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Restoration of skeletal muscle homeostasis by hydrogen sulfide during hyperhomocysteinemia-mediated oxidative/ER stress condition[1]

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Abstract

Elevated homocysteine (Hcy), i.e., hyperhomocysteinemia (HHcy), causes skeletal muscle myopathy. Among many cellular and metabolic alterations caused by HHcy, oxidative and endoplasmic reticulum (ER) stress are considered the major ones; however, the precise molecular mechanism(s) in this process is unclear. Nevertheless, there is no treatment option available to treat HHcy-mediated muscle injury. Hydrogen sulfide (H_2S) is increasingly recognized as a potent anti-oxidant, anti-apoptotic/necrotic/pyroptotic, and anti-inflammatory compound and also has been shown to improve angiogenesis during ischemic injury. Patients with CBS mutation produce less H_2S, making them vulnerable to Hcy-mediated cellular damage. Many studies have reported bidirectional regulation of ER stress in apoptosis through JNK activation and concomitant attenuation of cell proliferation and protein synthesis via PI3K/AKT axis. Whether H_2S mitigates these detrimental effects of HHcy on muscle remains unexplored. In this review, we discuss molecular mechanisms of HHcy-mediated oxidative/ER stress responses, apoptosis, angiogenesis, and atrophic changes in skeletal muscle and how H_2S can restore skeletal muscle homeostasis during HHcy condition. This review also highlights the molecular mechanisms on how H_2S could

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Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

be developed as a clinically relevant therapeutic option for chronic conditions that are aggravated by HHcy.

Résumé:

La hausse des taux d'homocystéine (Hcy) (c.-à-d. l'hyperhomocystéinémie (HHcy)) provoque une myopathie du muscle squelettique. Des nombreuses modifications cellulaires et métaboliques que provoque l'HHcy, on compte le stress oxydatif et du réticulum endoplasmique (RE) parmi les plus importantes, mais le(s) mode(s) d'action moléculaire(s) précis de ce processus demeurent à clarifier. Néanmoins, il n'existe aucune option thérapeutique qui soit accessible pour traiter les lésions musculaires médiées par l'HHcy. On considère de plus en plus le sulfure d'hydrogène (H2S) comme étant un puissant composé antioxydant, anti-apoptotique/nécrotique/pyroptotique et anti-inflammatoire, aussi décrit comme pouvant améliorer l'angiogenèse au cours des lésions ischémiques. Les patients porteurs de la mutation CBS produisent moins de H_2S, ce qui les rend vulnérables aux dommages cellulaires médiés par l'Hcy. De nombreuses études ont rapporté la régulation bidirectionnelle du stress du RE dans l'apoptose par l'intermédiaire de l'activation du gène JNK, ainsi que l'atténuation concomitante de la prolifération cellulaire et de la synthèse protéique passant par l'axe PI3K/AKT. On n'a pas étudié si l'H_2S permet de mitiger ces effets délétères de l'HHcy dans le muscle. Dans cet article de synthèse, nous discutons des modes d'action moléculaires des réactions de stress oxydatif et du RE, d'apoptose, d'angiogenèse et de changements atrophiques médiés par l'HHcy dans le muscle squelettique, ainsi que sur la manière dont l'H_2S peut permettre de rétablir l'homéostasie du muscle squelettique en situation d'HHcy. Cet article de synthèse met aussi en lumière les modes d'action moléculaires qui pourraient sous-tendre le développement de l'H_2S en tant qu'option thérapeutique pertinente sur le plan clinique en cas de maladies chroniques aggravées par l'HHcy. [Traduit par la Rédaction]

Keywords

angiogenesis; apoptosis; atrophy; endoplasmic reticulum stress; ischemia; myopathy; redox imbalance (ROS); inflammation; JNK; cystathionine-β synthase

Mots-clés

angiogenèse; apoptose; atrophie; stress du réticulum endoplasmique; ischémie; myopathie; déséquilibre redox (dérivés réactifs de l'oxygène); inflammation; JNK; cystathionine-β synthase

Introduction

Homocysteine (Hcy) has been studied extensively for over 30 years for its unique involvement in an increasing number of human diseases (Hankey and Eikelboom 1999; Narayanan et al. 2014; Stipanuk and Ueki 2011). It is generated via methionine cycle (MET-cycle), and its level is controlled by 2 processes: around 50% of Hcy goes to transsulfuration pathway to produce cysteine and the remaining 50% is re-methylated back to methionine (MET) via folate cycle (Cascella et al. 2015; Majumder et al. 2017; Veeranki and Tyagi 2013). Normal total plasma Hcy concentration in our body is 5–10 μmol/L, however in a diseased condition, i.e., in hyperhomocysteinemia (HHcy), total plasma Hcy levels increases

(>15 μmol/L) (Lehotský et al. 2016). HHcy can be classified as moderate (15–30 μmol/L), intermediate (30–100 μmol/L), and severe (>100 μmol/L) (Lehotský et al. 2016; Majumder et al. 2017). There are 4 main ways that people can develop HHcy: (*i*) methionine-rich protein diet, (*ii*) vitamin B_{12} and (or) folate deficiency, (*iii*) heterozygous/homozygous for cystathionine-β synthase ($CBS^{+/-}$/$CBS^{-/-}$), (*iv*) obstruction of renal clearance (Sen et al. 2010).

HHcy has been associated with severe skeletal muscle dysfunction, but the precise mechanism(s) is still unknown (Brustolin et al. 2010; Kanwar et al. 1976; Kolling et al. 2013; Majumder et al. 2017; Miller et al. 2000; Valentino et al. 2010; Veeranki et al. 2015; Voskoboeva et al. 2018; Zoccolella et al. 2008). Children born with very high levels of Hcy, i.e., HHcy due to deficiency of functional CBS gene ($CBS^{-/-}$), show severe muscle myopathy and die shortly after birth, but heterozygous for CBS mutation ($CBS^{+/-}$) children can survive (Voskoboeva et al. 2018). Previous reports showed that HHcy could cause disruption of Z-discs, fiber size, banding pattern, and excessive collagen deposition in muscle (Kalra et al. 1985; Kanwar et al. 1976; Veeranki et al. 2015), but which pathway triggers such pathological effects in the skeletal muscles are not fully understood. Skeletal muscle is the largest organ in our body and constitutes 50%–75% of all the body's proteins. Loss of skeletal muscle mass (muscle wasting) is mediated mainly by 3 processes, apoptosis, poor vasculature, and atrophy (protein degradation exceeds protein synthesis over time) (Dupont-Versteegden 2005; Powers et al. 2016). Therefore identification of the precise molecular mechanism that regulates these processes during HHcy condition is essential to devise proper treatment strategies.

