

AMPK Impacts on Metabolic Function & Immune Health

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In the United States and many other industrialized countries, we are dealing with two simultaneous health threats: The global COVID-19 pandemic and the epidemic of poor metabolic health. Recent statistics indicate that a mere 12 percent of U.S. adults are metabolically healthy, indicating that a massive proportion of our population is metabolically unfit.¹ Unfortunately, our poor collective metabolic health appears to be a significant factor in the pandemic we currently face as a global society.

A rapidly-growing body of research indicates that disease outcomes in COVID-19 and poor metabolic health are inexorably linked. Poor metabolic health significantly increases the risk of suffering a severe course of COVID-19 and experiencing lingering, troublesome symptoms after the resolution of the illness, such as cognitive impairment.^{2,3} To survive this pandemic and protect our health going forward, we must prioritize our metabolic health. We can't just wait until metabolic health crumbles apart in full-blown Type 2 diabetes and cardiovascular disease; we must approach metabolic health head-on with proactive, evidence-based interventions. AMPK activation represents an emerging, powerful strategy for metabolic health optimization.

Article at a Glance

- What is AMPK?
- How AMPK Impacts Metabolic Function & Immune Health
- Autophagy and Cellular Detoxification
- Mitochondrial Efficiency
- Immune Health and Function
- Gut Health
- Liver Function
- Healthy Aging and Longevity
- Nutraceutical and Lifestyle Strategies for AMPK Activation
- The relationship between NAD+ and AMPK

AMPK-Activating Phytonutrients	Lifestyle Strategies
Berberine	Fasting
Quercetin	Ketogenic Diet
Resveratrol	Exercise
Apigenin	Sleep-Low Eating and Exercise Strategy
Curcumin	
Alpha Lipoic Acid	

¹ Araujo J, et al. Prevalence of optimal metabolic health in American adults: National health and nutrition examination survey 2009–2016. *Metab Syndr Relat Disord.* 2019; 17(1): 46-52.

² Ayres JS. A metabolic handbook for the COVID-19 pandemic. *Nature Metab.* 2020. 2: 572-585.

³ Zhou H, et al. The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res.* 2020; 129: 98-102.

What is AMPK?

AMP-kinase, known as AMPK, is an enzyme and cellular energy sensor that plays vital roles in cellular energy homeostasis. It is a central regulator of metabolism, energy, and body weight and is one of the body's most critical biochemical pathways. AMPK senses when cellular energy levels are depleted by detecting low adenosine monophosphate (AMP), an ATP with two of its high-energy phosphates removed. Upon sensing low AMP, AMPK activates pathways that promote cellular energy generation.⁴ AMPK is activated by various inputs, including calorie restriction, fasting, reduced blood insulin levels, and exercise. Activation of AMPK produces multiple beneficial health effects, including reduced inflammation and enhanced insulin sensitivity. We will expand on the many benefits of AMPK activation momentarily.

The mammalian/mechanistic target of rapamycin (mTOR) pathway works mostly in opposition to AMPK. Whereas AMPK is activated by a low cellular energy state, mTOR is an anabolic pathway activated when nutrients and cellular energy are plentiful. While mTOR activation plays essential roles in several physiological functions, including growth and development and the skeletal muscle response to exercise, chronic mTOR activation is problematic and promotes sustained inflammation and metabolic dysfunction.

In our ancestral environment, intermittent food availability necessitated periodic fasting. Today, scientific research indicates that fasting is one of the most potent activators of AMPK; this finding suggests that our bodies evolved to regularly experience intermittent AMPK activation. Conversely, living life in a chronically "fed" state, as many of us do in the modern-day Western world, inhibits AMPK and activates mTOR, preventing us from realizing the health benefits of the powerful AMPK pathway. When we miss out on AMPK activation, our metabolic health and immune function suffer. Conversely, an active AMPK pathway improves numerous physiological processes underlying metabolic wellbeing and healthy immune function.

How AMPK Impacts Metabolic Function & Immune Health

The AMPK protein has profound, far-reaching effects on metabolic health.⁵ More recently, AMPK has also been identified as an essential player in regulating the immune system. An active AMPK pathway **powers metabolic health and robust immunity**, two aspects of health that have never been more important than in our current environment.

