Commentary

Cell death signaling mechanisms in cardiac failure caused by magnesium deficiency: relationship to etiology of atherogenesis and sudden death ischemic heart disease

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Introduction

Globally, cardiovascular disease (CVD) is the number-one cause of deaths. Despite intensive research over the past 100 years, CV is on the rise in most countries. CVD is resulting in extremely high costs for treatment and hospitalization. Although many different pathways are now known to play important roles in death of cardiac cells via diverse molecular mechanisms, drugs are becoming costlier and costlier to the point that most countries can no longer afford the monies needed for prevention and treatment of CVD. Due to the aging population, globally, these costs will be prohibitive in most societies in the near future.

A major reason for inadequate prevention and treatment is, most likely, the diverse molecular mechanisms of programmed cardiac cell death.[1,2] At least four of these pathways, i.e., apoptosis, necroptosis, pyroptosis, and ferroptosis, appear to be pivotal in cardiac cell death found in myocardial infarctions (MI), ischemic heart disease (IHD), congestive heart failure (CHF), and sudden-death ischemic heart disease (SDIHD).[3–5] Another pathway which originally was thought to be a protective pathway, namely autophagy, has recently been found to contribute to cardiac cell death if this pathway is over activated.[6,7]

More than 50 years ago, two of us first provided experimental and clinical evidence that an overt, growing worldwide magnesium deficiency (MgD) may be an underlying major factor via its direct actions on coronary and cerebral arterial and arteriolar blood vessels.[8–18] Over the past 40 years, numerous investigators have found evidence to support our hypothesis.[19–25] Originally, we thought the major reason for death from MI, IHD, and SDIHD was a greater and greater coronary and cerebral arteriolar and arterial vasoconstriction, thus reducing nutrition and oxygenation of the coronary and cerebral micro vasculatures.[10,12–16,17,26] However, our research over the past 40 years, in conjunction with the work of other investigators, has made this original, simple idea much more complicated. Below, we review how the original idea of arteriolar and arterial vasoconstriction sets into motion (i.e., triggers) a massive series of molecular and cellular pathways leading to the diverse forms of programmed cell death and autophagy mentioned above.

Mg deficiency puts the squeeze on coronary and cerebral blood vessels

An early report from our laboratories suggested a progressive dietary and/or metabolic-induced loss of Mg during early developmental stages of life, particularly in coronary arteries could lead to coronary arterial vasospasm (CAV), ischemic heart disease (IHD), and sudden-death ischemic heart disease (SDIHD).[11,12] Autopsy-driven results from children who died due to accidental causes have been reported which show early signs of atherogenesis (i.e., fatty streaks on the walls of the aorta and carotid arteries) in young children as early as six years of age.[27]

Approximately 30 years ago, two of us using newly-developed selective ion-electrodes to measure blood, plasma and serum ionized Mg tested on some 35 cardiac patients presenting with Prinzmetal angina found, on average, a 35-40% decrease in the ionized Mg blood fraction with almost no change in the total Mg fraction;[28–30] cellular Mg^{2+}measured with ^{31}P-nuclear magnetic resonance spectroscopy fell in parallel to the fall in serum ionized Mg (Table 1). What is very important about these results is that ever since Dr. William Heberden's findings in 1768, it has been known that Prinzmetal angina is a result of coronary arterial vasospasm.[31] So, it is very difficult to not associate our clinical findings on these cardiac patients with anything but coronary arterial vasospasm. Moreover, we have reported that when coronary arterial vessels are placed in contact with low concentrations of Mg^{2+}, they go into intense vasospasm; the lower the Mg^{2+}concentration, the greater the vasospasm.[11,12] Moreover, in the presence of circulating neurohumoral agents (e.g., norepinephrine, angiotensin II, numerous vasoactive peptides), the coronary arterial spasms become larger (obviously being potentiated

in strength).[12,14] In addition, using ^{31}P-nuclear magnetic resonance spectroscopy (^{31}P-NMRS) and perfused rat hearts, we confirmed that just reducing the Mg^{2+}, in the perfusates, caused reduced cardiac levels of ATP, ADP, and Mg^{2+}, along with elevations in hydrogen ion concentration and inorganic phosphate combined with reductions in cardiac output, reduced ventricular contraction and reductions in coronary flows.[32,33] Thus, we strongly believe, with such experimental and clinical biochemical observations low blood, tissue and cellular data, "Mg deficiency puts the squeeze on coronary arteries". Similar observations have been made by our group on isolated cerebral arteries and intact cerebral and medullary blood vessels.[34–36]

Table 1 Serum and red blood cell ionized mg in 35 prinzmetal patients

	Serum, mM/l	RBC, uM
Controls	0.69 +/- 0.08	310+/-18
Patients	0.52+/- 0.04	275+/-10

All values are means +/- S.E.M. Patient values are significantly different from age-matched male controls(P<0.05).