Findings from our group and others groups determined that HHcy induces oxidative stress in the cardiac microvascular endothelial cells (Tyagi et al. 2005), skeletal tissue (Behera et al. 2018), vascular smooth muscle cells (Yan et al. 2006), skeletal muscle (Majumder et al. 2018a), liver tissue (Matté et al. 2009), and brain (George et al. 2018a). Oxidative stress has been implicated in many diseases associated with protein misfolding and reduction of efficiency of protein folding pathways (Merad-Boudia et al. 1998; Nakamura and Lipton 2007; Plaisance et al. 2016; Uehara et al. 2006; Werstuck et al. 2001; Zhang and Kaufman 2008), but the cellular pathways that are involved in these stress-related conditions have not been elucidated. During severe ER stress conditions, activated IRE1 recruits TNF receptor-associated factor 2 (TRAF2) and apoptosis signal-regulating kinase 1 (ASK–1), which further activate c-Jun N-terminal kinase (JNK) (Deng et al. 2001; Lei and Davis 2003; Sano and Reed 2013). However whether HHcy can compromise cell survival via activation JNK is not known. AKT is a major survival factor promoting cell proliferation, and its dys-regulation has been detected in muscle wasting (Bodine et al. 2001; Manning and Cantley 2007; Romanino et al. 2011). A previous study showed that activated JNK could induce inhibitory phosphorylation of IRS-1 at Ser307 (Aguirre et al. 2000). Since Ser^{307} phosphorylation promotes general inhibition of IRS-1 signaling, it suggests that JNK-activation may impair PI3/AKT axis (Aguirre et al. 2002).

JNK controls cell response to the harmful extracellular stimulus (Ogata et al. 2006; Xie et al. 2011). JNK/c-Jun pathway regulates pro-apoptotic genes expression (TNF-a, Fas-L, and Bak) (Dhanasekaran and Reddy 2008). Whether HHcy-mediated oxidative/ER stress can

induce apoptosis has not been studied in muscle yet. HHcy is implicated in vascular toxicity, causing endothelial cell damage and dysfunction (McCully 2007). Previously, our lab showed that HHcy antagonizes the angiogenic signals via reduced expression of HIF1-[H9251], VEGF, and eNOS in skeletal muscle (Chen et al. 2014; Veeranki et al. 2014, 2015). Although several markers of ER stress including CHOP have been shown to increase in a model of skeletal muscle atrophy, whether HHcy-mediated ER stress can play a role in muscle atrophy is still unclear (Yu et al. 2011). Additionally, several models of atrophy showed that inhibition of PI3K/Akt signaling induces nuclear import of forkhead box protein O (FOXO) regulating Atrogin-1, MurF-1 expression (Clavel et al. 2010; Shimizu et al. 2017). Some studies have already demonstrated that HHcy inhibits Akt activation in endothelial cells, but whether FOXO could remain un-phosphorylated during HHcy condition and allow it to translocate to the nucleus and upregulate MuRF-1 and Atrogin-1 in muscle cells is not studied yet (Manning and Cantley 2007).

H_2S is increasingly being recognized as an important signaling molecule in the cardiovascular and nervous systems via its ability to neutralize a variety of ROS (Kimura et al. 2010; Mironov et al. 2017; Yang et al. 2015), as well as via increased cellular glutathione levels through activation/expression of γ-glutamylcysteine synthetase, and also via reduced disulfide bonds in proteins (Calvert et al. 2010; Elsey et al. 2010; Fiorucci et al. 2006; Gadalla and Snyder 2010; Kimura 2010; Predmore and Lefer 2010; Szabó 2007; Wang 2003). Cystathionine γ-lyase (CSE) and CBS are main H_2S producing enzymes, which produce H_2S from Hcy in transsulfuration reactions (Kabil et al. 2011). Patients with CBS gene mutation lead to dysfunction in endogenous H_2S biosynthesis (Beard and Bearden 2011), suggesting that these patients are more prone to oxidative stress-mediated damages due to malfunction in Hcy metabolism and inefficient H_2S biosynthesis (Szabó 2007). CBS is a crucial enzyme in the transsulfuration pathway, and heterozygous CBS deficient (CBS $^{+/-}$) has proved a useful model for HHcy, which shows mild to a severe endogenous elevation of Hcy in several tissues in mice (Familtseva et al. 2014; Nandi and Mishra 2017; Narayanan et al. 2013; Tyagi et al. 2011, 2012; Watanabe et al. 1995; Winchester et al. 2018; Yang et al. 2018). Studies have been performed using the CBS model to show that these mice have less H_2S levels in their blood and showed oxidative stress-mediated damages (Ishihara et al. 2008; John et al. 2017).

In this review we discuss HHcy-mediated oxidative/ER stress responses, apoptosis, angiogenesis, atrophy in skeletal muscle, and potential mechanisms and whether H_2S has any beneficial effects on mitigating these conditions. We also highlight the molecular mechanisms of how H_2S could be developed as a clinically relevant therapeutic option for chronic conditions like HHcy that are implicated in a host of cellular stress conditions, including the apparent defect in skeletal muscle functions.

Metabolism of homocysteine and hyperhomocysteinemia

Homocysteine (Hcy) is a sulfur-containing nonproteinogenic amino acid that is produced during the metabolism of methionine (MET)viathe1-carbonmetabolism(intheMET-cycle) (Stipanuk and Ueki 2011). Post absorption, MET is converted into *S*-adenosylmethionine (SAM) by ATP and catalyzed by methionine adenosyltransferase (MAT), leaving it with a

transferrable methyl group. This methyl group is donated for cellular methylation requirements and becomes *S*-adenosyl-homocysteine (SAH). SAH hydrolase is an enzyme that reversibly hydrolyzes SAH, in turn, that produces Hcy (Lan et al. 2018). Hcy is present in blood in 3 different forms: around 1% as free thiol, 70%–80% as a disulfide bound to a swath of plasma proteins, and the remaining 20%–30% as a homodimer/heterodimer along with other thiols (Hankey and Eikelboom 1999). After generation of Hcy by MET-cycle, around 50% goes to the transsulfuration pathway for production of glutathione (an antioxidant), and the rest is re-methylated back to MET via the folate cycle (Fig. 1) (Cascella et al. 2015; Stipanuk and Ueki 2011; Veeranki and Tyagi 2013).

In healthy individuals, the generation and elimination of Hcy stay in the balance; however, once this homeostasis is disturbed, it leads to HHcy (Tiahou et al. 2009). HHcy can be developed via consumption of an excess amount of the methionine-rich diet, vitamin B_{12}/folate deficiency, the occurrence of heterozygous/homozygous CBS gene mutation, and the obstruction of renal clearance (Sen et al. 2010). Besides these, there can be genetic mutations in any Hcy metabolism pathway-regulated genes; the most common one are the variants such as 677C > T and 1298A > C in the *MTHFR* gene that can also lead to HHcy (Brustolin et al. 2010; Iqbal et al. 2009; Kharb et al. 2016; Verhoef et al. 2005). Other determinants such as age, sex, physical activity, alcohol intake, certain medications, and even different disease conditions can offset the rate of methionine cycle, thereby influencing the corresponding increase in the total Hcy levels in the blood (Diakoumopoulou et al. 2005). During HHcy conditions, the methylation cycle is generally dysregulated (Maddocks et al. 2016). This leads to disruption of multiple signaling pathways, because it is the only pathway that gives rise to the production of essential methyl groups needed for the subsequent biosynthesis of cellular compounds such as creatine, epinephrine, carnitine, phospholipids, proteins, and polyamines and also the epigenetically governed cellular processes like methylation of DNA, RNA, and histones that are dependent upon Hcy metabolism (Laha et al. 2018; Majumder et al. 2017). Although HHcy conditions can cause multi-organ pathologies via oxidative and ER stress systems (Ishii et al. 2010; Majumder et al. 2017; Veeranki and Tyagi 2015a; Veeranki et al. 2015; Winchester et al. 2014), the precise mechanisms of multi-organ pathology due to HHcy remain elusive.

