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Review Article

Role of AMP-activated protein kinase (AMPK) in cancer cell metabolism

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Abstract

AMP-activated protein kinase (AMPK) is an essential enzyme that participates in cellular energy homeostasis. AMPK activates to control the ATP synthesis during a shortage of energy, which regulates energy requirement during metabolic reactions. Also, AMPK is a known target for treating type 2 diabetes. Recent studies showed AMPK as an emerging tumour suppressor and a promising target for cancer treatment. Recent studies indicate that treatment with metformin (a drug used to treat type 2 diabetes), an AMPK activator reduces the occurrence of cancer. Anti-cancer effects of AMPK include promoting autophagy (removing damaged cells) and DNA repair after UV damage. Cancer cells have specific metabolic changes that differ from normal cells, and AMPK prevents the deregulated processes in cancer. AMPK controls mammalian target of rapamycin (mTOR) through tuberous sclerosis (genetic disorder) complex 2 (TSC2) phosphorylation and phosphatase and tensin homolog (PTEN), considered as central cell growth controller signals in diseases like cancer. This review focuses on AMPK and its role in cancer cell metabolism.

Keywords: *AMP-activated protein kinase, homeostasis, tumour suppressor, cancer, metformin, treatment, mTOR, metabolism.*

1. Introduction

Cancers are a group of diseases that have abnormal cell growth and function that can move to many parts of the body(Hausman 2019). tumours become highly heterogeneous during cancer progression(Klein 2020), creating a mixed population of cells characterized by different features and diverse responsivity to therapies. Usually, cancer is a global and homogeneous disease, and tumours are considered a whole population of cells (group). AMP-Activated protein kinase, or AMPK, is an enzyme that plays an essential role in cellular

energy homeostasis(Russell and Hardie 2020). AMPK works to restore cellular ATP levels by modifying diverse metabolic and cellular pathways(Scott and Oakhill 2017). It is a heterotrimeric serine/threonine-protein kinase that is activated by cellular perturbations related to ATP depletion(Wang et al. 2018). AMPK is a heterotrimer of three subunits, α, β, and γ. The 63-kDa α-subunit has the kinase domain and also contributes to the AMP-binding site. Two isoforms of both the α- and β-subunits have been expressed and are designated α_1, α_2, β_1, and β_2(Yan et al. 2018). Thus, a deep understanding of these complex phenomena is fundamental to designing specific drugs and therapies. AMP-activated protein kinase is a type of enzyme which helps to control cellular energy homeostasis. Current evidence suggests that AMPK can act as a tumour suppressor by modulating Inflammation, opposing metabolic changes that occur during tumorigenesis, and directly generating a cell-cycle arrest(Faubert et al. 2013).

AMPK stops the *de novo* synthesis of fatty acids (FAs), cholesterol, and triglycerides (TGs) and activates FA uptake and β-oxidation (FAO)(McFadden and Corl 2009)(Esquejo et al. 2018). AMPK inhibits FA synthesis(Qu et al. 2020) (FAS) by producing the inhibitory phosphorylation of two targets: 1.) acetyl-CoA carboxylase 1 (ACC1), which catalyses the rate-limiting step in FA synthesis by converting acetyl-CoA to malonyl-CoA(Gross et al. 2019), and 2.) sterol regulatory element-binding protein 1c (SREBP1c)(Y. Li et al. 2011).

In skeletal muscles, AMPK restores glucose uptake by translocating GLUT4-having intracellular vesicles throughout the plasma membrane(Den Hartogh et al. 2020)(Vlavcheski et al. 2020). Fusion of these vesicles with the plasma membrane requires Rab family G proteins in their active GTP-bound state(G. Li and Marlin 2015). AMPK phosphorylates and inhibits the Rab-GTPase-activating protein TBC1D1(Chavez et al. 2008)(Pehmøller et al. 2009), which increases the activity of Rab family G proteins and induces the fusion of GLUT4 vesicles with the plasma membrane. Interestingly, a recent study showed that AMPK also increases glucose uptake in HEK293 cells by blocking endocytosis and promoting GLUT1 expression. AMPK-induced GLUT1 regulation is mediated by the phosphorylation and degradation of TRX-interacting protein, which induces GLUT1 internalization(Wu et al. 2013). AMPK also increases the mRNA expression of the genes encoding GLUT4 and hexokinase 2 to facilitate glucose uptake.

AMPK upregulates several antioxidant genes(Jayachandran et al. 2019), e.g., the encoding superoxide dismutase and uncoupling protein 2, which reduce superoxide levels and thioredoxin (TRX), a disulphide reductase phosphorylating and activating FOXO.

Cancer metabolism is when cancer cells make the energy they need to grow and spread abnormally(Vazquez et al. 2016). Cancer cell metabolism(Kroemer and Pouyssegur 2008) is a direct result of the modulation of intracellular signalling pathways interrupted by mutated oncogenes(Torry and Cooper 1991) and tumour-suppressor genes. Mutated oncogenic genes can directly start cancer cell metabolism. Similarly, mutated metabolic enzymes can facilitate malignant transformation(Dhillon et al. 2007)(Davies et al. 2002). Thus, metabolism has an energy-producing process of which cells have advantages for maintaining cell homeostasis and growth and proliferation. It is characterized by a phenomenon called the Warburg effect(Liberti and Locasale 2016)(Vaupel, Schmidberger, and Mayer 2019).