Modulates Inflammatory Balance

At a foundational level, AMPK modulates the body's inflammatory balance. Chronic, low-level inflammation is an underlying factor in numerous chronic diseases, including dysfunctional metabolic states such as type 2 diabetes and cardiovascular disease. By resolving inflammation, AMPK creates a foundation for whole-body health, including healthy metabolic function and immunity.

⁴ Garcia D and Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. *Mol Cell*. 2017; 66(6): 789-800.

⁵ Garcia D, et al. Genetic liver-specific AMPK activation protects against diet-induced obesity and NAFLD. *Cell Rep*. 2019; 26(1): 192-208.e6.

Improves Insulin Sensitivity and Glycemic Homeostasis

AMPK has profound impacts on glycemic homeostasis. AMPK activation attenuates insulin resistance and hyperinsulinemia, stepping stones in the progression of metabolic dysfunction.⁶ These changes shift the body from burning primarily glucose for fuel to utilizing fat for fuel. The shift to fat burning for energy production reduces reactive oxygen species generation, creating cleaner-burning energy.

The shift towards fat-burning also helps the body better access fat stores for fuel; this may reduce body fat mass. Reducing body fat mass alleviates the vicious cycle of inflammation and metabolic dysfunction perpetuated by excessive amounts of adipose tissue, a highly metabolically-active organ that produces proinflammatory cytokines.⁷

Improves Lipid Homeostasis

While the idea that total cholesterol, and even total LDL cholesterol, contribute appreciably to cardiovascular disease has been debunked, several more nuanced subcategories of blood lipids do indeed influence cardiometabolic disease pathogenesis. The subcategories include the total LDL particle number and oxidized LDL levels. Here too, AMPK activation exerts beneficial modulatory effects.

AMPK inhibits acetyl coenzyme A carboxylase (ACC) and 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMGCR), the rate-limiting enzymes for fatty acid and cholesterol biosynthesis. The inhibition of these enzymes reduces total cholesterol production and may reduce the number of LDL particles generated by the body.⁸ It also inhibits endoplasmic reticulum stress, a form of cellular stress, triggered by oxidized LDL particles.⁹ AMPK also improves cardiovascular health by improving carbohydrate metabolism.¹⁰

AMPK activation also inhibits NF kappa B, reducing vascular inflammation. Vascular inflammation is a critical risk factor for cardiovascular disease.¹¹ It also increases endothelial nitric oxide synthase (eNOS) and nitric oxide production while decreasing reactive oxygen species, further improving vascular function.

Promote Autophagy and Cellular Detoxification

AMPK is a potent activator of autophagy, the body's cellular "housekeeping" system. Autophagy via AMPK activation and mTOR blocking offers a profound level of detoxification that cleanses the body at a cellular level.

Abundant research indicates that both exogenous and endogenous toxins drive metabolic and immune dysfunction. Clearing toxins from the system through detoxification is essential for achieving metabolic clarity and optimal immune health. By promoting autophagy, AMPK activation jump-starts the removal of health-hindering toxins.

⁶ Ruderman NB, et al. AMPK, insulin resistance, and the metabolic syndrome. *J Clin Invest.* 2013; 123(7): 2764-2772.

⁷ Zatterale F, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and Type 2 diabetes. *Front Physiol.* 2019; 10: 1607.

⁸ Foretz M and Viollet B. Activation of AMPK for a break in hepatic lipid accumulation and circulating cholesterol. *EBioMedicine.* 2018; 31:15-16.

⁹ Dong Y, et al. Activation of AMP-activated protein kinase inhibits oxidized LDL-triggered endoplasmic reticulum stress in vivo. *Diabetes.* 2010; 59(6): 1386-1396.

¹⁰ Srivastava RAK, et al. AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases. *J Lipid Res.* 2012; 53(12): 2490-2514.

¹¹ Shirwany NA, et al. AMPK in cardiovascular health and disease. *Acta Pharmacol Sin.* 2010; 31(9): 1075-1084.

Increase Mitochondrial Efficiency

As discussed earlier, one of the primary goals of AMPK activation is to restore cellular ATP levels. One mechanism through which AMPK accomplishes this goal is via the activation of mitochondrial biogenesis.¹² Improvements in mitochondrial function induced by AMPK exert downstream benefits on blood glucose regulation and inflammation.