Metabolism of Hcy depends on several factors, the level of methionine in the diet, SAM level, and the type of cells in which methionine metabolism takes place (Laster et al. 1965). High SAM levels can act as an allosteric inhibitor for methylenetetrahydrofolate reductase (MTHFR). MTHFR catalyzes the conversion of 5,10-MTHF to 5-MTHF, which is a co-substrate of Hcy in the remethylation reaction (Finkelstein and Martin 1984). Therefore, high SAM levels prevent Hcy from entering the remethylation pathway. High SAM levels also act as an allosteric activator for CBS of the transsulfuration pathway (Finkelstein et al. 1975; Stabler et al. 2002). Altogether it appears that the presence of high levels of SAM favors Hcy entering the transsulfuration pathway. However, only a few organs in our body such as the liver, kidney, pancreas, brain, adipose tissue, and small intestine synthesize CBS (Finkelstein 1990; Mudd et al. 1965). Vascular muscle tissues do not express CBS, so high SAM levels lead to transient accumulation of Hcy (Veeranki and Tyagi 2015a). Hcy metabolism also depends on dietary MET load, which can affect the rate of SAM synthesis, which in turn will determine the pathway Hcy takes up at the remethylation and

transsulfuration junctions (Selhub 1999; Selhub et al. 1999; Stolzenberg-Solomon et al. 1999). When diet contains a basal methionine level, Hcy cycles through remethylation pathway about 1.5–2.0 times before being directed towards the transsulfuration pathway, but when dietary methionine content is half the basal level, the cycling of Hcy via the remethylation pathway increases 2-fold. Conversely, when the dietary MET level is high, Hcy cycling through the remethylation is reduced by 1.5-fold (Eloranta et al. 1990). High levels of intracellular Hcy is exported out into the circulation (Gupta et al. 1998), however the exact mechanism of Hcy export is not identified yet. Although HHcy is found in ~5% of the general population and is associated with increased risk of cardiovascular disease, osteoporosis, skeletal muscle myopathy, and other metabolic complications (Ishii et al. 2010; Majumder et al. 2017; Veeranki and Tyagi 2015a; Veeranki et al. 2015; Winchester et al. 2014), precise molecular pathways that lead to multi-organ dysfunction remain mostly unexplored.

Structural aspects of skeletal muscle functioning

Skeletal muscle is the largest organ in our body (roughly 40% to 50% of the body's total mass in average human), which constitutes 50%–75% of the body's proteins (Frontera and Ochala 2015; Pedersen 2013; Smith et al. 2013). Muscle contains very long multi-nucleated cells (myocytes) that are bundled up and surrounded by connective tissues. Skeletal muscle has 2 primary functions: (*i*) production of contractile force that provides breathing, locomotion, and postural support and (*ii*) thermogenesis during periods of cold stress. Force production, depending on the primary function of the muscle, may consist of either fast twitch (type I) or slow twitch (type II) fibers (Talbot and Maves 2016). Type I fibers are used for repetitive, low-intensity functions such as postural support. These fibers provide less force generation but are fatigue resistant and have a higher reliance on oxidative metabolism and therefore have more density of mitochondria and oxidative enzymes (Talbot and Maves 2016). Type II fibers are divided into two fiber subsets: type IIx and type IIa (Talbot and Maves 2016). Type IIx fibers are very glycolytic and produce high contractile force but are susceptible to fatigue due to a lower mitochondrial density (Talbot and Maves 2016). Type IIa fibers are an intermedi ate fiber type (Talbot and Maves 2016). They provide a moderate contractile force and are more fatigue resistant than Type IIx fibers (Talbot and Maves 2016).

Myocytes, unlike most other cell types, contain multiple nuclei and are striated because of contractile segments called sarcomeres (Talbot and Maves 2016). Within each myocyte are structures called myofibrils, which contain the contractile proteins of the muscle, called actin and myosin (Talbot and Maves 2016). On the actin filamentthere are 2 additional proteins known as troponin and tropomyosin, which are used for contractile regulation (Talbot and Maves 2016). The striated regions, called sarcomeres, are within the myofibrils and consist of areas of myosin/actin overlap, as well as an area where myosin does not overlap with actin called the H zone (Talbot and Maves 2016). Sarcomeres are divided by a wall of structural proteins, which makes up a region of the sarcomere called the Z line (Talbot and Maves 2016). Based on "sliding filament theory," during contraction, the required energy comes from the de-phosphorylation of adenosine triphosphate (ATP), wherein myosin heads "cock" form cross-bridges with actin and then pivot inward towards the H zone (Allen and

Westerblad 2007), which ultimately decrease the sarcomere length from Z line to Z line (Mi-Mi and Pruyne 2015).

Surrounding each myofibril is a network of channels that serve as a storage site for calcium, which is crucial for regulation of muscle contraction (Gehlert et al. 2015). This structure is called the sarcoplasmic reticulum (Gehlert et al. 2015). The transverse tubules are another set of channels that pass through the muscle fiber (Gehlert et al. 2015). Each myocyte is connected to a branch of a motor neuron through a neuromuscular junction serving as the site of electrochemical transmission (Deschenes 2011). Collectively, all the myocytes that are innervated by a single motor neuron are termed a motor unit (Deschenes 2011). Upon generation of an action potential high enough to cause contraction, the neural impulse is transmitted to the myocyte through the neuromuscular junction and is propagated down the transverse tubules to the sarcoplasmic reticulum, causing Ca^{++} to be released (Kuo and Ehrlich 2015). Ca^{++} binds to the troponin molecule, which creates a shift in tropomyosin position (Kuo and Ehrlich 2015). This allows for exposure of the actin active sites and myosin-actin cross bridge formation, resulting in contraction (Kuo and Ehrlich 2015).

In adults, repair of degenerated muscles relies on a small population of skeletal muscle stem cells known as satellite cells (Mauro 1961). Satellite cells, a popular of quiescent muscle precursor cells that reside beneath the basal lamina, provide the predominant source of additional myonuclei for muscle growth (Mitchell and Pavlath 2001; Rosenblatt et al. 1994). Once activated, satellite cells give rise to myoblasts that proliferate, differentiate, and fuse to form new muscle fibers or to repair damaged muscle fibers (Chargé and Rudnicki 2004; Hawke and Garry 2001). The availability of a pool of myoblasts for myogenesis is essential for the development of muscle (Miyake et al. 2011). A decreased number of muscle fibers could be due to the reduced myoblast proliferation or cytotoxicity. Moreover in most cases, the apoptosis of myoblasts serves as a physiological behavior to remove excess myoblasts during myogenesis or muscle regeneration, while inappropriate apoptosis will pathologically lead to degeneration that is associated with various muscular dystrophies and atrophies (Tews and Goebel 1997; Tidball et al. 1995). Therefore, identification of toxicants that regulate myoblast cytotoxicity is essential in understanding skeletal muscle growth, disease, and regeneration.

