GSK-3 protein and the heart: friend or foe?

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Metabolic syndrome manifesting as obesity, insulin resistance and type 2 diabetes mellitus is currently pandemic. Each of these, in its own right, is strongly related to the development of cardiovascular disease. The cardiomyopathy associated with these disorders is characterised by curtailed glucose uptake and utilisation, elevated risk of damage after ischaemia and contractile dysfunction. Current research has indicated that the serine/threonine kinase, glycogen synthase kinase 3 (GSK-3), may play a central role in the development of all these dysfunctions. The development of new generations of inhibitors of this kinase, has renewed interest in its utilisation as therapeutic target. This review has therefore focused on the role of GSK-3 in the development of the obesity-related cardiomyopathy and has highlighted and discussed the detrimental as well as beneficial effects of the GSK-3 inhibitors that are currently available. We have discussed the different roleplayers such as the insulin signalling pathway, modulation of apoptosis and mitochondrial function, SERCA2 expression and regulation of the development of hypertrophy in the context of GSK-3 activity. SAHeart 2010; 7:48-57

Glycogen synthase kinase-3 (GSK-3) was identified in the early 1980s as an enzyme involved in the control of glycogen metabolism, and extensively researched, especially in the context of the metabolic actions of insulin. Currently, interest in this kinase has flared because of the development of new generations of inhibitors with specific clinical implications, especially in the potential of these inhibitors to treat diseases that currently have significant limitations in therapeutic treatments, e.g. type 2 diabetes, Alzheimer’s disease, stroke and bipolar- and mood disorders. The prototype of a GSK-3 inhibitor is lithium, although the mechanism of this inhibition is not understood. There is no clinical data available at present on the inhibition of GSK-3, but preclinical data supports an important future role. Scant preclinical data is available in the field of heart research, but, as this review has tried to summarise, the available evidence, as well as the multiplicity of actions of this kinase, argue strongly that its inhibition may also become an important future drug target in this field.

A CENTRAL ROLE FOR GSK-3 IN INSULIN SIGNALLING

Whole-body glucose homeostasis is a continuous process and a function of the production of glucose by the liver and the peripheral disposal of glucose, primarily by skeletal muscle. These two processes are regulated by several endocrine factors, the most important of which are insulin and glucagon, produced by the pancreatic β- and α-cells respectively.

Hepatic glucose production is mediated by both glycogenolysis and gluconeogenesis. When there is increased glucose demand by peripheral tissue, e.g. muscle contraction during exercise, the liver must produce glucose accordingly to prevent development of
hypoglycemia. These processes are governed by a decrease in insulin secretion and an increase in glucagon secretion, as well as by changes in adrenaline and cortisol secretion.

As a continuously contracting muscle, the heart uses between 3.5 and 5 kg of ATP per day. To produce this, glucose, fatty acids, amino acids and ketones are readily used as fuel substrates. Muscle glucose utilisation is acutely regulated by insulin (Figure 1). This is accomplished through a series of events initiated by binding of insulin to the α-subunit of the insulin receptor, leading to autophosphorylation of the membrane-spanning β-subunit. The activated insulin receptor, a proto-type tyrosine kinase enzyme, leads to the sequential activation of a kinase cascade involving insulin receptor substrate proteins (IRSs), PI-3-Kinase (phosphatidylinositol-3-kinase) and protein kinase B/Akt. Activation of PKB/Akt is a prerequisite for the translocation of the insulin regulated glucose transporter, Glut 4, from intracellular storage vesicles to the cell membrane to facilitate glucose uptake. Glut 4 is the major transporter responsible for uptake of glucose into heart muscle after stimulation with insulin or after anoxia or ischaemia of the muscle. Glut 1, previously taken to be responsible for basal glucose uptake, is apparently more concentrated in the endothelial cells of the microvasculature of the heart and does not respond to insulin with translocation from one compartment to another.

On cell entry, glucose can either be shunted into glycolytic pathways and metabolised to pyruvate or converted to glycogen via activation of the enzyme glycogen synthase (GS). Stimulation of muscle cells with insulin activates pathways that enhance glycogen formation. PKB/Akt was initially described as the kinase leading to activation of GS after insulin stimulation via phosphorylation of glycogen synthase kinase-3.

