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HYPERTROPHY OF CARDIAC CELLS DUE TO AMP-REGULATED PROTEIN KINASE SIGNALLING

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ABSTRACT

The AMP-protein kinase (AMPK) pathway regulates cellular energetic balance in many different tissues in the heart or cardiovascular system. Important cellular characteristics like signalling and regulation in cardiovascular and tumour biology are gaining prominence. A relation between anti-I.E, therapy and susceptibility to cardiac disease are new establishments in these days. Some anti-I.E, drugs induced to an increased risk of cardiac disease, underlined by de-regulation of AMPK signalling. This article explores the AMPK signalling axis in both cardiac and tumour metabolism. Observation of targeted AMPK inhibition by I.E, drugs and how this may translate into increased risk of cardiovascular disease was carried out. The connection of decontrolled AMPK signalling during various stages of cardiac hypertrophy has been conferred. Development of more effective treatment for IE and cardiovascular disease is only possible by gaining a proper understanding of molecular pathway behind this pathological processes.

KEYWORDS: protein kinase, Hypertrophy, Cardiotoxicity, Metabolism, AMP.

Structure of AMPK

AMP-activated protein kinase (AMPK) is a heterotrimeric compound composed of a catalytic α subunit and regulatory β and γ subunits. Each subunit has at least two different isoforms, which are controlled by specific genes. They differ slightly in their structure and have a differential way of expression across tissues.[1-3] The α subunit has 2 isoforms (α1 and α2), contains the AMPK serine/threonine kinase domain, and is phosphorylated on at least three residues. Phosphorylation of threonine 172 by upstream kinases is critical for AMPK activity and is often used as a sign of the activation state of the kinase.[4] Other phosphorylation sites are Thr258 and Ser485, but their activity remains to be unfound.[5] The α subunit also has an

autoinhibitory site (AID). The AID interacts with the kinase site and together they start a conformational change in response to AMP interaction with the γ subunit, which leads to AMPK activation.[6–8] AMPKα1 is originally found in discharging cells, while AMPKα2 is largely expressed in skeletal and heart muscle.[10]

The β–subunit of AMPK links α- and γ-subunits by means of its C-terminal sequence. Its purpose is not confined to operating the AMPK heterotrimer together since it comprises a central non-catalytic glycogen-binding region, which senses the status of cellular energy reserved in the form of glycogen.[11] Coupling of glycogen with a single glucose α1–6 branches to the β subunit of AMPK allosterically hinders phosphorylation of α subunit by upstream kinases.[12]

AMPKβ-subunit has two isoforms, β1 and β2, that only vary in the first 65 of 275 residues.[13] Despite the high structural identity, they have differential tissue arrangement; with β1 being denoted in a wide range of tissues and β2 essentially is limited to the brain, kidney and striated muscle.[14]

The γ subunit can be found as 3 isoforms (γ1, γ2 and γ3) and is made out of four cystathionine β-synthetase (CBS) motifs that pack together creating two Bateman domains (CBS1 + 2 and CBS3 + 4). The symmetry of the CBS site generates four potential adenyl-binding sites.[15] The 2' and 3' hydroxyl groups of each AMP ribose groups interact with an aspartic acid remainder located on the first turn of the α-helix adjacent to the site. In the fourth potential adenyl-binding site, an arginine residue is replaced instead, which probably makes AMP binding to this domain impossible. So, mammalian AMPK binds three AMP molecules; one binds to "site 4" and does not exchange for ATP and co-purifies with the proteins since it is tightly united. The other two AMP molecules compete for binding with Mg-ATP and/ or ATP to sites "1" and "3" and are responsible for adenyl-sensing characteristics of the mammalian enzyme.[16]

The γ isoforms have the greatest structural variability between all AMPK subunits. The most broadly expressed isoform is γ1, comprised of 331 residues.[17] The γ2 subunit is 569 -residues long and is mainly present in the heart, brain, placenta and skeletal muscle.[3] The third isoform γ3 is comprised of 489 residues and is only present in skeletal muscle.[17]