Target Protein	Protein Function	Effect of Phosphorylation	Tissue	Effect on Pathway
Acetyl-CoA carboxylase-1	Metabolic enzyme	↓activity ↓malonyl-CoA	All cells	↓ fatty acid synthesis
Acetyl-CoA carboxylase-2	Metabolic enzyme	↓ activity ↓malonyl-CoA	Muscle, liver	↑ fatty acid oxidation
3-hydroxy-3methylglutaryl-CoA reductase	Metabolic enzyme	↓activity	liver	↓ sterol synthesis
Glycerol phosphate acyltransferase	Metabolic enzyme	↓activity	Adipose tissue	↓ triglyceride synthesis
Hormone-sensitive lipase	Metabolic enzyme	Antagonizes activation by PKA	Adipose tissue	↓ lipolysis
TBC1D1	Rab-GAP	Dissociation activation by PKA	Skeletal muscle	↑ glucose uptake
Glycogen synthase 1	Metabolic enzyme	↓ activity in low (Glucose-6-P)	Skeletal muscle	↓ glycogen synthesis
Glycogen synthase 2	Metabolic enzyme	↓ activity in low (Glucose-6-P)	liver	↓ glycogen synthesis
5-phosphofructo-2kinase PFKFB2	Cell signalling	↑ fructose-2,6-biphosphate	Cardiac muscles	↑ glycolysis
5-phosphofructo-2kinase PFKFB3	Cell signalling	↑ fructose-2,6-biphosphate	macrophages	↑ glycolysis

(Table-1)- Few Protein targets regulations by AMPK(Hardie 2013)

2. Current Traditional Treatments for Cancer

Immunotherapy(Yang 2015) for malignancies, including rare cancers, has enabled remarkable clinical achievements to be made in the last few years. Genetically modified T-cell therapy(Smith and Blomberg 2017)(DeRenzo and Gottschalk 2020) has recently been attempted using the T-cell receptor (TCR therapy) (Zhao and Cao 2019)approach and the chimeric antibody receptor (CAR-T) approach against rare cancers, including malignant melanoma and synovial sarcoma. The development of virotherapy, which destroys tumours using genetically engineered viruses, has also been highly promoted in recent years.

Surgery is a procedure in which a surgeon removes cancer (Tumour) from your body(Querleu 2013).

Radiation Therapy uses high-powered energy beams, such as X-rays or protons to kill cancer cells. Radiation treatment can come from a machine outside your body (external beam radiation), or it can be placed inside your body (brachytherapy)(Baskar et al. 2012)(Abshire and Lang 2018)(Tanderup et al. 2017).

Bone Marrow Transplant can use your bone marrow stem cells or those from a donor. In addition, a bone marrow transplant allows you to use higher doses of chemotherapy to treat your cancer(Ford and Eisenberg 1990).

Chemotherapy can cure or control cancer or help ease its symptoms by using specific drugs(Fujita and Kotake 2014).

3. Targeting AMPK for Cancer Treatment

3.1 Different Drugs Used

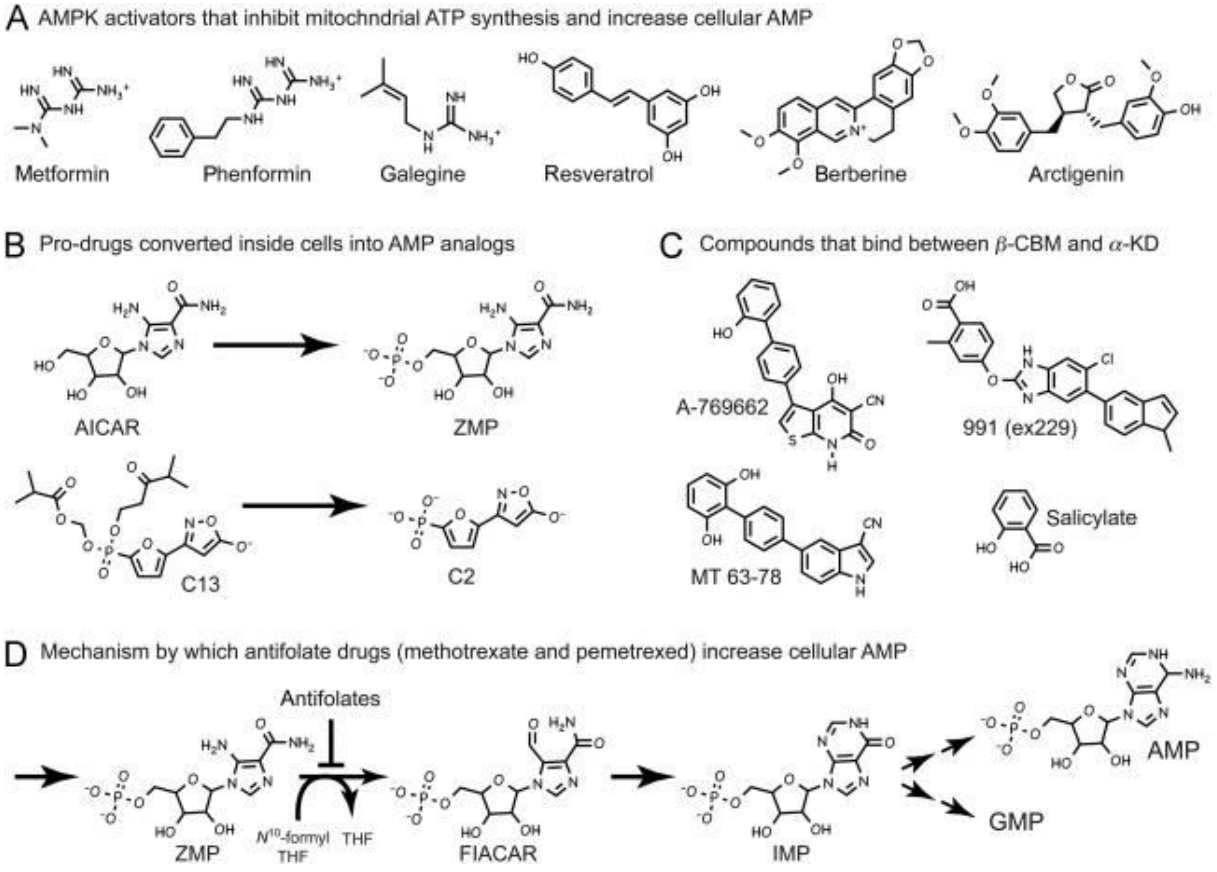
Non-Steroidal anti-inflammatory drugs(Bindu, Mazumder, and Bandyopadhyay 2020) Inflammation has been shown to play an essential role in tumour initiation and growth(Aguilar-Cazares et al. 2019). Aspirin has been shown to correlate with a decreased risk of developing cancer, mainly preventing colorectal cancer(Pence et al. 1995)(C. S. Lee, McNamara, and O'Morain 2012). However, it is believed that aspirin may prevent CRC by inhibiting COX-2(inhibitor)(Waluga et al. 2018)(Sostres, Gargallo, and Lanas 2014). This ultimately led to developing a new class of NSAIDs that are more selective for COX-2 inhibition for use as chemo preventive agents. Aspirin and other NSAIDs have also been shown to activate AMPK(King et al. 2015). When colorectal cancer cells were treated with aspirin, there was a significant increase in AMPK activation and inhibition of downstream mTOR signalling. Aspirin use has also been shown to correlate with the stopping of several other cancers like lung and liver(J. Chen et al. 2019)(Dickson 2020). It is likely that once aspirin or other NSAIDs activate AMPK, there is regulation of other inflammatory regulatory pathways. Therefore, the anti-inflammation drugs targeting AMPK activation might play a more meaningful role for the treatment of cancer-associated Inflammation in the future.