The mammalian heart expresses 2 isoforms of glycogen synthase kinase-3 (GSK-3). GSK-3α and GSK-3β exhibit a high degree of sequence similarity and have molecular masses of 51 and 47 kDa.
respectively. PKB/Akt phosphorylates both isoforms of GSK-3 on Ser21 and Ser9 respectively. GSK-3 is constitutively active in resting cells and its activity is negatively regulated by this phosphorylation. As reviewed by Sugden et al.,
this negative regulation can also be accomplished by other kinases such as ribosomal S6 kinase, (S6K), p90-ribosomal S6 kinase (RSK), the mitogen and stress activated protein kinases (MSK’s), serum and glucocorticoid-regulated kinase (SGK’s) as well as cAMP-dependent protein kinase, PKA. All of these signalling pathways are highly relevant in cardiovascular physiology and pathophysiology. In vivo, inhibition of GSK-3 and activation of GS by insulin, is mainly regulated by the pathway involving PI-3-Kinase and PKB/Akt. Besides glycogen synthesis, the expression and activation of GSK-3 protein impacts on diverse cellular processes such as glucose transport, gene transcription, cell differentiation, cell survival or –death (apoptosis), as well as muscle contractility.

INSULIN RESISTANCE

The pre-dominant role of insulin is the maintenance of whole body glucose homeostasis. Although this has been known for many years, it was not until 1949 that the ability of insulin to stimulate glucose uptake was experimentally demonstrated. PKB/Akt, as mediator of the metabolic effects of insulin, promotes glucose uptake in vascular-, skeletal muscle and adipose tissue. It is well-established that insulin stimulates glucose uptake also in heart muscle. Using 2-deoxy-D-[H] - glucose (2DG) uptake in primary neonatal or adult rat cardiomyocytes as a readout of insulin response, it was demonstrated that insulin stimulation leads to increased 2DG uptake. Cardiac glucose uptake is dependent on the transmembrane glucose gradient as well the content of sarcolemmal glucose transporters, glut 1 and glut 4, with glut 4 considered to be the principal contributor to the regulation of glucose uptake by insulin. Insulin via PKB/Akt activation induces the translocation of glut 4 from the intracellular storage vesicles to the sarcolemmal membrane to facilitate glucose entry.

Metabolic syndrome is a cluster of metabolic disturbances that together define a progressive condition associated with development of type 2 diabetes mellitus and cardiovascular disease. It is estimated that metabolic syndrome affects approximately one quarter of the population in developed countries. The National Cholesterol Education Programme’s Adult Treatment Panel III (NCEP, ATP III) and the European Group for the Study of Insulin Resistance, identified central–abdominal obesity, atherogenic dyslipidaemia (hypertriglyceridaemia and reduced high-density lipo-protein-cholesterol), raised blood pressure, insulin resistance and glucose intolerance as components for metabolic syndrome. Furthermore, it has been reported that each component of the syndrome may be considered as independent risk factors for cardiovascular disease. Over the past two decades, the number of people with metabolic syndrome has increased at an alarming rate. This increase is associated with the global epidemic of both obesity and diabetes. The inability of cells to respond appropriately to a certain level of insulin, is termed insulin resistance. This is a defect associated with a variety of disorders including metabolic syndrome, atherosclerosis, hypertension, dyslipidaemia, type 2 diabetes and heart failure. Increased cardiovascular risk is central to all these disorders and has been ascribed by some to the elevated plasma insulin levels that accompany insulin resistance. However, the United Kingdom Prospective Diabetes Study could not detect a correlation between higher cardiovascular risk and elevated insulin levels. Alternatively, obesity, with the accompanying elevated plasma free fatty acid levels, has been identified as probable cause of myocardial insulin resistance and is recognised as an independent risk factor of cardiovascular disease.