Irregularities in daily diets are known to induce inflammatory lesions, which are believed to mediate the initiation process of atherogenesis.[37,38] Further, the same dietary disturbances have been reported to promote lipid deposition and accelerate the growth and transformation of the smooth muscle cells in the vascular walls. We have found that dietary deficiency of Mg in rabbits accelerates lipid deposition and plaques on the arterial walls.[39] However, if we maintained microcirculatory blood flow and nutritive peripheral arterial and arteriolar blood flows, despite Mg deficiency, the lipid deposition and plaque depositions were reduced.[40] So, we believe maintenance of microcirculatory blood flows (and thus, prevention/amelioration of vasospasms) is an important key to amelioration of the CAV and inflammations required for atherogenesis, IHD and SDIHD. Upon close examination of the coronary and aortic arterial smooth muscle cells of the rats and rabbits fed low Mg diets, and using transmission EM, we noticed some strange morphological alterations akin to apoptosis, necroptosis, ferroptosis, and pyroptosis in different cells.[41–44]

Regulated necroptosis, ferroptosis, and pyroptosis as well as apoptosis found in vascular smooth muscle cells of animals fed low Mg diets

Necroptosis

Recently, a new form of cell death has been found which combines both necrosis and apoptosis termed "necroptosis".[1–3] Necroptosis is tightly regulated by a group of characteristic signaling pathways and requires activation by two major enzyme receptor-interacting protein kinases, RIPK1 and RIPK3.[3] Different cytokines have been found to participate in the cell death response produced by these kinases.[1–3] Necroptosis has been proposed as a major component in the pathology of heart diseases, atherosclerosis, myocardial infarction, and cardiac remodeling.[1–3] Morphologically, necroptosis is characterized by increases in cell volume and swelling of cell organelles (i.e., mitochondria, Golgi, and ER, etc).[3] Using transmission EM, and Mg-deficient animals (dietary deficiency for 21 days), and excised ventricular myocytes, peripheral and cerebral arterial cells, we noted that some of these cells demonstrated rupture of plasma membranes, swelling of cell organelles (i.e., mitochondria, Golgi, and ER), characteristic signs of necroptosis.[41] ELISA assays clearly demonstrated activation of RIPK3, thus proving necroptosis was activated in the diverse cardiac and arterial myocytes of the Mg-deficient animals.[41] Interestingly, treatment of the Mg-deficient animals with an inhibitor of RIPK3, viz., necrostatin -1 reduced the activation of NF-kB; NF-kB inhibition is known to reduce necroptosis. Overall, our new data would suggest that activation of necroptosis probably plays an important role in inflammation and atherogenesis seen in experimentally-induced cardiac and vascular diseases.

Pyroptosis

Another recently-discovered form of regulated cell death, viz., pyroptosis, has been implicated in atherosclerosis.[4] Pyroptosis is dependent upon activation of several inflammatory proteases that are part of the family of cysteine-dependent aspartate-specific proteases (caspases).[4] Morphologically, pyroptosis is different from apoptosis and necroptosis. Characteristically, pyroptosis demonstrates rapid plasma membrane rupture, release of intracellular contents, activation of caspase-1 (ELISA assays) and release of proinflammatory mediators, e.g., IL-1beta,IL-18, but usually no loss of mitochondrial contents.[4] Examination of cardiac and arterial myocytes from the 21-day Mg-deficient animals revealed that some of these myocytes showed these characteristic signs of pyroptosis.[43] Examination of coronary arterial tissues from patients undergoing bypass surgery in our hospitals revealed falls in serum ionized Mg and intracellular free Mg contents of red blood cells (Table 2), elevated serum IL-1beta, IL-18 and caspase-1, thus suggesting that many of the arterial cells underwent pyroptosis.[43,44] Scanning EM of several of the arterial muscle cells of these bypass patients showed distinct, characteristic signs of ruptured plasma membranes.[45]

Table 2 Serum and red blood cell ionized mg levels in coronary by-pass patients

	Serum, mM/l	RBC, uM
Controls	0.68+/- 0.06	314+/- 0.12
Patients	0.54+/- 0.06	268+/- 0.08

All values are means +/- S.E.M. Patient values are significantly different from age-matched male patients (P<0.05).