Hyperhomocysteinemia-mediated skeletal muscle pathophysiology

HHcy is a known risk factor for vascular diseases (Ganguly and Alam 2015), however several studies also reported that HHcy leads to skeletal muscle weakness and functional impairment (Kalra et al. 1985; Kanwar et al. 1976; Veeranki et al. 2014, 2015; Veeranki and Tyagi 2013, 2015a; Winchester et al. 2018). Children born with severe homocystinuria due to CBS deficiency exhibit reduced body weight, skeletal muscle myopathy, and die in teenage years (Majumder et al. 2017). A clinical manifestation of HHcy displays decreased body mass and loss of skeletal muscle mass, which ultimately lead to myopathy (Kalra et al. 1985; Kanwar et al. 1976; Veeranki et al. 2014; 2015; Veeranki and Tyagi 2013, 2015a; Winchester et al. 2018). Results from our laboratory previously showed that HHcy mice ($CBS^{+/-}$gene) have lower body mass and less fatigue resistance and produce less contractile force, have lower muscle ATP levels, low dystrophin, and mitochondrial transcription factor

A (mtTFA) compared to control mice (C57BL/6J) (Veeranki and Tyagi 2015a). In a study, Kanwar et al. (1976) found that HHcy can cause focal fragmentation, disruption, and smearing of the Z-discs and disorganization of the myofilaments in the skeletal muscles (Kanwar et al. 1976). They showed that HHcy could reduce cellular metabolic activity and induce energy imbalance in gastrocnemius rat skeletal muscle by decreasing the activity of pyruvate kinase, creatine kinase, and noticed increased activity of succinate dehydrogenase (Kolling et al. 2013). Similarly, Veeranki and Tyagi showed that Hcy affects fatty acid oxidation affecting energy metabolism in skeletal muscle via PGC-1αspecific protein nitrotyrosylation and a concomitant reduction in association with PPAR-γ (Veeranki and Tyagi 2015a). On the other hand, many neurological disorders such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis affect muscle degeneration, and these medical conditions are connected to HHcy (Valentino et al. 2010). HHcy also significantly lowers physical functions by deteriorating skeletal muscle functions in older people compared to age-matched healthy subjects (Kado et al. 2002), which suggests that aging is one of the potential risk factors to be considered in this process (Westerblad et al. 2010).

Disorders such as muscular dystrophy, sarcopenia, and immobilization have been extensively researched, however there is not enough data available that consider the effects of HHcy on these conditions. Swart et al. demonstrated that in elderly individuals (~75.6 years of age), plasma Hcy levels had a strong inverse correlation with grip strength and functional capabilities (Swart et al. 2013). High Hcy levels resulted in poor grip strength in men and lowered functional ability including walking, climbing stairs, and rising from a chair (Swart et al. 2013). In heterozygous CBS-deficient mice ($CBS^{+/-}$), a model of mild to moderate HHcy, it was observed that 28 days post induction of hindlimb ischemia $CBS^{+/-}$ mice displayed blunted hind limb perfusion and lower collateral blood vessel development when compared to WT mice (Majumder et al. 2018b; Singh et al. 2018; Veeranki et al. 2014). This study also found that $CBS^{+/-}$ mice had lower vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF1-α), and peroxisome proliferator-activated receptor coactivator 1-α (PGC1-α) after 28 days of ischemic recovery, when compared to control (Veeranki et al. 2014). We also showed that excessive circulating Hcy could cause oxidative and endoplasmic reticulum (ER) stress in skeletal muscle that may induce skeletal muscle atrophy (Majumder et al. 2018a).

Hyperhomocysteinemia mediates oxidative/ER stress responses in skeletal muscle

During metabolic processes, a certain amount of pro-oxidative ROS are formed. Intracellular environment is predominantly a reducing environment, first due to the presence of enzymes like glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase, which breakdown ROS into water and oxygen, and second due to a series of built-in redox defense systems that inactivate ROS, which include reduced glutathione (GSH), NADH, thioredoxin, and free radical scavengers such as vitamins C and E (Gasparetto et al. 2005; Yamamoto et al. 2003; Zima et al. 2004). Oxidative stress occurs when there is an imbalance between free radical production and antioxidant capacity in a given cell, as shown in Fig. 2. Previous studies revealed that Hcy contains -SH group-like thiols (RSH), which can undergo

oxidation to form a disulfide (RSSR) even at physiological pH in the presence of metal catalysts and molecular oxygen [O °$_2$] (Kalra et al. 1985). Further, Hcy can also produce hydrogen peroxide (H_2O_2, a pro-oxidant molecule) during the metal-catalyzed oxidation step and peroxynitrite ($ONOO^-$, a potent oxidant) in the presence of nitric oxide (NO) and superoxide anion ($\cdot O^-_2$) (Lubos et al. 2008). Findings from our laboratory and others demonstrated HHcy effects on oxidative stress in cardiac microvascular endothelial cells (Tyagi et al. 2005), vascular smooth muscle cells (Yan et al. 2006), and the liver tissue (Matté et al. 2009). Although these phenomena have been studied in multiple tissue types, whether HHcy exerts its detrimental effects on muscle through similar mechanisms is not yet elucidated.

Several studies have reported that HHcy creates oxidative stress that promotes apoptosis, inflammation, insulin resistance, and dysregulation of lipid metabolism in different organs (Hayden and Tyagi 2004; Homme et al. 2018; Lentz 2005; Majumder et al. 2017; Veeranki and Tyagi 2013). Increased ROS level due to HHcy were also found to be involved in lipid peroxidation, protein denaturation, and DNA damage, which ultimately damage cellular components, modulates gene expression, alters cell signaling pathways, and produce energy imbalance. Besides, Hcy can also form Hcy-thiolactone and acetylates free amino groups in proteins, which further intensify the exaggerated oxidative stress condition (Hayden and Tyagi 2004). DiBello et al. showed that proteins (PRDX1, PRDX2, and HSP90AA), which are produced as a response to oxidative stress, were significantly upregulated in the liver during HHcy (Mishra et al. 2010). One study showed that production of ROS was ameliorated by PPAR-γ activation in ECs (Hayden and Tyagi 2004), as previously reported by our laboratory, indicating that PPARγ was reduced in HHcy condition (Laha et al. 2018; Mishra et al. 2010), suggesting that HHcy can induce ROS levels via PPAR-γ mediated pathway. Furthermore, Hcy also uses the cysteine transporter (ASC transporter: alanine–serine–cysteine transporter) to enter into the endothelial cells (Büdy et al. 2006), so maybe Hcy also uses the same transporter while entering muscle cells. Hence during HHcy, Hcy competitively inhibits cysteine entrance inside the cells (Veeranki et al. 2017). As cysteine is indis pensable for the synthesis of glutathione (GSH), lack of cysteine inside cells in HHcy conditions can compromise the cellular anti-oxidant potential in skeletal muscle (Brustolin et al. 2010). Since HHcy leads to oxidative stress, which interferes with different cellular signaling pathways in various organs other than muscle, it suggests that HHcy may have similar pathological effect in muscle tissue.