Amplify Immune Health

The global pandemic has brought the human immune system into the spotlight, highlighting the need for novel immune-modulating strategies that can enhance our resilience against this, and future, environmental immune challenges. While most of the world waits with bated breath for a vaccine for SARS CoV-2, we at Quicksilver Scientific believe in taking a more proactive approach by bolstering our own internal immune defenses. One powerful, yet underappreciated, way to enhance healthy immune function is through AMPK activation.

Metabolism can either inhibit or enhance immune vigilance, the process by which the immune system surveys the body's internal environment for immune threats such as pathogens. A primary mechanism through which poor metabolic health may increase the risk of contracting threats, such as viral infection, is by impairing immune surveillance. AMPK activation may improve immune function by enhancing immune surveillance and the host defenses against infectious invaders.¹³

Emerging research indicates that modulation of autophagy also impacts immune function.^{14,15} Here too, AMPK can play a supportive role via its autophagy-enhancing effects.

A special subset of autophagy, called xenophagy, is also activated by AMPK.¹⁶ Xenophagy is a selective form of autophagy by which macrophages capture pathogens in autophagosomes, and then fuse the autophagosomes with lysosomes to eliminate the pathogens. Xenophagy is an essential component of the innate immune response, the body's frontline defense against pathogens.

Optimize Gut Health

Over 80 percent of the human immune system resides in the gut, making gut health the foundation for a robust, resilient immune system.¹⁷ Furthermore, a growing body of research indicates that gut health and the gut microbiota influence metabolic health parameters, including blood glucose control.¹⁸ Here too, AMPK plays an essential role.

AMPK activation has been found to repair paracellular tight junctions, improving intestinal barrier integrity and inhibiting "leaky gut," a phenomenon that may underlie numerous chronic diseases.¹⁹ Fascinatingly, research indicates that certain gut bacteria modulate AMPK activity, influencing the course of metabolic

¹² Herzig S and Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat Rev Mol Cell Biol.* 2018; 19(2): 121-135.

¹³ Silwal P, et al. AMP-activated protein kinase and host defense against infection. *Int J Mol Sci.* 2018; 19(11): 3495.

¹⁴ Jang YJ, et al. Modulation of autophagy for controlling immunity. *Cells.* 2019; 8(2): 138.

¹⁵ Levine B, et al. Autophagy in immunity and inflammation. *Nature.* 2011; 469: 323-335.

¹⁶ Losier TT, et al. AMPK promotes xenophagy through priming of autophagic Kinases upon Detection of Bacterial Outer Membrane Vesicles. *Cell Rep.* 2019; 26(8): 2150-2165.

¹⁷ Vighi G, et al. Allergy and the gastrointestinal system. *Clin Exp Immunol.* 2008; 153 (Suppl 1): 3-6.

¹⁸ Janssen AWF, et al. The role of the gut microbiota in metabolic health. *FASEB J.* 2015; 29(8): 3111-3123.

¹⁹ Sun X and Zhu MJ. AMP-activated protein kinase: a therapeutic target in intestinal diseases. *Open Biol.* 2017; 7(8): 170104.

function. Gut microbes may exert these modulatory effects on AMPK through short-chain fatty acids (SCFA), metabolites produced through microbial metabolism of dietary fibers.²⁰

Facilitate Liver Function

A healthy liver is a prerequisite for metabolic health. However, poor metabolic health also contributes to compromised liver function, mainly through the development of non-alcoholic fatty liver disease (NAFLD). In NAFLD, excess fat builds up in the liver due to impairments in glucose and lipid metabolism caused by overnutrition, chronic inflammation, and gut dysbiosis.

AMPK activation attenuates fatty liver disease by reducing inflammation, attenuating the adverse metabolic effects of overnutrition, and upregulating autophagy.²¹

Promote Healthy Aging and Longevity

Preliminary research indicates that accelerated biological aging predicts an increased risk of contracting and suffering from COVID-19.²² Whether accelerated biological aging is associated with other infections remains to be seen; regardless, these findings suggest that attenuating the biological aging process is vital for supporting immune function and resilience.

AMPK activates the production of two sets of proteins involved in healthy aging and longevity, the sirtuins and FOXO proteins. Sirtuins are a family of seven proteins that play regulatory roles in almost all cellular functions. Sirtuins regulate inflammation, cell growth, circadian rhythms, energy metabolism, neuronal function, and stress resistance.²³ FOXO proteins, on the other hand, are transcription factors that bind to specific regions on DNA, controlling the transmission of genetic information.