AMPK Activation process

AMPK activity is controlled in response to the cellular energy state, which is shown in the ratio of AMP to ATP. During energy usage, ATP is split down to generate ADP, which can be transformed to AMP through the action of adenylate kinase. Binding of AMP promotes phosphorylation of the activation loop at Thr172 by AMPK kinase (AMPKK) and reduces the dephosphorylation rate of AMPK by the PP2C-a phosphatase.[19] AMP-binding to AMPK begins allosteric and conformational modifications that affect the synergy between the kinase and the autoinhibitory domains of AMPKα.[7,20] AMP, as the primary activator of AMPK, has a much greater affinity to AMPK than that of ATP even when the cellular concentrations of ATP are much higher than those of AMP. In addition to AMP, ADP can also bind to AMPK, shielding the enzyme from dephosphorylation.[18]

The phosphorylation state of Thr172 indicates the activation status of AMPK and is affected by the balance between the action of upstream kinases and protein phosphatases. So far, two AMPKKs have been identified: Calcium-calmodulin-dependent protein kinase β (CaMKKβ)[21] and the tumour suppressor kinase complex LKB1.[22,23] The LKB1 complex comprises of LKB1 and two associate subunits, STRAD and MO25, both of which are needed for LKB1 activity (Figure 2).[22–24] There are at least two protein phosphatases that can repress AMPK activation: protein phosphatase 2A (PP2A) and protein phosphatase 2C (PP2C). PP2A inhibits AMPK phosphorylation in response to rise in intracellular calcium concentrations.[25] It is not clear what drives PP2C action on AMPK, but alterations in PP2C expression modulate AMPK activation in the heart.[26]

In addition to phosphorylation, AMPK can be post-translationally altered by acetylation on its α subunit. Acetylation state of AMPKα is ascertained by opposing catalytic activities of HDAC1 and p300. Deacetylation intensifies the catalytic activity of AMPK by increasing its association with the upstream kinase LKB1.[27] Post-translational modifications also occur on the regulatory subunits of AMPK. The β subunit can be modified by N-terminal myristoylation of the Gly2 residue.

Role of AMPK in cardiac metabolism

Fatty acids are the favoured substrate for energy generation in the heart.[29] AMPK changes fatty acid metabolism in different ways. AMPK targets and phosphorylates acetyl-CoA carboxylase activity (ACC) thus inhibiting the ACC activity.[30,31] Because ACC speedup the carboxylation of acetyl-CoA to yield malonyl-CoA, which is a substrate for the production of

fatty acids, inhibition of ACC activity reduces fatty acid biosynthesis. The main point of management of fatty acid oxidation lies in the capacity to transport the long-chain fatty acyl-CoA from the cytosol into the mitochondria where it is oxidized to produce acetyl-CoA. The Carnitine palmitoyltransferase (CPT-1) is the rate-limiting enzyme in this process. CPT-1 catalyses the transfer of the fatty acyl group from acyl-CoA to carnitine, making it transportable from the cytosol into mitochondria. Malonyl-CoA allosterically hinders CPT-1 activity, reducing the β-oxidation of fatty acids.[32]

AMPK controls the fatty acid assembly and β-oxidation

Fatty acid transportation across the cell membrane in cardiomyocytes is also controlled by AMPK. AMPK activation excites the expression of the fatty acid binding protein (FABPpm).[33] It also increases the expression and transfer of the fatty acid transporter FAT/CD36 from intracellular stores to the plasma membrane.[34] Ultimately, AMPK excites mitochondrial biogenesis, by yet not fully known mechanisms.[35]

The Added supply of ATP generation in the heart is produced by glucose catabolism. AMPK enhances glucose uptake by improving glucose transporter 4 (GLUT4) and GLUT1-mediated transport [36–38]. AMPK can also phosphorylate 6-phosphofructo-2-kinase (PFK 2), an enzyme capable of controlling glycolysis and gluconeogenesis. which lead eto increase in glycolysis during states of energetic stress occurs during myocardial ischemia.[39,40] AMPK also affects glucose storage, by phosphorylating and inactivating glycogen synthase (GS), thus favouring glucose flux by glycolysis.[41,42]

AMPK in tumour metabolism

The connection of AMPK signalling to I.E dates back to the discovery of LKB1. LKB1 was first recognized as a tumour suppressor mutated in an acquired I.E, susceptibility known as Peutz-Jegher's syndrome.[43,44] More recently, it has also been connected to some types of breast I.E,[45] It is not shocking that AMPK signalling is associated with I.E, metabolism thinking that tumour cells must adapt their metabolism to produce the energetic and biosynthetic intermediates needed to promote increased cell division in the circumstances of stress, such as hypoxia and nutrient loss.[46] AMPK and LKB1 are both negative regulators of aerobic glycolysis. Loss of LKB1 or AMPK activity promotes glucose and glutamine metabolism, boosting growth and biosynthetic capacity of tumour cells, by increasing HIF-1α expression.[49,50]