Oxidative stress has been implicated in many diseases associated with protein misfolding. Indeed, in a study by Malhotra et al. showed that antioxidants reduce endoplasmic reticulum stress and improve protein secretion in Chinese hamster ovary (CHO)-H9 cells (Malhotra et al. 2008). Similarly, a study using differential display analysis in HUVECs found that GRP78 (78-kDa glucose-regulated protein-an ER stress marker) was upregulated in Hcy treated cells compared to controls (Kokame et al. 1996). GRP78, also known as immunoglobulin heavy-chain binding protein (BiP), is a chaperone protein belonging to the HSP70 family and predominantly resides in the lumen of the ER (Panayi and Corrigall 2014). HHcy can induce ER stress (Werstuck et al. 2001), but which pathways are affected by this condition is poorly understood. It is known that after translation, protein folding occurs inside ER, but that during stress conditions, misfolded proteins accumulate inside the

ER lumen and induce unfolded protein response (UPR) (Oslowski and Urano 2011). UPR increases transcription of chaperones genes to facilitate protein folding, helps to attenuate translation process, and finally it degrades misfolded proteins accumulated in ER (Kaufman 2002; Mori 2000; Ron 2002). In the mammalian system, UPR is mediated through inositol-requiring protein 1 (IRE1), PRKR-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (Rutkowski and Kaufman 2004). IRE1 promotes X-box binding protein 1 (XBP1) mRNA splicing, which finally activates ER chaperones (e.g., BiP/GRP78 (BiP), EDEM and ERdj4). PERK phosphorylates eukaryotic translation initiation factor 2α (eIF2α) and that stops translation. ATF6 regulates the expression of chaperones genes and ER-associated degradation (ERAD) genes (Adham et al. 2005; Kondo et al. 2005; Zhang et al. 2006). Several studies showed that HHcy could worsen ER stress by reducing the efficiency of protein folding pathways and increasing the production of misfolded proteins (Plaisance et al. 2016). ER stress might play a key role in mediating adverse effects during HHcy in muscle (Cao 2015).

In the mammalian system, there are 2 isoforms of IRE1: IRE1γ and IRE1β. Both of these proteins are transmembrane proteins and contain a Ser/Thr kinase domain and an endoribonuclease domain (Hassler et al. 2012; Shamu and Walter 1996). In a stress-free environment, IRE1 remains in an inactivated form bound with GRP78, however in stress conditions, its dissociates from GRP78 and becomes auto-phosphorylated (Gardner et al. 2013). Then the endonuclease activity of activated IRE1 cleaves a 26 bp intron from ubiquitously expressed XBP1u mRNA. Removal of this intron causes a frameshift in the XBP1 coding sequence resulting in the translation of XBP-1s isoform (Oslowski and Urano 2011). XBP-1s encodes a specific basic leucine zipper-containing transcription factor, known as X-Box Binding Protein-1 (XBP1), to promote cell survival (Gardner et al. 2013; Hollien et al. 2009; Maurel et al. 2014). However, during severe ER stress conditions, IRE1 recruits TNF receptor-associated factor 2 (TRAF2) and apoptosis signal-regulating kinase 1 (ASK-1), then activates c-Jun N-terminal kinase (JNK) and induces apoptosis (Deng et al. 2001; Lei and Davis 2003; Sano and Reed 2013). Although many studies also reported bidirectional regulation of ER stress in apoptosis through JNK activation, and concomitant attenuation of cell proliferation and protein synthesis via PI3K/AKT axis, whether HHcy exerts its detrimental effect in muscle through a similar mechanism(s) remains unexplored (Fig. 3).

Hyperhomocysteinemia mediated cell death pathways

Apoptosis is programmed cell death and is required for normal development; however, very higher amounts of apoptotic cell death due to environmental stress can be detrimental (Renehan et al. 2001). Excessive apoptosis is observed in many well-known diseases such as ischemic heart disease, AIDS, Alzheimer's, and Parkinson's, etc. (Kerr et al. 1994; Lockshin and Zakeri 2007; Thompson 1995). Apoptosis occurs in 2 phases; namely the death decision phase and execution phase. Death decision phase is controlled by 2 proteins, pro-apoptotic proteins (Bax and Bak) and anti-apoptotic proteins (BCL-XL and BCL-2). The execution phase is regulated by caspases (proteolytic enzymes), responsible for the execution of apoptosis after the death decision is confirmed (Elmore 2007). Unlike necrosis, apoptosis occurs at the single cell level (Elmore 2007). Studies showed that an increase in oxidative

stress could lead to caspase activation (Green and Reed 1998; Morel and Barouki 1999; Richter 1993; Zamzami et al. 1996). This oxidative stress-mediated apoptosis was further supported by other studies demonstrating that antioxidants such as N-acetylcysteine (NAC) treatment could block apoptosis in a similar way that caspase inhibitors do (Kannan and Jain 2000; Okamoto et al. 2016). Several mechanisms have been proposed pointing to the fact that oxidative stress generated by HHcy can lead to multi-organ pathologies. This argues that no stimulus other than redox imbalance during HHcy is capable of inducing apoptotic cell death. Even though findings suggested that HHcy could be causal in a wide range of disorders, including skeletal muscle myopathy, the action mechanism of Hcy in different types of cell deaths (apoptotic, necrotic, and pyroptotic) is yet to be fully explained.

A study showed that Hcy reduced DNA synthesis and induced apoptotic EC death (Bessede et al. 2001). Similarly, another finding revealed that Hcy causes apoptosis in HUVECs via activation of UPR, which was mediated through IRE1 activation (Zhang et al. 2001). A similar finding suggested that Hcy can induce trophoblast cell death during embryonic development (Di Simone et al. 2003). Hcy was also found to induce apoptosis in bone marrow mesenchymal stem cells (BMSCs) via oxidative stress mechanism, and it was mediated through JNK activation (Cai et al. 2013). Folate deficiency could induce apoptotic cell death in RINm5F pancreatic Islet β-cells, through oxidative-nitrosative stress (Hsu et al. 2013); as folate deficiency is one of the causes of HHcy, this suggests that during HHcy apoptosis remains a favored outcome in various organs. Mesangial cell apoptosis via inducing ROS and p38-MAPK activation had also been reported (Shastry et al. 2007). Hcy induces apoptosis via upregulation of DNA damage response in neurons, and this process is mediated through PARP activation and p53 induction (Kruman et al. 2000). Our lab, using genetically engineered heterozygous CBS deficiency mouse model ($CBS^{+/-}$), reported that HHcy causes cell death via upregulation of mitochondria-mediated cell death pathway (BAX, caspase-9, and caspase-3) (Familtseva et al. 2016). Hydrogen sulfide (H_2S) is known to involved in modulation of many physiological pathways. A study found that H_2S-releasing sildenafil (ACS6) treatment could protect HHcy-mediated apoptosis in PC12 cells (Tang et al. 2011).