FOXO proteins are transcriptional regulators that influence cell replication, DNA repair, autophagy, and metabolism. At the nexus of these pathways, FOXO also appears to influence aging.²⁴ The AMPK and FOXO pathways are closely linked in that active AMPK directly phosphorylates FOXO. In fact, the relationship between AMPK and FOXO may play a crucial role in the longevity-enhancing effects of caloric restriction.²⁵

Nicotinamide adenine dinucleotide (NAD⁺) is an essential cofactor for sirtuins.²⁶ Without sufficient NAD⁺, sirtuins cannot effectively perform their numerous vital roles within the body.

²⁰ Yu H, et al. Alteration of the gut microbiota and its effect on AMPK/NADPH oxidase signaling pathway in 2K1C rats. *Biomed Res Int*. 2019; Article ID 8250619.

²¹ Zhao P and Saltiel AR. From overnutrition to liver injury: AMP-activated protein kinase in non-alcoholic fatty liver diseases. *J Biol Chem*. 2020; 295(34): 12279-12289.

²² Kuo CL, et al. COVID-19 severity is predicted by earlier evidence of accelerated aging. MedRxiv. 2020; doi: <https://doi.org/10.1101/2020.07.10.20147777>.

²³ Rajman L, et al. Therapeutic potential of NAD-boosting molecules: the in vivo evidence. *Cell Metab*. 2018; 27(3): 529-547.

²⁴ Martins R, et al. Long live FOXO: unraveling the role of FOXO proteins in aging and longevity. *Aging Cell*. 2016; 15(2): 196-207.

²⁵ Greer EL, et al. AMP-activated protein kinase and FoxO transcription factors in dietary restriction-induced longevity. *Ann N Y Acad Sci*. 2009; 1170: 688.

²⁶ Imai SI and Guarente L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol*. 2014; 24(8): 464-471.

Nutraceuticals for AMPK Activation

The role of phytochemicals as mediators of human metabolic health has an evolutionary basis. Just as our bodies are evolutionarily wired to benefit from AMPK signaling, so too are our bodies biologically designed to interact with and reap health benefits from phytochemicals present in edible plants.²⁷ In fact, some scientists suggest that a dietary deficiency of phytochemicals contributes to disorders of energy metabolism; a lack of consumption of AMPK-activating phytochemicals may be an important part of our metabolic health puzzle.

A variety of phytonutrients have been found to activate AMPK. Let's discuss each of these phytochemicals in turn.

Berberine

Berberine is an alkaloid compound found in the root, rhizomes, and bark of a variety of plants, including plants in the *Berberis* genus such as Barberry and Oregon Grape. It has powerful effects on glycemic control and blood lipid homeostasis that can be traced back to its impact on the induction of AMPK activity.

Induction of AMPK activity by berberine results in improvements in insulin sensitivity due to increased GLUT4 translocation into cells, allowing for increased cellular glucose uptake and reduced lipid accumulation in 3T3-L1 adipocytes, a cell line of adipose cells used in animal research.²⁸ Through AMPK activation, berberine may help cells use up stored fat energy from adipocytes and suppresses inflammatory responses in macrophages.²⁹ In clinical trials, berberine has been found to beneficially alter the lipid profile of individuals at risk for cardiovascular disease.³⁰

Quercetin

Quercetin is a flavonoid found in an array of fruits and vegetables, including apples, capers, onions, and berries. It offers antioxidant activity largely through AMPK activation. It inhibits lipid accumulation in the liver in response to a high-fat, high carbohydrate processed diet.³¹ Quercetin also activates AMPK and SIRT1 to reduce obesity-associated inflammation.³²

Resveratrol

Resveratrol is a polyphenol primarily concentrated in red grapes and red wine. Resveratrol is a potent AMPK activator.³³ It has been found to reduce reactive oxygen species generation and increase reduced

²⁷ Johns T. Phytochemicals as evolutionary mediators of human nutritional physiology. *Int J Pharmacognosy*. 1996; 34(5): 327-334.

²⁸ Lee YS, et al. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes*. 2006; 55(8): 2256-2264.

²⁹ Jeong HW, et al. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. *Am J Physiol*. 2009; 296(4): E955-E964.

