line HepG2	AMPK/MnSOD signaling	HBV suppresses mitochondrial superoxide level and exerts an anti-apoptotic effect in HBV-infected HepG2 cells	[24] (2016)
	In vitro, human HCC cell lines Huh7, HepG2 and Hep3B; In vivo, male NOD/SCID mice	The tumor suppressor CEBPD expression	The combinatorial treatment of metformin and rapamycin can enhance autophagic cell death of HCC	[25] (2017)

	In vitro, human HCC cell lines used, HepG2, Bel-7402, Huh-7, SMMC-7721 and SMMC-7402	GRP78–AMPK–mTOR signaling	Endoplasmic reticulum stress and autophagy were involved in cell death evoked by meloxicam in HCC cells	[26] (2015)
	In vitro, the human normal liver cell line (L02 cells) and the HCC cell lines (HepG2 and SMMC-7721 cells)	Autophagy-induced apoptosis via AMPK signaling	SCD1 regulates autophagy via AMPK signaling	[27] (2014)
	In vitro, the human HCC cell lines HepG2, PLC/PRF/5 and Hep3B; MHCC97L cell line; the human normal hepatic cell line L-02	AMPKα/mTOR-dependent autophagy and the triggered XIAP heading lysosomal degradation pathway	Timosaponin AIII induces HCC cell apoptosis through a p53-independent mechanism	[28] (2013)
Regulation on cell invasion and metastasis	In clinic, liver tumors and paired adjacent normal livers; In vitro, HepG2, A549, U87 and PC3 cell lines; Huh7, HCCLM3, SK-Hep1, SMMC-7721, LO2, HGC-27 and U251 cell lines; In vivo, female NOD/SCID mice	AMPK-MITA1-Slug axis	MITA1 is a crucial driver of HCC metastasis	[29] (2019)
	In clinic, HCC tissue specimens and adjacent normal tissues; In vitro, human normal hepatic cell LO-2 cells and HCC HepG2.2.15 cells	The AMPK signaling pathway by targeting CCNA1	MiR-1271 overexpression conferred protection against cell proliferation, migration, and invasion in HBV-associated HCC	[30] (2019)
	In vitro, the HCC SK-Hep1 cells, human umbilical vein endothelial cells (HUVECs)	The resistin effect on SK-Hep1 cell adhesion to HUVECs	The inhibitory effect of AMPK activation under the resistin stimulation	[31] (2014)
Regulation of cancer metabolism	In vivo, the rAAV-infused G6pc−/− mice	AMPK/sirtuin-1 and FGF21/β-klotho signalings combined with down-regulation of STAT3/NFκB-mediated inflammatory and tumorigenic signaling	The absence of hepatic tumors in AAV-NT mice	[32] (2017)
	In vitro, HepG2 (ATCC HB-8065) human liver cancer; In vivo, ACC KI mice, male Wistar rats	AMPK-mediated ACC phosphorylation	The importance of DNL and dysregulation of AMPK-mediated ACC phosphorylation in accelerating HCC	[33] (2019)
	In vitro, human HCC cell line HepG2 and MHCC97L; In vivo, female BALB/c nu/nu athymic nude mice	eEF2K/AMPK	Huanglian Jiedu Decoction mediates eEF2 inactivation in HCC cells	[34] (2015)
	In vitro, primary rat hepatocyte system	AMPK-mTORC1 axis	Inhibition of AMPK decreased HBV replication	[35] (2016)

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