The insulin resistant state is characterised by impaired signalling via the IRS-1/PI-3-Kinase/PKB/Akt-pathway. Reduced insulin receptor- and IRS-1 tyrosine phosphorylation and IRS-1 associated PI-3-Kinase activity have been reported in adipocytes while lower PKB/Akt activity was found in the rat heart. In animal models of obesity and type 2 diabetes as well as in humans, attenuated muscle glucose transport has been documented, coupled to ineffective attenuation of hepatic glucose production. In addition, several studies have drawn negative correlations between GSK-3 activity, glucose uptake and muscle glycogen content. Currently, there is no evidence for genetic mutations in either one of...
the two GSK-3 genes associated with the development of type 2 diabetes mellitus but there are studies demonstrating upregulation of expression and higher activity of GSK-3 protein in skeletal muscle of type 2 diabetic patients and in adipose tissues of obese diabetic rodent models. In addition, it was shown that inhibition of GSK-3 improves insulin action in skeletal muscle of obese, insulin resistant rodents. The potential benefits of GSK-3 inhibition for the treatment of insulin resistance and type 2 diabetes, as demonstrated in different animal models, is elegantly reviewed by Wagman et al. In view of the vast amount of literature on this subject, this review will focus mainly on the cardiovascular effects of GSK-3 inhibition with special reference to insulin resistance.

**THE HEART IN OBESITY AND INSULIN RESISTANCE**

Studies have suggested that several agents are able to induce myocardial insulin resistance by activation of serine/threonine kinases that phosphorylate IRS-1 and inhibit its function. These agents include tumor necrosis factor α (TNFα), free fatty acids, cellular stress, angiotensin II and hyperinsulinemia. Insulin itself may also stimulate serine kinases that promote phosphorylation of IRS-1. According to Gual et al., the inhibition of IRS-1 function may represent the unifying mechanistic link between all factors involved in insulin resistance. GSK-3 protein, in its active state, also has the ability to phosphorylate IRS-1 on 2 serine residues (Ser307 and 332). This phosphorylation by GSK-3 is associated with downregulation of signalling via IRS-1 and may potentially exacerbate insulin resistance and compromise glucose uptake as it is associated with impaired tyrosine phosphorylation of IRS-1 and decreased PI-3-Kinase activation. The importance of this observation is underscored by the work of Rao et al. showing enhanced myocardial glucose uptake when GSK-3 is inhibited in high-fat-fed mice and a correction of diabetes in mice with a genetic deficiency of GSK-3β. The latter study indicated that some of the effects of GSK-3 may also lie in the preservation of beta cell mass, therefore insulin secretory abilities.

These effects of GSK-3β therefore argue for a loop of reactions that, once set in motion, will exacerbate insulin resistance. Thus, insulin resistance causes inhibition of the inhibitory phosphorylation of GSK-3β by PKB/Akt, allowing GSK-3β to phosphorylate IRS-1 on serine residues which will further inhibit its activation leading to attenuated GLUT4 translocation and glucose uptake. Enhanced activity of GSK-3β will also phosphorylate GS thereby inhibiting glycogen formation with resultant elevation of glucose levels (Figure 1).

**GSK-3 AND MYOCARDIAL CONTRACTILITY**

The diabetic heart is characterised by reduced contractility independent of vascular disease. One of the role players in the changes in contractile function in diabetes, is the calcium pump (SERCA2) of the sarcoplasmic reticulum. Total SERCA2 expression is decreased in hearts from diabetic mice, while myocardial contractility in diabetic mice can be improved by cardiac-specific over expression of SERCA2. It has been reported that GSK-3β protein is a critical regulator of calcium handling in the heart. Using genetically manipulated mice that over express myocardial GSK-3β, Michael and co-workers showed that GSK-3β acts directly on the SERCA2 promoter to downregulate its expression, leading to systolic and diastolic dysfunction. In addition, they reported impaired fractional shortening and reduced +dP/dt values measured by echocardiographic methods. Cytosolic calcium was significantly elevated in diastole. This was coupled to lower mRNA levels and lower expression of SERCA2a protein. In addition, the non-specific GSK-3 inhibitor LiCl completely reversed the inhibition of SERCA2 mRNA expression. To underscore these results, King et al. using the protein phosphatase-1/inhibitor-2 complex to regulate the phosphorylation state of GSK-3, demonstrated increased SERCA2 expression. GSK-3 protein, by regulating SERCA2 expression, if elevated, may therefore be intimately involved in the contractile abnormalities of the diabetic heart.

**GSK-3 AND DEVELOPMENT OF CARDIAC HYPERTROPHY**

Diabetes is associated with left ventricular hypertrophy and diastolic dysfunction which may eventually lead to clinical heart
failure. Pre-clinical abnormalities of cardiac structure and function have been reported in diabetes of short duration while echocardiographic studies pointed out the evidence of left ventricular remodeling and demonstrated the existence of a discreet diabetic cardiomyopathy.