³⁰ Derosa G, et al. Effects of berberine on lipid profile in subjects with low cardiovascular risk. *Exp Opin Biol Ther*. 2013; 13(4): 475-482.

³¹ Liu L, et al. Quercetin alleviates high-fat diet-induced oxidized low-density lipoprotein accumulation in the liver: Implication for autophagy regulation. *Biomed Res Int*. 2015; Article ID: 607531.

<https://doi.org/10.1155/2015/607531>

³² Dong J, et al. Quercetin reduces obesity-associated ATM infiltration and inflammation in mice: a mechanism including AMPK α 1/SIRT1. *J Lipid Res*. 2014; 55(3): 363-374

³³ Price NL, et al. SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. *Cell Metab*. 2012; 15(5): 675-690.

glutathione levels via a mechanism dependent on AMPK activation.³⁴ By enhancing the activation of AMPK, resveratrol also promotes mitochondrial biogenesis and neurogenesis; notably, these effects are interdependent on sirtuins, demonstrating clear connections between the NAD⁺-dependent sirtuin proteins and AMPK.

Interestingly, a combination of quercetin and resveratrol has been found to attenuate obesity and adipose tissue inflammation in animals fed a high-fat, high-sugar processed diet.³⁵

Apigenin

Apigenin is a flavonoid found in parsley, celery, onions, chamomile, thyme, oregano, and basil. Unlike berberine, quercetin, and resveratrol, it is not a potent direct AMPK activator. On the contrary, it exerts rather weak AMPK-activating effects. However, it may indirectly support AMPK activity, and other metabolic pathways that intersect with AMPK, by inhibiting CD38, a glycoprotein found on immune cells that is a prolific consumer of NAD⁺.³⁶ The inhibitory effects of apigenin on CD38 preserve cellular NAD⁺ homeostasis, sparing NAD⁺ for other crucial functions, such as sirtuin activation.

Curcumin

Curcumin is a phytochemical found in the bright orange root of the turmeric plant, *Curcuma longa*. Curcumin is a truly pleiotropic molecule, with effects ranging from antioxidant activity to prebiotic properties on the gut microbiota. Recent research has added another function to the long list of curcumin's effects – AMPK activator. Curcumin's AMPK-activating effects dampen gluconeogenesis, enhance insulin sensitivity, and induces autophagy.^{37,38,39}

Alpha Lipoic Acid (ALA)

While not a phytochemical, alpha-lipoic acid is a naturally-occurring thiol-based molecule and nutraceutical with AMPK activity, and thus is worthy of our attention. Alpha-lipoic acid enhances skeletal muscle function and endothelial function and exerts anti-obesity effects through AMPK activation.^{40,41,42}

Phytochemical-based AMPK activators exist on a spectrum, with quercetin, resveratrol, and berberine exerting the strongest AMPK-activating effects.

³⁴ Moraes DS, et al. Sirtuins, brain and cognition: A review of resveratrol effects. *IBRO Reports*. 2020; 9: 46-51.

³⁵ Zhao L, et al. Combination treatment with quercetin and resveratrol attenuates high fat diet-induced obesity and associated inflammation in rats via the AMPK α 1/SIRT1 signaling pathway. *Exp Ther Med*. 2017; 14(6): 5942-5948.

³⁶ Escande C, et al. Flavonoid Apigenin Is an Inhibitor of the NAD⁺-ase CD38

Implications for Cellular NAD⁺ Metabolism, Protein Acetylation, and Treatment of Metabolic Syndrome. *Diabetes*. 2013; 62(4): 1084-1093.

³⁷ Kim T, et al. Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochem Biophys Res Commun*. 2009; 388(2): 377-382.

³⁸ Mohiti-Ardekani J, et al. *Cogent Food Agr*. 2019; 5(1): Article: 1577532.

³⁹ Xiao K, et al. Curcumin induces autophagy via activating the AMPK signaling pathway in lung adenocarcinoma cells. *J Pharmacol Sci*. 2013; 123(2): 102-109.

⁴⁰ Wang Y, et al. Alpha-lipoic acid increases energy expenditure by enhancing AMPK-PGC-1 α signalling in the skeletal muscle of aged mice. *Metabolism*. 2010; 59(7): 967-976.

⁴¹ Lee WJ, et al. Alpha-lipoic acid prevents endothelial dysfunction in obese rats via activation of AMP-activated protein kinase. *Arterioscler Thromb Vasc Biol*. 2005; 25(12): 2488-2494.