AMPK is a Tumor inhibiting enzyme

Controlled AMPK activation is linked to worsening overall diagnosis in several I.E,s and is seldom linked to enhanced metastasis.[57–59] An outcome of decreased AMPK signalling is enhanced cell reproduction irrespective of the molecular energy levels. This is accomplished through uncontrolled activation of the mTOR pathway. Usually, AMPK inhibits mTORC1 signalling by through phosphorylation of TSC2[60] and the mTORC1 regulatory subunit, Raptor.[61] LKB1/AMPK dependent repression of the mTOR pathway acts as a tumour suppressor in transformed cells, adding to cell outgrowth hindrance and suppression of oncogenic mRNA reading in response to energy pressure.[62,63] AMPK tumour suppressor potential also acts by the Akt/FOXO3 signalling axis. Activated AMPK decreases Akt induced phosphorylation of FOXO3a, stimulating this transcription factor and leading to repression of unregulated growth. Reduction of Akt activity also checks the epithelial-mesenchymal transformation of I.E, cells, thereby inhibiting intrusion of basement membranes starting to metastasis.[64,65]

The p53 gene which is a tumour suppressor gene and mutation of these genes is responsible for induction of a tumour. Recently, a connection joining AMPKα2 subunit isoform expression and p53 activation have been established. AMPK α2 amount is decreased in certain tumours, which involve breast I.E, when matched to their normal equivalents.[66] When the AMPKα2 concentration in those cells gets back to normal, it increases p53 acetylation by repressing the deacetylase activity of SIRT1, and due to stabilization of p53 gene apoptosis is triggered.

I.E, Drugs Increases the Risk of Cardiac Disease by inhibiting AMPK

It has been seen that IE, drugs have the adverse effect of cardiotoxicity. Anthracene in the structure of IE, drugs is responsible for the cardiotoxic effect.[68] The mechanisms underlying anthracyclines cardiotoxicity are adequately investigated. A broadly admitted mechanism of this cardiotoxicity is by the production of reactive oxygen species (ROS) starting to oxidative force.[69] Alternative mechanisms of cardiotoxicity have also been proposed. One common model is deregulation of cardiac AMPK activity. Anthracyclines, such as doxorubicin, cause cardiac damage by stimulating myofilament apoptosis, decreasing myofilament protein synthesis and remodelling cardiac energy metabolism.[70] The latter is accomplished by reducing phosphocreatine (PCr)/ATP, AMPK expression and activation.[71,72]

More newly it has been shown to cause myocyte injury in-vivo, reduce ATP concentration in

cardiomyocytes and impair AMPK's ability to phosphorylate downstream targets in the cell.[75] These conclusions imply that off-target repression of AMPK accounts, at least in part, for Sunitib cardiotoxicity. Herceptin (trastuzumab), adapted to treat HER-2 positive breast I.E, impairs cardiac AMPK activation resulting in failure to induce stress-related survival mechanisms.[76] It also lowers intracellular ATP levels in cardiomyocytes, leading to apoptosis, which is moreover intensified by TNFα.[77]

Pharmacological activation of AMPK inhibits protein synthesis and gene transcription correlated with cardiac hypertrophy.[80,81] Inactivation of AMPK in neonatal rat cardiomyocytes is permitted to development of hypertrophy.[82] This is denoted by AMPK capacity to inhibit mTOR signalling.[80] Similarly, a reduction in AMPK action increases hypertrophic growth and heart failure which lead to transverse aortic constriction.[83]

Concluding Remarks

The heart is a highly energy-consuming organ. Alterations in AMPK signalling can start a range of downstream molecular events that modify the way heart reacts to outside provocations, particularly those provocations that drive to energetic stress. Considering the nature of the energetic force, long- vs. short-term or pathological vs. physiological, AMPK signalling can either increase or decrease the development of cardiac disease. Outer determinants, like anti-I.E, drugs. deregulate cardiac AMPK signalling resulting in undesired and conceivably serious cardiovascular side-effects. Coming studies are needed to fully describe all anti-tumour agents that influence cardiac AMPK signalling and negatively impact cardiac health. Pharmacological alteration of currently accessible drugs and advancement of new I.E, drugs is a key move to more efficient therapy.

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