Ferroptosis

Another form of regulated CD which has gained considerable attention is iron-dependent, i.e., ferroptosis.[1,2,5] Ferroptosis has been found in the pathogenesis of some cancers, tissue injuries, cell inflammations, and T-cell immunity.[1,2,5] Unlike apoptosis or necroptosis, there are no membrane ruptures or nuclear condensations. Ferroptosis is characterized by mitochondrial abnormalities such as smaller than normal mitochondria, dissolution of mitochondrial cristae with ruptures, and increased mitochondrial outer membrane density with ruptures.[5] Using cardiomyocytes and arterial smooth muscle cells, from living rats placed on Mg-deficient diets for 21 days, we found that the mitochondrial membranes were broken in many cells and showed loss of cristae, characteristic of ferroptosis.[42,44] Application of histochemical staining to detect membrane iron (i.e., acid ferrocyanide and ammonium sulfate), we noted areas of the Mg-deficient cells to contain deposits of non-heme iron, a clear sign of ferroptosis.[42,44] It is important to point-out here that a major property of iron-loaded cells is this causes accumulation and release of hydroxyl

free radicals through the Fenton reaction or the iron-catalyzed Haber-Weiss reaction in the presence of H_2O_2 or O_2.[5] We and others have shown that Mg-deficiency in cardiovascular tissues from Mg-deficient animals accumulate numerous free radicals.[46–51] In earlier studies from our laboratories we showed that short-term Mg deficiency results in an up-regulation of p53[52] which is known to initiate ferroptosis.[5]

Recent studies by our group have reported that two ferroptosis inhibitors, ferrostatin-1 and liproxstatin-1, prevent CD and mitochondrial dysfunction, and CD induced by low Mg, thus linking ferroptosis to the mitochondrial damage observed in the cardiovascular cells and tissues.[42,44]

Mg deficiency and autophagy in cell death

Accumulating evidence is mounting to implicate a cell death process, autophagy, in many diseases.[6,7] This process involves a catabolic pathway that involves a turnover of long-lived proteins and organelles via lysosomal degradation.[6,7] In cardiac tissues, this pathway plays an important pro-survival role during cellular stresses by extirpating protein aggregates and damaged organelles, thus preventing ischemic events.[6,7] But, when severely-triggered, reperfusion can lead to cardiac failure and CD.[6,7] The hallmark of autophagy is de novo formation of autophagosomes.[6,7]

Tumor necrosis factor-alpha (TNF-alpha), which we have reported to be up-regulated in Mg-deficient animals,[53] induces an up-regulation of beclin 1 (which we found up-regulated in Mg-deficient animals) [unpublished findings] activates coronary and aortic vascular smooth muscle autophagy.[44,54] Many atherosclerotic plaques demonstrate autophagy.[6,7] Damaged (and disintegrating) vascular smooth muscle cells in atherosclerotic plaques demonstrate several signs of autophagy in both humans and our Mg-deficient cholesterol-fed rabbits.[6,7,40,54] In our latter Mg-deficient rabbit atherosclerotic models, we have found plaques on coronary arteries and aortas that contain characteristic autophagic proteins, i.e., Atg 1 and Atg 13.[54] Autophagic cell death is known to be caused by activation of the Atg 1-Atg 13 pathway.[6,7] Although it is not yet known what is the precise pathway(s)-mechanisms for induction of autophagic CD, we believe that our morphologic and biochemical data, so far, point to Mg deficiency as an important trigger for autophagic CD, at least in experimental animals.

Conclusions and future thoughts

During the past decade, a considerable amount of experimental and clinical data has appeared to implicate several cell death pathways in the etiology of cardiovascular diseases such as atherogenesis, ischemic heart disease, hypertension, and sudden death ischemic heart disease. Epigenesis is a growing factor as a link between several of these cell death pathways and alterations in structural and morphogenetic alterations in cardiac and vascular muscle pathways and developmental disease processes. More than 50 years ago, two of us found that reductions in ionized Mg levels, both in-vivo and in-vitro, would cause coronary, cerebral, peripheral and uterine blood vessels to go into spasm and demonstrate increases in vascular reactivity to neuro-humoral constrictor agents and circulating vasopeptides. Dietary deficiency in rats resulted in methylation of DNA, histone modifications, increased tissue levels of certain micro-RNAs, and oxidation of DNA as well as down-regulation in telomerases in cardiac and vascular muscle cells. Use of specifically-designed, sensitive electrodes for measurement of blood ionized Mg levels, in both humans and experimental animals, we found evidence to demonstrate that pregnant women show reductions in blood levels of Mg^{2+} towards term with some women who developed transient hypertension and gestational diabetes. Drug-resistant hypertensive patients and Mg-deficient animals exhibit increase in high blood pressure with concomitant increased pulse pressure and show structural/morphogenetic alterations in both cardiac and vascular muscle cells with atherogenesis. Careful investigation of these muscle cells, using transmission electron microscopy, showed that many of these cells were undergoing different forms of cell death: apoptosis, necroptosis, pyroptosis, ferroptosis, and/or autophagy. We believe our new studies provide presumptive evidence that dietary Mg deficiency can lead to epigenetic alterations in cardiac and vascular muscle phenotypic alterations which could induce cardiovascular diseases such as atherosclerosis, drug-resistant hypertension, diabetes mellitus, ischemic heart disease, preeclampsia-eclampsia, and sudden-death ischemic heart disease. In view of our studies, all pregnant mothers and babies should be monitored for ionized Mg levels and treated accordingly.

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Conflicts of interest

The author declares there are no conflicts of interest.

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