Accumulating data indicate that ER stress is a potent trigger of autophagy (Bernales et al. 2006; Criollo et al. 2007; Fujita et al. 2007; Høyer-Hansen and Jäättelä 2007; Kamimoto et al. 2006; Kouroku et al. 2007; Yorimitsu et al. 2006). Autophagy is a process that degrades misfolded proteins and plays a role in cell survival (Ding et al. 2007; Hart et al. 2012; Høyer-Hansen et al. 2007). This process is initiated by class III PI3-kinase complex and ATG proteins, where a microtubule-associated protein light chain 3 II (LC3-II) is formed due to conjugation of phosphatidylethanolamine (PC) and LC3-I (Fujita et al. 2007). A double membrane vacuole is formed called autophagosome, which finally fuses with the lysosomal membrane to deliver the contents into the autolysosome to degrade and recycle macromolecules (Nixon 2006). In addition to UPR, ER stress also leads to release of Ca^{2+} from the ER and possibly may have some role in autophagy signaling (Høyer-Hansen et al. 2007; Høyer-Hansen and Jäättelä 2007). Although autophagy occurs at basal levels in most tissues and in addition to turnover of cellular components, it plays a role in development, differentiation, and tissue remodeling. It is unclear how high homocysteine can modulate autophagy process in different tissues (Momoi 2006).

Hyperhomocysteinemia mediated dysregulation of angiogenesis

Although many studies have been conducted to identify the mechanism(s) of skeletal muscle myopathy, fewer studies have demonstrated the potential risk factors that inhibit skeletal muscle adaptability in response to chronic ischemia. Poor angiogenic capacity is known to play a vital role in skeletal muscle adaptability (Olfert et al. 2016; Yan et al. 2011). Lack of revascularization is already reported in elderly frailty and in many metabolic disorders, where metabolic factors and associated signaling pathways are found to be involved in a variety of skeletal muscle dysfunction (Evans et al. 2010). In addition, HHcy is well studied in the cardiovascular system, where it has been shown to increase HHcy-mediated increased oxidative stress causing dysfunction of endothelial cells (ECs), swelling and vacuolization of ECs, fibrin deposition, and even clot formation in vessels (Loscalzo 2009; Refsum et al. 1998).

Angiogenesis is a physiological process, where new blood vessels form from pre-existing ones. It is vital for growth and development, which depend on supply of nutrients, oxygen, and waste disposal (Logsdon et al. 2014). Previous studies demonstrated that HHcy impairs angiogenesis in multiple tissues (Duan et al. 2000; Jacovina et al. 2009; Nagai et al. 2001; Oosterbaan et al. 2012; Zhang et al. 2012). During angiogenesis, the main angiogenic signal is that vascular endothelial growth factor (VEGF) binds to VEGF receptor on EC surface. This promotes EC growth and migration towards the source of VEGF. An early study showed that Hcy treatment on chicken embryos (embryonic day 3.5) causes inhibition of early extraembryonic vascular development, altered composition of the vascular beds, and reduction of VEGF-A and VEGFR-2 expression (Oosterbaan et al. 2012). Similarly, when HUVEC cells were treated with Hcy, it reduced the cell numbers, viability, and induced a G1/S arrest as well as attenuate the cell migration capacity and inhibited tube-like formation on Matrigel (Zhang et al. 2012). This study showed that this effect is mediated through VEGF/VEGFR, Akt, and ERK½ inhibition (Zhang et al. 2012). Similarly, a study demonstrated that Hcy inhibits angiogenesis by preventing proliferation and migration of endothelial cells in a dose-dependent manner (Nagai et al. 2001). In an in vivo rat model, it was reported that HHcy impaired ischemia-induced angiogenesis and collateral vessel formation, which is partly mediated through the reduction in bioactivity of endogenous NO (Duan et al. 2000). Also, many groups showed that Hcy-mediated defective angiogenesis is largely due to decreasing in glutathione peroxidase (GPx) expression and consequent increase in oxidant stress, leading to endothelial progenitor cell dysfunction (Galasso et al. 2006; Handy et al. 2005), reduction of the bioavailability of NO (Eberhardt et al. 2000; Upchurch et al. 1997), and dysregulation of matrix metalloproteinases (MMPs) (Kundu et al. 2009, 2015).

Our lab showed that HHcy inhibits expression of HIF1α and VEGF after hindlimb ischemia; however the molecular mechanisms were not precisely studied. Previous studies already showed that high Hcy can be toxic to endothelial cells and can induce endothelium dysfunction (Harker et al. 1983; Lee and Wang 1999; Lentz et al. 1996; Wang et al. 1997). Along these lines, a study proposed that this effect may be mediated through a hypomethylation-related mechanism (Wang et al. 1997). It also noticed that Hcy affects ECs via inhibiting cyclin A (Jamaluddin et al. 2007). When they transduced cyclin A in ECs, the

inhibitory effect of ECs was rescued. These studies have been conducted in an in vitro system; however there is much less evidence reported for in vivo system. Nevertheless there is no treatment strategy to improve endothelium dysfunction during HHcy-mediated myocardial/skeletal muscle ischemia, peripheral arterial disease, and organ transplantation, where endothelial damage is a major characteristic.

Hyperhomocysteinemia mediated skeletal muscle atrophy

As mentioned earlier skeletal muscle is the largest organ in our body, containing 50%–75% of the body's proteins. Loss of skeletal muscle mass is commonly referred to as muscle atrophy. Several E3 ubiquitin ligases such as MuRF1, MAFBx (Atrogin-1), Nedd4.1, TRAF6, and MUSA1 have been identified, which mediate proteolytic degradation of both thick and thin filament proteins in skeletal muscle (Bodine and Baehr 2014; Bonaldo and Sandri 2013). Although several markers of ER stress including CHOP have been shown to increase in a model of skeletal muscle atrophy, the mechanisms are unclear (Yu et al. 2011). The purpose of capillaries is to serve as the interface for delivery of oxygen and removal of metabolites to/from tissues. Angiogenesis plays a vital role, and it is required during tissue injury/wound repair, the endometrial cycle, and striated muscle adaptation to stress/exercise, etc. (Olfert et al. 2016). Hcy has been implicated in vascular toxicity, causing endothelial cell damage and dysfunction (McCully 2007). Our group showed that HHcy antagonizes the angiogenic signals via reduced expression of HIF1-α, VEGF, and eNOS in skeletal muscle (Chen et al. 2014; Veeranki et al. 2014, 2015). Although HHcy inhibits Akt (also known as protein kinase B) activation in endothelial cells that has been linked to improving angiogenesis, but whether these 2 processes potentiate myopathy is not studied yet (Manning and Cantley 2007).

It has been reported that HHcy is associated with a decline in physical performance and skeletal muscle dysfunction in genetically engineered CBS deficient mice ($CBS^{+/-}$) (Veeranki and Tyagi 2013, 2015a; Veeranki et al. 2015). Skeletal muscle dysfunction and poor physical performance can result from a reduction of muscle mass and (or) structural and metabolic alteration (Filler et al. 2014; Myhill et al. 2009; Westerblad et al. 2010). Indeed, a study found that cystathionine γ-Lyase-deficient mice have lethal myopathy and oxidative injury, wherein dietary cysteine supplementation could mitigate this effect (Ishii et al. 2010). Another group reported patients with HHcy due to methyltetrahydrofolate reductase (MTHFR) mutations (C677T and A1298C) showed poor survival and muscle pain (Osian et al. 2009). Similarly, a study from our lab concluded that vasodilation in skeletal muscle arterioles is decreased during HHcy because of reduced expression of gap junction proteins (connexins 37, 40, and 43) and increased expression of myostatin in the skeletal muscle (Givvimani et al. 2013).