Cardiac hypertrophy can be either physiological or pathological. Pathological hypertrophy is associated with activation of neurohumoral pathways (endothelin I, angiotensin II, catecholamines) eventually leading to release of calcium from intracellular stores (mainly the sarcoplasmic reticulum). This, in turn, will activate the calcium dependent phosphatase calcineurin, which regulates changes in gene expression associated with hypertrophy. One of the more prominent transcription factors regulated by calcineurin is nuclear factor of activated T-cells (NFAT). These authors showed that cardiac hypertrophy is induced by calcineurin, which dephosphorylates NFAT-3, enabling it to translocate to the nucleus. NFAT-3 interacts with the cardiac zinc finger transcription factor GATA4, resulting in activation of gene transcription. GSK-3β can counteract the activity of calcineurin by phosphorylating NFAT. Studies done with models of myocardial overexpression of GSK-3β have shown that GSK-3β is one of the most powerful anti-hypertrophic entities described thus far. Using LiCl, a non-specific inhibitor of GSK-3, Haq et al. demonstrated that inhibition of GSK-3 activity leads to features of cardiac hypertrophy. This observation is underscored by the finding that deletion of GSK-3β in mice resulted in hypertrophic cardiomyopathy. No live GSK-3β−/− pups were recovered in this study. The embryos had cardiac developmental defects caused by cardiomyocyte hyperproliferation associated with increased expression and nuclear translocation of 3 regulators of proliferation – GATA4, cyclin D1 and c-Myc. It is also interesting to note that many hypertrophic stimuli inhibit GSK-3β, thereby removing its negative constraints on the development of hypertrophy.

Besides the abovementioned inactivation of GSK-3β through phosphorylation on Ser9, it can also be inactivated by activation of the Wnt/frizzled pathway (Figure 2). This inactivation is apparently

![Image of Wnt signaling in the context of GSK-3 involvement.](image-url)

**FIGURE 2:** A schematic representation of Wnt signalling in the context of GSK-3 involvement.

Wnt ligand of the frizzled receptor Dvl: disheveled is an intermediate protein relaying the signal from the receptor to a target protein. GSK-3β: glycogen synthase kinase-3 beta, NFAT: nuclear factor of activated T-cells, GATA4: transcription factor.
because of sequestration of the kinase rather than phosphorylation thereof. Blankestein and co-workers(58) reviewed the role of the Wnt/frizzled pathway in the inhibition of GSK-3β, arguing for a therapeutic anti-hypertrophic strategy by inhibiting Wnt/frizzled signalling.

It is generally accepted that there is re-expression of the fetal gene programme in the hypertrophic heart,(63) therefore, according to Blankestein, Wnt/frizzled signalling may be reactivated in the hypertrophic heart. They could show upregulation of frizzled-2 expression in pressure overload hypertrophy in the rat(64) and demonstrated a causal relationship between this expression and the development of hypertrophy.(65)

But, as highlighted by the result of Kerkela et al.,(62) inhibition of GSK-3 remains a 2-faced Janus. The Wnt glycoproteins are essential for proper embryonic development due to their role in the regulation of cellular proliferation, differentiation, motility and polarity.(66-68) Already in 1995, Klein & Melton put forward a hypothesis that the effects of lithium on development of diverse organisms, was because of the inhibition of Wnt signalling by GSK-3β.(69) Wnts act as ligands for the frizzled family of receptors. It elicits a response via the stabilisation of β−catenin, resulting in accumulation of the latter in the cytosol and nucleus where it results in activation of transcription of Wnt target genes.(66) GSK-3β phosphorylates β−catenin, targeting it for ubiquitination and proteasomal degradation.(68) Mutations in β−catenin at the residues that can be phosphorylated by GSK-3β is associated with development of numerous types of cancer.(70)

GSK-3 AND MYOCARDIAL CELL DEATH OR CELL SURVIVAL

It is well-recognised that, clinically, diabetes results in increased mortality and enhanced left ventricular dysfunction following myocardial infarction after ischaemia/reperfusion.(71,72) Recently, Sena et al.(73) used cardiomyocyte-restricted insulin receptor knock out (CIRKO) mice to investigate possible mechanisms responsible for this. In a model of proximal coronary artery ligation to induce infarction, they followed changes in the heart over a 14 day period. Notably, they demonstrated enhanced left ventricular dysfunction coupled to accelerated mitochondrial dysfunction as well as attenuated expression of several proteins involved in glucose and fatty acid oxidation. In addition, SERCA2 expression was down regulated in the CIRKO mice.