Curcumin(Kotha and Luthria 2019) is a yellow pigment present in turmeric, is one of largely investigated phytochemicals (natural chemical in plats) in the field of chemoprevention and is used in early clinical trials as an anti-cancer agent(Ranjan et al. 2019)(Brown and Rufini 2015). Curcumin has been shown to suppress tumour progression in various animal models of cancer(Pan et al. 2019)(Man et al. 2020). Recently, AMPK was found to be a new molecular target of curcumin(Soltani et al. 2019). In cancer cells, AMPK was found to act as a regulator of ERK1/2, p38, and COX-2. Thus, activation of AMPK by curcumin and its downstream targets such as PPAR-g, MAP kinases, and COX-2 is important in regulating cancer cells(Kaur and Moreau 2021).

Metformin is a drug used to decrease hyperglycaemia (high glucose) in patients with type-2 diabetes(Shlomai et al. 2016), in part by activating AMPK and is currently under investigation as a possible treatment for several types of cancer(Chiang et al. 2017). Clinical data suggest a benefit of metformin treatment in preventing certain cancers(Gronich and Rennert 2013). Recent preclinical studies were able to demonstrate metformin efficacy in various cancer types. Metformin was shown to significantly reduce aberrant crypt foci(Hosono et al. 2010)(D. Li 2011)(Bordini et al. 2017), the precursors to colon polyps with a modest reduction in polyp formation in animals treated with chemical carcinogen Azoxymethane(Bader et

al. 2018). In melanoma, metformin inhibits invasion and metastasis development through AMPK/p53 axis activation(Liang, Wang, and Wang 2018)(Y. C. Chen, Li, and Wang 2020).

Nanomedicine(B. Y. S. Kim, Rutka, and Chan 2010)**:** Nanoparticles are small particles with peculiar physicochemical properties due to their size and high surface-to-volume ratio. Biocompatible nanoparticles are used in cancer medicine to overcome some of the issues related to conventional therapies, such as the low specificity and bioavailability of drugs or contrast agents(Sztandera, Gorzkiewicz, and Klajnert-Maculewicz 2019)(S. W. L. Lee et al. 2019).



(Figure-1)

3.2 Advantages of AMPK in Cancer Treatment

1. AMPK activation give rise to a cell cycle delay(Yoon et al. 2019) which is associated with stabilization of p53 and the cyclin-dependent kinase inhibitors $p21^{WAF1}$ and $p27^{c1p1}$(Drakos et al. 2009).
2. AMPK hinders the synthesis of many macromolecules needed for cell growth, like lipids, ribosomal RNA and proteins(Liu et al. 2012).

3. By promoting oxidative metabolism and inhibiting glycolysis(Ganapathy-Kanniappan and Geschwind 2013) by inhibition of mTORC1 and consequent downregulation of expression of hypoxia-inducible factor-1α, AMPK promotes a switch away from the fast glycolysis observed in many tumour cells (the Warburg effect) and toward the oxidative metabolism used by most quiescent cells(Shen, Gerrard, and Du 2008).

4. Mechanism of AMPK Regulations

AMPK is a heterotrimeric protein that contains catalytic α and β and γ subunits. Each subunit of α and is encoded with 2 genes (α1 and α2 or β1 and β2), while γ subunit is encoded with 3 genes (γ1, γ2, and - 3). AMPK is activated when AMP and ADP levels in cells rise due to a variety of stress factors, as well as pharmacy inducers(Carling et al. 2011). Increased LKB1 kinase activates it in response to an increase in AMP(Shaw et al. 2005)(Lin and Hardie 2018), while CAMKK2 activates AMPK in response to an increase in calcium(Vara-Ciruelos et al. 2018)(Fogarty et al. 2016). AMPK is used directly to phosphorylates a number of substrates to significantly affect metabolism and growth, as well as phosphorylating a number of prescribing moderators who mediate long-term drug reuptake(J. Kim et al. 2011).