Mitigation of skeletal muscle dysfunction by H_2S

H_2S is increasingly being recognized as a novel endogenous gasotransmitter like nitric oxide (NO) and carbon monoxide (CO) (Gadalla and Snyder 2010; Polhemus and Lefer 2014; Szabó 2007). Being a potent anti-apoptotic/anti-necrotic (Jiang et al. 2016; Sun et al. 2017), anti-inflammatory (Sağlam et al. 2017), and cytoprotective agent (Gemici et al. 2015), H_2S

plays crucial roles in physiological homeostasis, wherein it reduces oxidative damage (George et al. 2018b; Mironov et al. 2017; Xie et al. 2016). H_2S is produced endogenously from Hcy in various mammalian tissues by 2 main enzymes (CBS and CSE) in the transsulfuration pathway (Asimakopoulou et al. 2013). As mentioned earlier, high SAM levels can act as an allosteric inhibitor for MTHFR of remethylation pathway (Finkelstein and Martin 1984) and allosteric activator for CBS of the transsulfuration pathway (Finkelstein et al. 1975; Stabler et al. 2002). Together these results suggest that the presence of a high level of SAM favors Hcy entering the transsulfuration pathway, however in patients with CBS mutation, a high SAM level builds up (due to methionine load) leading to transient accumulation of Hcy and reduction of H_2S levels. The endogenous H_2S production ranges from 1–10 pmoles per second per mg protein (Doeller et al. 2005). Patients with CBS mutation have a high amount of Hcy and tend to produce a lesser amount of H_2S (Beard and Bearden 2011; Kozich ˇ et al. 2016), suggesting that these patients are likely more prone to oxidative stress-mediated damage (Szabó 2007). Studies revealed that endogenous H_2S could modulate multiple signaling pathways, upregulate endogenous antioxidant systems, and exert additive effects with known antioxidants (Xie et al. 2016), suggesting that exogenous supplementation of H_2S could be employed as a beneficial strategy to improve redox imbalance owing to HHcy.

H_2S and oxidative/ER stress

Multiple studies demonstrated the cytoprotective (anti-necrotic/apoptotic/pyroptotic) effects of H_2S in different in vitro models, all relating to its ability to neutralize a variety of reactive species (Whiteman et al. 2004, 2005; Yan et al. 2006) and reduction of a disulfide bond in proteins (Greiner et al. 2013; Szabó 2007). H_2S in water dissociates into H^+, HS^-, and S^{2-} ions. HS^- has a capacity to scavenge ROS (Fig. 4). H_2S itself has also been recognized to be a reducing agent, as it can react directly with and quench the super-oxide anion (O^{2-}) (Al-Magableh et al. 2014; Predmore et al. 2012) and free radicals like peroxynitrite (Whiteman et al. 2006) as well as other ROS in vitro. Micro concentrations of H_2S generated from Na2S/NaHS were found to neutralize free oxyradicals (Geng et al. 2004), peroxynitrite (Whiteman et al. 2004), hypochlorous acid (Whiteman et al. 2005), and homocysteine (Yan et al. 2006) in in vitro conditions. There is no sulfide receptor in mammalian cells that is responsible for the biological actions of sulfide, hence sulfide, as a thiol with strong reducing activities, may also be a redox-controlling molecule similar to other small thiols, such as cysteine and glutathione (Kimura and Kimura 2004; Whiteman et al. 2004). A study by Kimura and Kimura (2004) using primary cultures of neurons, found that H_2S increases the cellular glutathione levels by enhancing the activity of gamma-glutamylcysteine synthetase upregulating cystine transport (Kimura and Kimura 2004). Similarly, another study reported that 100 μmol/L NaHS induces glutamate uptake by assisting glial glutamate transporter-1 (GLT-1) and enhances cysteine transport and GSH synthesis (Lu et al. 2008). In support of this effect, multiple studies demonstrated that H_2S induces cellular GSH in the brain (Tyagi et al. 2009), spinal cord (Kesherwani et al. 2013), heart (Huang et al. 2013), lung (Wang et al. 2011), kidney (Sen et al. 2009), liver (Wang et al. 2011), and gastrointestinal tract. Moreover, recent reports suggested that H_2S could attenuate cellular oxidative stress by improving activities of CAT (Fu et al. 2008; Huang et al. 2013; Wen et al. 2013; Zhu et al. 2013) and GPx (Benetti et al. 2013; Liu et al. 2013; Su et al. 2009). In

addition to oxidative stress, HHcy also induces ER stress in multiple tissues. Many studies showed that H_2S attenuates ER stress in numerous tissue types (Majumder et al. 2018a). A study found that H_2S attenuated HHcy-induced cardiomyocytic ER stress in rats (Wei et al. 2010). Li et al. (2015) demonstrated that H_2S protected against myocardial ischemia/reperfusion injury in rats by inhibiting ER stress (Li et al. 2015). Likewise, another study also reported that H_2S exerts its protection against the neurotoxicity of formal-dehyde by overcoming ER stress in PC12 cells (Li et al. 2014).

H_2S and cell death pathways

In addition to an antioxidant effect of H_2S, several studies also proposed that it has the ability to reduce cell death in multiple tissues. An in vitro study using nucleus pulposus (NP) from patients with lumbar disc herniation showed that exogenous H_2S donor attenuated hypoxia (generated by $CoCl_2$ treatment) induced apoptosis in primary rat NP cells (Sun et al. 2018). Similarly, a study using a rat model found that H_2S mitigates cigarette smoke-induced apoptosis via reducing ER stress (Lin et al. 2017). H_2S also decreased Hcy-mediated ER stress and apoptosis in the hippocampus of rats via enhancing the BDNF-TrkB pathway (Wei et al. 2014). In support of this, a study showed that NaHS supplementation could significantly inhibit hypoxia-induced neuronal apoptosis through inhibition of ROS (mainly H_2O_2)-activated Ca^{2+} signaling pathway in mouse hippocampal neurons (Luo et al. 2012). In another study, it was observed that H_2S attenuated gentamicin-induced apoptosis via reducing ROS moiety in normal rat kidney-52E cells, where they found the protein levels of Bax, Caspase-3, and cleaved-caspase-3 were decreased, and the expression of Bcl-2 was increased (Wu et al. 2017). Similarly, NaHS (H_2S donor) administration significantly inhibited the early phosphorylation of JNK and decreased the number of apoptotic cells, lowered cytochrome C release, and enhanced Bcl-2 expression in cardiomyocyte after ischemia-reperfusion (I/Re) injury (Shi et al. 2009). H_2S also attenuated 1-methyl-4-phenylpyridinium ion (MPP(+))-induced apoptosis in PC12 cells by attenuating an overproduction of intracellular ROS. Exogenous NaHS could ameliorate early brain injury after subarachnoid hemorrhage (SAH) by inhibiting neuronal apoptosis by reducing the activity of the MST1 protein (Yin et al. 2009).