In the context of ischaemic heart disease, the concept of ischaemic and pharmacological preconditioning has been intensively researched in the last decade. Ischaemic preconditioning refers to the phenomena whereby a series of short periods of myocardial ischaemia interspersed with reperfusion, has the ability to protect the heart against a successive longer period of ischaemia.(74) Because ischaemic preconditioning is still the most powerful endogenous protective mechanism that can be elicited in the heart, research centered on elucidating the mechanism thereof with the aim of duplicating it via pharmacological means. This was no easy matter as research demonstrated that different stimuli have the ability to mimic ischaemic preconditioning, leading to the search for a common denominator or end-effector. Since the balance between cell death and cell survival is central to ischaemic damage to the heart, research centered on signalling pathways that influence mitochondrial function and integrity. Some of these pathways implicated in preconditioning, are endogenous ligands released during ischaemia which would activate G-protein coupled receptors (adenosine, bradykinin, isoproterenol or opioids) that, in turn, activated a cascade of protein kinases (e.g. PKB, PKC, PKA, ERK, p38MAPK) that could influence mitochondrial integrity.(75-79)

Following on the observation of Tong et al.(80) that preconditioning resulted in phosphorylation and inactivation of GSK-3β via a PI-3Kinase mediated pathway, the work of Juhaszova et al.(81) took this one step further and demonstrated that the upstream effector that could integrate all the diverse signalling effects implicated in preconditioning, was GSK-3β. Using two of the new-generation GSK-3 inhibitors, Das and colleagues(82) demonstrated that pre-treatment of hearts before ischaemia, with these inhibitors, was as protective as preconditioning. They furthermore confirmed the mitochondria as end-target of this protection. According to their results, GSK inhibition decreased mitochondrial membrane potential with less calcium loading and less oxygen radical production, thereby conferring protection. In addition, mitochondrial
affinity for the anti-apoptotic protein Bcl-2 increased, with more Bcl-2 associated with mitochondria in the presence of GSK-3 inhibition, inferring a pro-apoptotic role for GSK-3. This conclusion is substantiated by the work of Hirotani et al.,\(^{(83)}\) using a transgenic mouse with cardiac-specific expression of a dominant negative form of GSK-3\(\beta\), who demonstrated accumulation of the anti-apoptotic molecule MCL-1 in these animals. This, as well as the anti-apoptotic effects of GSK-3 inhibition, could be abolished by knock down of MCL-1 with small inhibitory RNA molecules. All these effects could therefore contribute to the observed cardioprotective effect of the GSK inhibitors. It must be kept in mind that a pro-apoptotic role for GSK-3 would also argue for an inhibition of hypertrophy, as discussed previously.

As mentioned before, there are studies demonstrating upregulation of expression and higher activity (therefore more of the less phosphorylated form) of GSK-3 protein in skeletal muscle of type 2 diabetic patients and in adipose tissues of obese diabetic mice.\(^{(38,39)}\) Investigating the protection afforded by post-conditioning (where, in contrast to pre-conditioning, the short, repetitive episodes of ischaemia/reperfusion are implemented immediately at the onset of reperfusion to elicit protection)\(^{(84)}\) Wagner et al. (2008) could not elicit post-conditioning in a rat model with metabolic syndrome.\(^{(85)}\) This was accompanied by a failure of post-conditioning to result in phosphorylation and inhibition of GSK-3\(\beta\).