The production of AMPK improves both the secretion and transmission of GLUT4, leading to an increase in insulin-dependent glucose uptake. In addition, it stimulates recovery processes such as fatty acid oxidation and glycolysis with ACC inhibition and PFK2 activation. AMPK negatively regulates a number of proteins between ATP-activation processes such as TORC2, glycogen synthase, SREBP-1 and TSC2(Tuo et al. 2019), leading to a reduction in regulation or inhibition of gluconeogenesis, glycogen, lipid and protein synthesis.

In mammals, there are two genes encoding the AMPK α catalytic subunit (α1 and α2), two genes (β1 and β2) and three genes (γ1, γ2 and -3)(Ross, MacKintosh, and Hardie 2016). Exposure to some of these isoforms was inhibited by tissue, and a functional separation of the two catalytic subunits was reported, particularly AMP- and LKB1 reactions and the localization of AMPKα2 versus α1.

Conclusion

A large amount of evidence supports the fact that AMPK activation might act as a metabolic tumour suppressor in the coming future. AMPK activation has shown to decrease the symptoms related to type-2 diabetes and metabolic syndrome and is well-established therapeutic for these disorders. Studies suggest that patients with type-2 diabetes taking metformin have a lower risk of developing cancer; But ironically, patients having diabetes have higher occurrence of cancer. It is being said that AMPK activation might oppose tumour development by reprogramming cellular metabolism and targeting one of the important requirements important for cancer development.

References

Abshire, Dorothy, and Matthew K Lang. 2018. "The Evolution of Radiation Therapy in Treating Cancer." *Seminars in Oncology Nursing* 34 (2): 151–57. https://doi.org/10.1016/j.soncn.2018.03.006.

Aguilar-Cazares, Dolores, Rodolfo Chavez-Dominguez, Angeles Carlos-Reyes, César Lopez-Camarillo, Olga N Hernadez de la Cruz, and Jose S Lopez-Gonzalez. 2019. "Contribution of Angiogenesis to Inflammation and Cancer." *Frontiers in Oncology* 9: 1399. https://doi.org/10.3389/fonc.2019.01399.

Bader, Jackie E, Reilly T Enos, Kandy T Velázquez, Meredith S Carson, Mitzi Nagarkatti, Prakash S Nagarkatti, Ioulia Chatzistamou, et al. 2018. "Macrophage Depletion Using Clodronate Liposomes Decreases Tumorigenesis and Alters Gut Microbiota in the AOM/DSS Mouse Model of Colon Cancer." *American Journal of Physiology. Gastrointestinal and Liver Physiology* 314 (1): G22–31. https://doi.org/10.1152/ajpgi.00229.2017.

Baskar, Rajamanickam, Kuo Ann Lee, Richard Yeo, and Kheng-Wei Yeoh. 2012. "Cancer and Radiation Therapy: Current Advances and Future Directions." *International Journal of Medical Sciences* 9 (3): 193–99. https://doi.org/10.7150/ijms.3635.

Bindu, Samik, Somnath Mazumder, and Uday Bandyopadhyay. 2020. "Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Organ Damage: A Current Perspective." *Biochemical Pharmacology* 180 (October): 114147. https://doi.org/10.1016/j.bcp.2020.114147.

Bordini, Heloíza Paranzini, Jean Lucas Kremer, Tatiane Renata Fagundes, Gabriella Pasqual Melo, Ivete Conchon-Costa, Suelen Santos da Silva, Alessandra Lourenço Cecchini, Carolina Panis, and Rodrigo Cabral Luiz. 2017. "Protective Effect of Metformin in an Aberrant Crypt Foci Model Induced by 1,2-Dimethylhydrazine: Modulation of Oxidative Stress and Inflammatory Process." *Molecular Carcinogenesis* 56 (3): 913–22. https://doi.org/10.1002/mc.22545.

Brown, Karen, and Alessandro Rufini. 2015. "New Concepts and Challenges in the Clinical Translation of Cancer Preventive Therapies: The Role of Pharmacodynamic Biomarkers." *Ecancermedicalscience* 9: 601. https://doi.org/10.3332/ecancer.2015.601.

Carling, David, Faith V Mayer, Matthew J Sanders, and Steven J Gamblin. 2011. "AMP-Activated Protein Kinase: Nature's Energy Sensor." *Nature Chemical Biology* 7 (8): 512–18. https://doi.org/10.1038/nchembio.610.

Chavez, Jose A, William G Roach, Susanna R Keller, William S Lane, and Gustav E Lienhard. 2008. "Inhibition of GLUT4 Translocation by Tbc1d1, a Rab GTPase-Activating Protein Abundant in Skeletal Muscle, Is Partially Relieved by AMP-Activated Protein Kinase Activation." *The Journal of Biological Chemistry* 283 (14): 9187–95. https://doi.org/10.1074/jbc.M708934200.

Chen, Jinghua, Ruilian Xu, Junxian Xia, Jiacheng Huang, Binbin Su, and Senming Wang. 2019. "Aspirin Inhibits Hypoxia-Mediated Lung Cancer Cell Stemness and Exosome Function." *Pathology, Research and Practice* 215 (6): 152379. https://doi.org/10.1016/j.prp.2019.03.008.