⁴² Kim MS, et al. Anti-obesity effects of alpha-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. *Nat Med*. 2004; 10(7): 727-733.

Lifestyle Strategies for AMPK Activation

Fasting

Fasting is a well-known activator of AMPK. AMPK activation in skeletal muscle during fasting results in the phosphorylation and inhibition of acetyl-CoA carboxylase and a subsequent increase in fatty acid oxidation, otherwise known as “fat burning.”⁴³

Ketogenic Diet

A ketogenic diet, defined as a very-low-carb, moderate protein, high-fat diet, is another tool for activating AMPK. By suppressing insulin levels, the ketogenic diet removes an important barrier to AMPK activation. Furthermore, beta-hydroxybutyrate, one of the ketone bodies produced in nutritional ketosis, suppresses inflammation through AMPK activation.⁴⁴

Exercise

Skeletal muscle is a metabolically active tissue that plays a vital role in the body's metabolic homeostasis. It is a significant site for the uptake of circulating blood glucose; accelerated uptake of glucose by active skeletal muscle reduces blood glucose levels, inhibiting hyperglycemia and improving blood sugar homeostasis. Another mechanism through which skeletal muscle influences metabolism is its impact on AMPK activation when the muscle is actively engaged in exercise.

Several forms of exercise have been found to activate AMPK, including sprints, high-intensity interval training (HIIT), and aerobic exercise.^{45,46,47, 48} Interestingly, muscle AMPK activation may be impaired in those with pre-existing metabolic dysfunction, suggesting that a multifaceted approach may be needed in these individuals to improve skeletal muscle AMPK activity.

Sleep-Low Eating and Exercise Strategy

AMPK is clearly involved in the body's physiological adaptations to exercise. A robust body of research indicates that adaptations to exercise can be further enhanced with nutrition. One method for enhancing physiological adaptation to exercise that further capitalizes on AMPK activation is the “sleep low” nutrition strategy.

The “sleep low” nutrition strategy involves training late in the day and eating a low-carb meal for dinner, thereby causing you to go to bed in a carbohydrate-restricted state. The next morning, you do low-intensity exercise, such as jogging or walking, first thing in the morning while still in the fasted state. You then eat normally, with plenty of carbohydrates, for the rest of the day until you do another evening workout. This strategy is best used twice a week on days where you plan to engage in high-intensity workouts late in the day; it is not intended to be used daily. Research suggests it can offer significant

⁴³ Bujak AL, et al. AMPK Activation of muscle autophagy prevents fasting-induced hypoglycemia and myopathy during aging. *Cell Metab.* 2015; 21(6): 883-890.

⁴⁴ Bae HR, et al. β -Hydroxybutyrate suppresses inflammasome formation by ameliorating endoplasmic reticulum stress via AMPK activation. *Oncotarget.* 2016; 7(41): 66444-66454.

⁴⁵ Guerra B, et al. SIRT1, AMP-activated protein kinase phosphorylation, and downstream kinases in response to a single bout of sprint exercise: influence of glucose ingestion. *Eur J Appl Physiol.* 2010; 109(4): 731-743.

⁴⁶ Gibala MJ, et al. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1 α in human skeletal muscle. *J Appl Physiol.* 2009; 106(3): 929-934.

⁴⁷ Kido K, et al. Enhanced skeletal muscle insulin sensitivity after acute resistance-type exercise is upregulated by rapamycin-sensitive mTOR complex 1 inhibition. *Sci Rep.* 2020; 10: 8509.

⁴⁸ Kjobsted R, et al. AMPK in skeletal muscle function and metabolism. *FASEB J.* 2018; 32(4): 1741-1777.

exercise performance benefits, in part through AMPK activation, when incorporated into a comprehensive training regimen.⁴⁹

The Relationship Between NAD+ and AMPK

How are NAD+ and AMPK related? NAD+ is a critical cofactor for sirtuins, a family of seven proteins involved in cellular health and longevity. Sirtuins and AMPK, in turn, engage in crosstalk and share many common target molecules.⁵⁰ For example, sustained activation of AMPK activates sirtuins. Sirtuins and AMPK, in turn, work together to regulate aspects of metabolic health, including the metabolic health benefits of exercise.⁵¹

The sirtuin-activating effects of AMPK necessitate a high level of NAD+, an essential cofactor for sirtuin activation. Without sufficient NAD+, it may not be possible to realize the full spectrum of health benefits offered by AMPK activation.