On the other hand, Nishino et al.,\(^{(86)}\) using a mouse line lacking the critical N-terminal serine within myocardial GSK-3\(\beta\) (Ser9) as well as Ser21 in GSK-3\(\beta\), still found protection via preconditioning in the isolated, perfused heart subjected to ischaemia, excluding a role for inhibition of GSK-3 in this phenomenon in the mouse heart as opposed to the findings of Juhaszova in the rat heart.\(^{(81)}\)

As mentioned, the kinase GSK-3, is involved in not only the regulation of glycogen synthesis and the development of insulin resistance and type 2 diabetes, but is implicated in an array of biological processes including cell death and survival and developmental patterning. It is also associated with the development of various neurodegenerative abnormalities e.g. Alzheimers disease, schizophrenia and possibly Huntington’s disease. It is furthermore implicated in the development of different forms of cancer, to name but a few.\(^{(87)}\) From this it can be deduced that the inhibition of GSK-3 has a very high therapeutic potential in a number of different human diseases.

As is indicated by the preceding discussion, in the field of cardiology, the list of “positives” of GSK-3 inhibition will probably outweigh that of the “negatives”. Inhibition of GSK-3 signalling will inhibit apoptosis, and therefore reduce the damage caused by myocardial ischaemia. It is protective in heart failure. It improves insulin sensitivity not only by enhancing hepatic glycogen synthesis and reducing hepatic glucose output, but also improves whole body glucose tolerance by the enhancement of glut 4 protein levels in the cell membranes of skeletal muscle cells. Inhibition of GSK-3 should improve contractile function in states of insulin resistance via upregulation of SERCA2 expression and it should also have anti-inflammatory effects via inhibition of activation of NF-\(\kappa\)B.\(^{(87)}\) The latter speculation is substantiated by one report showing that the GSK-3 inhibitor TDZD-8, when given to ex vivo perfused rat hearts at the start of reperfusion after ischaemia, presented with reduced NF-\(\kappa\)B activation coupled to smaller infarct size and reduced apoptosis.\(^{(88)}\) In addition, the work of Sato et al. (2004) demonstrated that a specific inhibitor of GSK-3 has the ability to maintain self-renewal and pluripotency in human and mouse embryonic stem cells.\(^{(89)}\) This was probably because of increased \(\beta\)-catenin activity from activation of the Wnt signalling pathway. Following on this, Tseng et al. (2006) published results to show that inhibition of GSK-3 was also able to raise \(\beta\)-catenin activity in neonatal rat cardiomyocytes.\(^{(90)}\) GSK-3 inhibition in these cells induced cell cycle entry at the S-phase and resulted in cell division. They tested whether this would hold true in adult rat cardiomyocytes and showed that GSK-3 inhibition also induced adult rat and mammalian cardiomyocytes to dedifferentiate and

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**GSK-3 PROTEIN AND THE HEART**

**A TUG-OF-WAR?**

At this stage, it would therefore seem as if the vote on inhibition of GSK-3 as a therapeutic intervention, especially with regards to the heart, is too close to call.
undergo mitosis. In the heart, with its lack of proliferative potential and formation of scar tissue after infarction, treatment able to induce proliferation and regeneration, will have enormous potential.

On the down side of inhibition of GSK-3 lies the fact that these inhibitors are mostly nonspecific, that their use may lead to development of cardiac hypertrophy because of a lift on the inhibition of calcineurin and furthermore, that GSK-3 inhibition may be teratogenic. In other tissue, inhibition of GSK-3 may induce different forms of cancer e.g. colorectal cancers have defects in elements of the Wnt pathway that lead to accumulation of β-catenin(91) that will be exacerbated by GSK-3 inhibition. However, available data do not show enhanced incidence of cancer in patients after long-term treatment with lithium. Furthermore, under some circumstances, GSK-3 inhibitors might be useful in treating specific cancers.(92)

Currently, more than 30 different GSK-3 inhibitors have been described.(93,94) As summarised by these reviews, they have a diversity of structure and size but most of them are small in order to reach GSK-3 where it is embedded in protein complexes, and most of them act by competing with ATP in the ATP-binding site of the kinase. Unfortunately, even the inhibitors described as more selective,(95) will also inhibit other protein kinases.(96) All of the available GSK-3 inhibitors will lead to elevated β-catenin levels.(97) Despite this, no deleterious effects have yet been reported in rodent studies. However, it seems that there is an absence of long-term studies with GSK-3 inhibitor treatment in rodent models of disease. Most of the negative effects have been reported using genetically modified animals. At the moment, the bottom line is still that, in the words of Sugden et al. (2008): “we just do not know whether to inhibit or activate GSK-3, or simply not to interfere!”(98)

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GSK-3 PROTEIN AND THE HEART

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