Chen, Yong Chang, He Li, and Jing Wang. 2020. "Mechanisms of Metformin Inhibiting Cancer Invasion and Migration." *American Journal of Translational Research* 12 (9): 4885–4901.

Chiang, Chi-Fu, Ting-Ting Chao, Yu-Fu Su, Chia-Chen Hsu, Chu-Yen Chien, Kuo-Chou Chiu, Shine-Gwo Shiah, Chien-Hsing Lee, Shyun-Yeu Liu, and Yi-Shing Shieh. 2017. "Metformin-Treated Cancer Cells Modulate Macrophage Polarization through AMPK-NF-KB Signaling." *Oncotarget* 8 (13): 20706–18. https://doi.org/10.18632/oncotarget.14982.

Davies, Helen, Graham R Bignell, Charles Cox, Philip Stephens, Sarah Edkins, Sheila Clegg, Jon Teague, et

al. 2002. "Mutations of the BRAF Gene in Human Cancer." *Nature* 417 (6892): 949–54. https://doi.org/10.1038/nature00766.

DeRenzo, Christopher, and Stephen Gottschalk. 2020. "Genetically Modified T-Cell Therapy for Osteosarcoma: Into the Roaring 2020s." *Advances in Experimental Medicine and Biology* 1257: 109–31. https://doi.org/10.1007/978-3-030-43032-0_10.

Dhillon, A S, S Hagan, O Rath, and W Kolch. 2007. "MAP Kinase Signalling Pathways in Cancer." *Oncogene* 26 (22): 3279–90. https://doi.org/10.1038/sj.onc.1210421.

Dickson, Iain. 2020. "Aspirin Associated with Lower Risk of Liver Cancer." *Nature Reviews. Gastroenterology & Hepatology* 17 (5): 260. https://doi.org/10.1038/s41575-020-0299-3.

Drakos, E, V Atsaves, J Li, V Leventaki, M Andreeff, L J Medeiros, and G Z Rassidakis. 2009. "Stabilization and Activation of P53 Downregulates MTOR Signaling through AMPK in Mantle Cell Lymphoma." *Leukemia* 23 (4): 784–90. https://doi.org/10.1038/leu.2008.348.

Esquejo, Ryan M, Christopher T Salatto, Jake Delmore, Bina Albuquerque, Allan Reyes, Yuji Shi, Rob Moccia, et al. 2018. "Activation of Liver AMPK with PF-06409577 Corrects NAFLD and Lowers Cholesterol in Rodent and Primate Preclinical Models." *EBioMedicine* 31 (May): 122–32. https://doi.org/10.1016/j.ebiom.2018.04.009.

Faubert, Brandon, Gino Boily, Said Izreig, Takla Griss, Bozena Samborska, Zhifeng Dong, Fanny Dupuy, et al. 2013. "AMPK Is a Negative Regulator of the Warburg Effect and Suppresses Tumor Growth in Vivo." *Cell Metabolism* 17 (1): 113–24. https://doi.org/10.1016/j.cmet.2012.12.001.

Fogarty, Sarah, Fiona A Ross, Diana Vara Ciruelos, Alexander Gray, Graeme J Gowans, and D Grahame Hardie. 2016. "AMPK Causes Cell Cycle Arrest in LKB1-Deficient Cells via Activation of CAMKK2." *Molecular Cancer Research : MCR* 14 (8): 683–95. https://doi.org/10.1158/1541-7786.MCR-15-0479.

Ford, R, and S Eisenberg. 1990. "Bone Marrow Transplant. Recent Advances and Nursing Implications." *The Nursing Clinics of North America* 25 (2): 405–22.

Fujita, Shin, and Kenjiro Kotake. 2014. "[Chemotherapy]." *Nihon rinsho. Japanese journal of clinical medicine* 72 (1): 102–7.

Ganapathy-Kanniappan, Shanmugasundaram, and Jean-Francois H Geschwind. 2013. "Tumor Glycolysis as a Target for Cancer Therapy: Progress and Prospects." *Molecular Cancer* 12 (December): 152. https://doi.org/10.1186/1476-4598-12-152.

Gronich, Naomi, and Gad Rennert. 2013. "Beyond Aspirin-Cancer Prevention with Statins, Metformin and Bisphosphonates." *Nature Reviews. Clinical Oncology* 10 (11): 625–42. https://doi.org/10.1038/nrclinonc.2013.169.

Gross, Angelina S, Andreas Zimmermann, Tobias Pendl, Sabrina Schroeder, Hannes Schoenlechner, Oskar Knittelfelder, Laura Lamplmayr, et al. 2019. "Acetyl-CoA Carboxylase 1-Dependent Lipogenesis Promotes Autophagy Downstream of AMPK." *The Journal of Biological Chemistry* 294 (32): 12020–39. https://doi.org/10.1074/jbc.RA118.007020.

Hardie, D Grahame. 2013. "AMPK: A Target for Drugs and Natural Products with Effects on Both Diabetes and Cancer." *Diabetes* 62 (7): 2164–72. https://doi.org/10.2337/db13-0368.

Hartogh, Danja J Den, Filip Vlavcheski, Adria Giacca, and Evangelia Tsiani. 2020. "Attenuation of Free Fatty Acid (FFA)-Induced Skeletal Muscle Cell Insulin Resistance by Resveratrol Is Linked to Activation of AMPK and Inhibition of MTOR and P70 S6K." *International Journal of Molecular Sciences* 21 (14). https://doi.org/10.3390/ijms21144900.

Hausman, Daniel M. 2019. "What Is Cancer?" *Perspectives in Biology and Medicine* 62 (4): 778–84. https://doi.org/10.1353/pbm.2019.0046.