Both NAD+ production and AMPK signaling decline with age, causing defects in metabolic function.^{52,53} In animal studies, restoring NAD+ levels ameliorates age-associated decrements in health, including impairments in metabolic health. Furthermore, immune cells rapidly use up NAD+ when fighting off pathogens; exposure to pathogens and other immune threats may thus deplete NAD+ stores.⁵⁴ Supplementation with NAD+ precursors, such as NMN, represent a potential intervention for restoring and maintaining our metabolic health and immune function as we age and in the presence of environmental immune threats.⁵⁵

An abundance of research at our fingertips indicates that AMPK activation is an essential process for optimizing metabolic health and immune resilience. Through diet and lifestyle changes and strategic supplementation, it is possible to induce a therapeutic activation of AMPK and experience the downstream benefits on multiple aspects of metabolic health and immunity.

⁴⁹ Jeukendrup AE. Periodized nutrition for athletes. *Sports Med.* 2017; 47(Suppl 1): 51-63.

⁵⁰ Ruderman NB, et al. AMPK and SIRT1: a long-standing partnership? *Am J Physiol Endocrinol Metab.* 2010; 298(4): E751-E760.

⁵¹ Vargas-Ortiz K, et al. Exercise and sirtuins: A way to mitochondrial health in skeletal muscle. *Int J Mol Sci.* 2019; 20(11): 2717.

⁵² Imai SI and Guarente L. NAD+ and sirtuins in aging and disease. *Trends Cell Biol.* 2014; 24(8): 464-471.

⁵³ Salminen A, et al. Age-related changes in AMPK activation: Role for AMPK phosphatases and inhibitory phosphorylation by upstream signaling pathways. *Ageing Res Rev.* 2016; 28: 15-26.

⁵⁴ Singhal A and Cheng CY. Host NAD+ metabolism and infections: therapeutic implications. *Int Immunol.* 2019; 31(2): 59-67.

⁵⁵ Omran HM, et al. Influence of NAD+ as an ageing-related immunomodulator on COVID 19 infection: A hypothesis. *J Infect Public Health.* 2020; 13(9): 1196-1201.

Article Summary

- **What is AMPK?** AMP-kinase, known as AMPK, is an enzyme and cellular energy sensor that plays vital roles in cellular energy homeostasis.
- **How AMPK Impacts Metabolic Function & Immune Health:** An active AMPK pathway powers metabolic health and robust immunity supporting inflammatory balance, insulin sensitivity, and lipid and glycemic homeostasis.
- **Autophagy and Cellular Detoxification:** AMPK is a potent activator of autophagy, the body's cellular "housekeeping" system. Autophagy via AMPK activation and mTOR blocking offers a profound level of detoxification that cleanses the body at a cellular level.
- **Mitochondrial Efficiency:** AMPK activates mitochondrial biogenesis to restore cellular ATP levels.
- **Immune Health and Function:** AMPK activation may improve immune function by enhancing immune surveillance and the host defenses against infectious invaders.
- **Gut Health:** AMPK activation has been found to repair paracellular tight junctions, improving intestinal barrier integrity and inhibiting "leaky gut," a phenomenon that may underlie numerous chronic diseases.
- **Liver Function:** AMPK activation attenuates fatty liver disease by reducing inflammation, attenuating the adverse metabolic effects of overnutrition, and upregulating autophagy
- **Healthy Aging and Longevity:** AMPK activates the production of two sets of proteins involved in healthy aging and longevity, the sirtuins and FOXO proteins.
- **Nutraceutical and Lifestyle Strategies for AMPK Activation:**

The role of phytochemicals as mediators of human metabolic health has an evolutionary basis. In fact, some scientists suggest that a dietary deficiency of phytochemicals contributes to disorders of energy metabolism; a lack of consumption of AMPK-activating phytochemicals may be an important part of our metabolic health puzzle.

AMPK-Activating Phytonutrients	Lifestyle Strategies
Berberine	Fasting
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- **The relationship between NAD⁺ and AMPK:** Sirtuins and AMPK, in turn, work together to regulate aspects of metabolic health, including the metabolic health benefits of exercise.