Hosono, Kunihiro, Hiroki Endo, Hirokazu Takahashi, Michiko Sugiyama, Takashi Uchiyama, Kaori Suzuki, Yuichi Nozaki, et al. 2010. "Metformin Suppresses Azoxymethane-Induced Colorectal Aberrant Crypt

Foci by Activating AMP-Activated Protein Kinase." *Molecular Carcinogenesis* 49 (7): 662–71. https://doi.org/10.1002/mc.20637.

Jayachandran, Muthukumaran, Ziyuan Wu, Kumar Ganesan, Sumbul Khalid, S M Chung, and Baojun Xu. 2019. "Isoquercetin Upregulates Antioxidant Genes, Suppresses Inflammatory Cytokines and Regulates AMPK Pathway in Streptozotocin-Induced Diabetic Rats." *Chemico-Biological Interactions* 303 (April): 62–69. https://doi.org/10.1016/j.cbi.2019.02.017.

Kaur, Harleen, and Régis Moreau. 2021. "Curcumin Represses MTORC1 Signaling in Caco-2 Cells by a Two-Sided Mechanism Involving the Loss of IRS-1 and Activation of AMPK." *Cellular Signalling* 78 (February): 109842. https://doi.org/10.1016/j.cellsig.2020.109842.

Kim, Betty Y S, James T Rutka, and Warren C W Chan. 2010. "Nanomedicine." *The New England Journal of Medicine* 363 (25): 2434–43. https://doi.org/10.1056/NEJMra0912273.

Kim, Joungmok, Mondira Kundu, Benoit Viollet, and Kun-Liang Guan. 2011. "AMPK and MTOR Regulate Autophagy through Direct Phosphorylation of Ulk1." *Nature Cell Biology* 13 (2): 132–41. https://doi.org/10.1038/ncb2152.

King, Tanya S, Otto Quintus Russe, Christine V Möser, Nerea Ferreirós, Katharina L Kynast, Claudia Knothe, Katrin Olbrich, Gerd Geisslinger, and Ellen Niederberger. 2015. "AMP-Activated Protein Kinase Is Activated by Non-Steroidal Anti-Inflammatory Drugs." *European Journal of Pharmacology* 762 (September): 299–305. https://doi.org/10.1016/j.ejphar.2015.06.001.

Klein, Christoph A. 2020. "Cancer Progression and the Invisible Phase of Metastatic Colonization." *Nature Reviews. Cancer* 20 (11): 681–94. https://doi.org/10.1038/s41568-020-00300-6.

Kotha, Raghavendhar R, and Devanand L Luthria. 2019. "Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical Aspects." *Molecules (Basel, Switzerland)* 24 (16). https://doi.org/10.3390/molecules24162930.

Kroemer, Guido, and Jacques Pouyssegur. 2008. "Tumor Cell Metabolism: Cancer's Achilles' Heel." *Cancer Cell* 13 (6): 472–82. https://doi.org/10.1016/j.ccr.2008.05.005.

Lee, Chun Seng, Deirdre McNamara, and Colm A O'Morain. 2012. "Aspirin as a Chemoprevention Agent for Colorectal Cancer." *Current Drug Metabolism* 13 (9): 1313–22. https://doi.org/10.2174/138920012803341384.

Lee, Sharon Wei Ling, Camilla Paoletti, Marco Campisi, Tatsuya Osaki, Giulia Adriani, Roger D Kamm, Clara Mattu, and Valeria Chiono. 2019. "MicroRNA Delivery through Nanoparticles." *Journal of Controlled Release : Official Journal of the Controlled Release Society* 313 (November): 80–95. https://doi.org/10.1016/j.jconrel.2019.10.007.

Li, Donghui. 2011. "Metformin as an Antitumor Agent in Cancer Prevention and Treatment." *Journal of Diabetes* 3 (4): 320–27. https://doi.org/10.1111/j.1753-0407.2011.00119.x.

Li, Guangpu, and M Caleb Marlin. 2015. "Rab Family of GTPases." *Methods in Molecular Biology (Clifton, N.J.)* 1298: 1–15. https://doi.org/10.1007/978-1-4939-2569-8_1.

Li, Yu, Shanqin Xu, Maria M Mihaylova, Bin Zheng, Xiuyun Hou, Bingbing Jiang, Ogyi Park, et al. 2011. "AMPK Phosphorylates and Inhibits SREBP Activity to Attenuate Hepatic Steatosis and Atherosclerosis in Diet-Induced Insulin-Resistant Mice." *Cell Metabolism* 13 (4): 376–88. https://doi.org/10.1016/j.cmet.2011.03.009.

Liang, Feng, Yu-Gang Wang, and Changcheng Wang. 2018. "Metformin Inhibited Growth, Invasion and Metastasis of Esophageal Squamous Cell Carcinoma in Vitro and in Vivo." *Cellular Physiology and Biochemistry : International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology* 51 (3): 1276–86. https://doi.org/10.1159/000495539.

Liberti, Maria V, and Jason W Locasale. 2016. "The Warburg Effect: How Does It Benefit Cancer Cells?" *Trends in Biochemical Sciences* 41 (3): 211–18. https://doi.org/10.1016/j.tibs.2015.12.001.

Lin, Sheng-Cai, and D Grahame Hardie. 2018. "AMPK: Sensing Glucose as Well as Cellular Energy

Status." *Cell Metabolism* 27 (2): 299–313. https://doi.org/10.1016/j.cmet.2017.10.009.

Liu, Lidan, Jannes Ulbrich, Judith Müller, Torsten Wüstefeld, Lukas Aeberhard, Theresia R Kress, Nathiya Muthalagu, et al. 2012. "Deregulated MYC Expression Induces Dependence upon AMPK-Related Kinase 5." *Nature* 483 (7391): 608–12. https://doi.org/10.1038/nature10927.

Man, Shuli, Jingwen Yao, Panpan Lv, Yu Liu, Li Yang, and Long Ma. 2020. "Curcumin-Enhanced Antitumor Effects of Sorafenib via Regulating the Metabolism and Tumor Microenvironment." *Food & Function* 11 (7): 6422–32. https://doi.org/10.1039/c9fo01901d.

McFadden, Joseph W, and Benjamin A Corl. 2009. "Activation of AMP-Activated Protein Kinase (AMPK) Inhibits Fatty Acid Synthesis in Bovine Mammary Epithelial Cells." *Biochemical and Biophysical Research Communications* 390 (3): 388–93. https://doi.org/10.1016/j.bbrc.2009.09.017.

Pan, Pan, Yi-Wen Huang, Kiyoko Oshima, Martha Yearsley, Jianying Zhang, Mark Arnold, Jianhua Yu, and Li-Shu Wang. 2019. "The Immunomodulatory Potential of Natural Compounds in Tumor-Bearing Mice and Humans." *Critical Reviews in Food Science and Nutrition* 59 (6): 992–1007. https://doi.org/10.1080/10408398.2018.1537237.

Pehmøller, Christian, Jonas T Treebak, Jesper B Birk, Shuai Chen, Carol Mackintosh, D Grahame Hardie, Erik A Richter, and Jørgen F P Wojtaszewski. 2009. "Genetic Disruption of AMPK Signaling Abolishes Both Contraction- and Insulin-Stimulated TBC1D1 Phosphorylation and 14-3-3 Binding in Mouse Skeletal Muscle." *American Journal of Physiology. Endocrinology and Metabolism* 297 (3): E665-75. https://doi.org/10.1152/ajpendo.00115.2009.

Pence, B C, D M Dunn, C Zhao, M Landers, and M J Wargovich. 1995. "Chemopreventive Effects of Calcium but Not Aspirin Supplementation in Cholic Acid-Promoted Colon Carcinogenesis: Correlation with Intermediate Endpoints." *Carcinogenesis* 16 (4): 757–65. https://doi.org/10.1093/carcin/16.4.757.

Qu, Yuan-Yuan, Rui Zhao, Hai-Liang Zhang, Qian Zhou, Fu-Jiang Xu, Xuan Zhang, Wen-Hao Xu, et al. 2020. "Inactivation of the AMPK-GATA3-ECHS1 Pathway Induces Fatty Acid Synthesis That Promotes Clear Cell Renal Cell Carcinoma Growth." *Cancer Research* 80 (2): 319–33. https://doi.org/10.1158/0008-5472.CAN-19-1023.

Querleu, Denis. 2013. "[Cancer surgery in 2025]." *Bulletin du cancer*. France.

Ranjan, Alok, Sharavan Ramachandran, Nehal Gupta, Itishree Kaushik, Stephen Wright, Suyash Srivastava, Hiranmoy Das, Sangeeta Srivastava, Sahdeo Prasad, and Sanjay K Srivastava. 2019. "Role of Phytochemicals in Cancer Prevention." *International Journal of Molecular Sciences* 20 (20). https://doi.org/10.3390/ijms20204981.

Ross, Fiona A, Carol MacKintosh, and D Grahame Hardie. 2016. "AMP-Activated Protein Kinase: A Cellular Energy Sensor That Comes in 12 Flavours." *The FEBS Journal* 283 (16): 2987–3001. https://doi.org/10.1111/febs.13698.

Russell, Fiona M, and David Grahame Hardie. 2020. "AMP-Activated Protein Kinase: Do We Need Activators or Inhibitors to Treat or Prevent Cancer?" *International Journal of Molecular Sciences* 22 (1). https://doi.org/10.3390/ijms22010186.

Scott, John W, and Jonathan S Oakhill. 2017. "The Sweet Side of AMPK Signaling: Regulation of GFAT1." *The Biochemical Journal* 474 (7): 1289–92. https://doi.org/10.1042/BCJ20170006.

Shaw, Reuben J, Katja A Lamia, Debbie Vasquez, Seung-Hoi Koo, Nabeel Bardeesy, Ronald A Depinho, Marc Montminy, and Lewis C Cantley. 2005. "The Kinase LKB1 Mediates Glucose Homeostasis in Liver and Therapeutic Effects of Metformin." *Science (New York, N.Y.)* 310 (5754): 1642–46. https://doi.org/10.1126/science.1120781.

Shen, Qingwu W, David E Gerrard, and Min Du. 2008. "Compound C, an Inhibitor of AMP-Activated Protein Kinase, Inhibits Glycolysis in Mouse Longissimus Dorsi Postmortem." *Meat Science* 78 (3): 323–30. https://doi.org/10.1016/j.meatsci.2007.06.023.

Shlomai, Gadi, Brian Neel, Derek LeRoith, and Emily Jane Gallagher. 2016. "Type 2 Diabetes Mellitus and

Cancer: The Role of Pharmacotherapy." *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 34 (35): 4261–69. https://doi.org/10.1200/JCO.2016.67.4044.

Smith, Edvard, and Pontus Blomberg. 2017. "[Gene therapy – from idea to reality]." *Lakartidningen* 114 (December).

Soltani, Arash, Arash Salmaninejad, Mohammad Jalili-Nik, Anvar Soleimani, Hossein Javid, Seyed Isaac Hashemy, and Amirhossein Sahebkar. 2019. "5'-Adenosine Monophosphate-Activated Protein Kinase: A Potential Target for Disease Prevention by Curcumin." *Journal of Cellular Physiology* 234 (3): 2241–51. https://doi.org/10.1002/jcp.27192.

Sostres, Carlos, Carla Jerusalen Gargallo, and Angel Lanas. 2014. "Aspirin, Cyclooxygenase Inhibition and Colorectal Cancer." *World Journal of Gastrointestinal Pharmacology and Therapeutics* 5 (1): 40–49. https://doi.org/10.4292/wjgpt.v5.i1.40.

Sztandera, Krzysztof, Michał Gorzkiewicz, and Barbara Klajnert-Maculewicz. 2019. "Gold Nanoparticles in Cancer Treatment." *Molecular Pharmaceutics* 16 (1): 1–23. https://doi.org/10.1021/acs.molpharmaceut.8b00810.

Tanderup, Kari, Cynthia Ménard, Csaba Polgar, Jacob Christian Lindegaard, Christian Kirisits, and Richard Pötter. 2017. "Advancements in Brachytherapy." *Advanced Drug Delivery Reviews* 109 (January): 15–25. https://doi.org/10.1016/j.addr.2016.09.002.

Torry, D S, and G M Cooper. 1991. "Proto-Oncogenes in Development and Cancer." *American Journal of Reproductive Immunology (New York, N.Y. : 1989)* 25 (3): 129–32. https://doi.org/10.1111/j.1600-0897.1991.tb01080.x.

Tuo, Lin, Jin Xiang, Xuanming Pan, Jieli Hu, Hua Tang, Li Liang, Jie Xia, et al. 2019. "PCK1 Negatively Regulates Cell Cycle Progression and Hepatoma Cell Proliferation via the AMPK/P27(Kip1) Axis." *Journal of Experimental & Clinical Cancer Research : CR* 38 (1): 50. https://doi.org/10.1186/s13046-019-1029-y.

Vara-Ciruelos, Diana, Madhumita Dandapani, Alexander Gray, Ejaife O Egbani, A Mark Evans, and D Grahame Hardie. 2018. "Genotoxic Damage Activates the AMPK-A1 Isoform in the Nucleus via Ca(2+)/CaMKK2 Signaling to Enhance Tumor Cell Survival." *Molecular Cancer Research : MCR* 16 (2): 345–57. https://doi.org/10.1158/1541-7786.MCR-17-0323.

Vaupel, Peter, Heinz Schmidberger, and Arnulf Mayer. 2019. "The Warburg Effect: Essential Part of Metabolic Reprogramming and Central Contributor to Cancer Progression." *International Journal of Radiation Biology* 95 (7): 912–19. https://doi.org/10.1080/09553002.2019.1589653.

Vazquez, Alexei, Jurre J Kamphorst, Elke K Markert, Zachary T Schug, Saverio Tardito, and Eyal Gottlieb. 2016. "Cancer Metabolism at a Glance." *Journal of Cell Science* 129 (18): 3367–73. https://doi.org/10.1242/jcs.181016.

Vlavcheski, Filip, Danja J Den Hartogh, Adria Giacca, and Evangelia Tsiani. 2020. "Amelioration of High-Insulin-Induced Skeletal Muscle Cell Insulin Resistance by Resveratrol Is Linked to Activation of AMPK and Restoration of GLUT4 Translocation." *Nutrients* 12 (4). https://doi.org/10.3390/nu12040914.

Waluga, M, M Zorniak, J Fichna, M Kukla, and M Hartleb. 2018. "Pharmacological and Dietary Factors in Prevention of Colorectal Cancer." *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society* 69 (3). https://doi.org/10.26402/jpp.2018.3.02.

Wang, Qi, Shudong Liu, Aihua Zhai, Bai Zhang, and Guizhen Tian. 2018. "AMPK-Mediated Regulation of Lipid Metabolism by Phosphorylation." *Biological & Pharmaceutical Bulletin* 41 (7): 985–93. https://doi.org/10.1248/bpb.b17-00724.

Wu, Ning, Bin Zheng, Adam Shaywitz, Yossi Dagon, Christine Tower, Gary Bellinger, Che-Hung Shen, et al. 2013. "AMPK-Dependent Degradation of TXNIP upon Energy Stress Leads to Enhanced Glucose Uptake via GLUT1." *Molecular Cell* 49 (6): 1167–75. https://doi.org/10.1016/j.molcel.2013.01.035.

Yan, Yan, X Edward Zhou, H Eric Xu, and Karsten Melcher. 2018. "Structure and Physiological Regulation of AMPK." *International Journal of Molecular Sciences* 19 (11). https://doi.org/10.3390/ijms19113534.

Yang, Yiping. 2015. "Cancer Immunotherapy: Harnessing the Immune System to Battle Cancer." *The Journal of Clinical Investigation* 125 (9): 3335–37. https://doi.org/10.1172/JCI83871.

Yoon, Kyeong Jin, Didi Zhang, Seok-Jin Kim, Min-Chul Lee, and Hyo Youl Moon. 2019. "Exercise-Induced AMPK Activation Is Involved in Delay of Skeletal Muscle Senescence." *Biochemical and Biophysical Research Communications* 512 (3): 604–10. https://doi.org/10.1016/j.bbrc.2019.03.086.

Zhao, Lijun, and Yu J Cao. 2019. "Engineered T Cell Therapy for Cancer in the Clinic." *Frontiers in Immunology* 10: 2250. https://doi.org/10.3389/fimmu.2019.02250.