H_2S and angiogenic defect

Apart from antioxidative effects of H_2S, it has been noticed that H_2S is also involved in vasodilation, vascular protection, regulation of blood pressure, and many other functions (Calvert et al. 2010; Elsey et al. 2010; Gadalla and Snyder 2010; Predmore and Lefer 2010; Szabó 2007). Like other gasotransmitters (CO and NO), H_2S can rapidly travel to vascular tissues without any transporter exerting a host of biological responses. Two independent groups reported, using either transformed endothelial cell line (RF/6A) or HUVECs, that H_2S induces proliferation and migration of ECs (Cai et al. 2007; Papapetropoulos et al. 2009). The pro-angiogenic effect of H_2S is further supported by the increase in tube-like structure formation in ECs in in vitro Matrigel assays (Cai et al. 2007; Papapetropoulos et al. 2009). H_2S exerts angiogenic effects via releasing VEGF in smooth muscle cells, ECs (Szabó and Papapetropoulos 2011;Wang et al. 2015). Apart from in vitro studies, some in vivo studies demonstrated that H_2S induced a concentration-dependent increase in the length and complexity of the vascular network (Cai et al. 2007; Papapetropoulos et al. 2009). When

ECs were exposed to H_2S donors, it activated multiple signaling pathways such as PI-3K/Akt and MAPK pathways during neovascularization (Cai et al. 2007; Papapetropoulos et al. 2009). Further evidence for H_2S-mediated VEGF induction during angiogenesis was reported in an ex vivo mouse aorta sprouting assay, where the VEGF-induced angiogenesis was markedly suppressed in aortic rings of the $CSE^{-/-}$ mice (Papapetropoulos et al. 2009). In an alternative pathway, exposure to H_2S increased calcium levels in ECs, which would lead to eNOS activation and increased NO release during angiogenesis (Bauer et al. 2010; Minamishima et al. 2009; Yusof et al. 2009).

H_2S and muscle atrophy

Skeletal muscles are now considered to be an endocrine organ, synthesizing and secreting a variety of bioactive molecules including inflammatory cytokines, growth factors, adipokines, carnitine, and more recently H_2S (Du et al. 2013). In this context, H_2S appears to protect against low oxygen and nutrient supply as well as ischemic injury in multiple organs including skeletal muscles (Du et al. 2013; Suzuki et al. 2011; Veeranki and Tyagi 2015b). Similarly, recent studies have confirmed that H_2S plays an anti-atherosclerotic role, and its deficiency leads to early development and progression of atherosclerosis (Wang et al. 2009). In agreement with this view, it was hypothesized that dysregulation of H_2S metabolism is involved in chronic fatigue syndrome, also called myalgic encephalomyelitis (Lemle 2009). Among the known cellular targets of H_2S, potassium channels have been the first to be discovered (Tang et al. 2005; Zhao et al. 2001). K_{ATP} channel activation has been suggested to be involved in the prevention of calcium overload and preservation of myofibre integrity during exercise, as well as recovery from muscle fatigue, rather than in normal muscle contractility and excitability (MacIntosh et al. 2012; Matar et al. 2000). Similarly, a significant decrease in H_2S content in muscle fibers, together with a reduction in SOD1 expression, was presented in a rat model of skeletal muscle ischemiareperfusion (I-R) injury (Du et al. 2013; Majumder et al. 2019).

Conclusions

So far, we and others have discovered apparent beneficial effects of H_2S on skeletal muscle dysfunction during chronic HHcy conditions, and the potential mechanistic role that H_2S plays during oxidative/ER stress responses, apoptosis, angiogenesis, and muscle atrophy (Fig. 5). However there is still a lot left to clarify with regards to skeletal muscle functions. (*i*) Most of the previous research has been done studying the effects of HHcy on skeletal muscle not exactly simulating the physiological conditions observed in HHcy patients, so a suitable animal model is still lacking. (*ii*) As the half-life of most of the H_2S donors is much less, most of the effects of H_2S vary in different studies. (*iii*) There are many more hurdles to overcome in regard to identifying a proper delivery method for H_2S, as skeletal muscle dysfunction ranges from general muscle weakness and soreness to severe myopathy, muscle wasting, and cachexia. (*iv*) These complex dysfunctions do not even necessarily originate from skeletal muscle; even though many studies have been devoted to clarifying the molecular mechanisms involved in E-C coupling in vitro, the real impact of these mechanisms are very difficult to assess in vivo settings because of the intrinsic complexity of this phenomenon.

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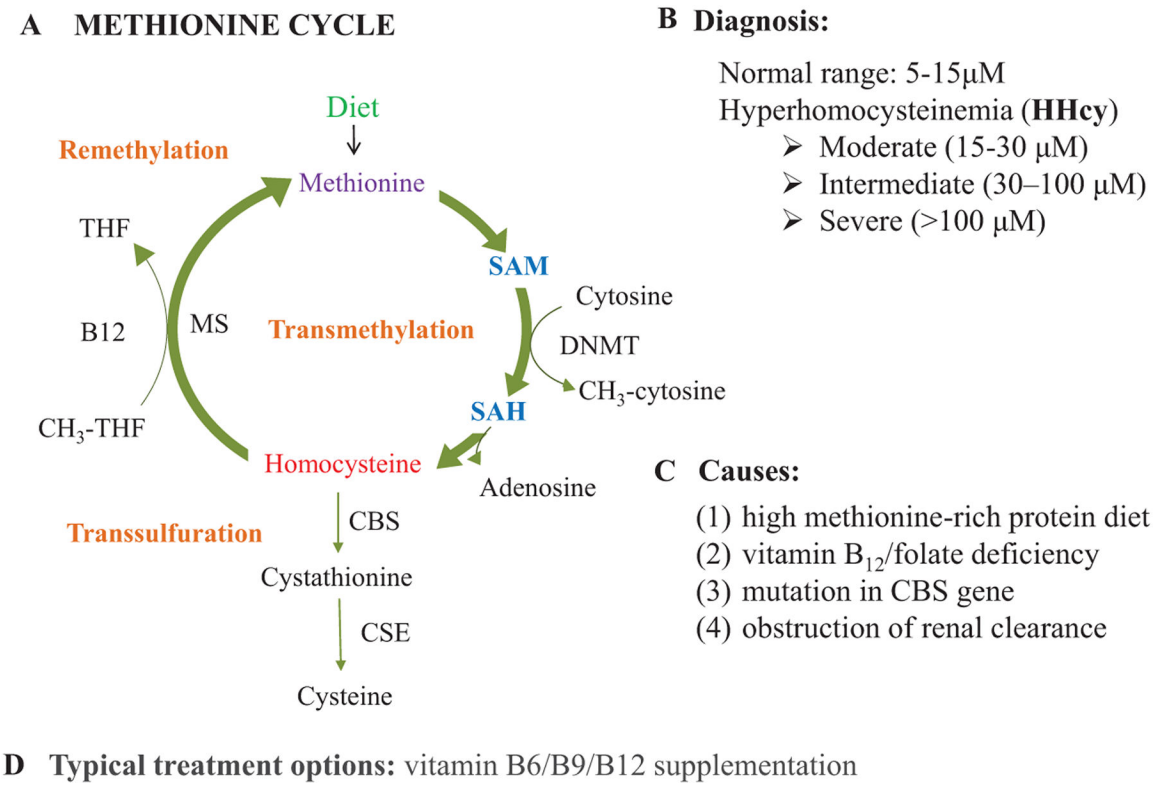

Fig. 1.

Etiology of hyperhomocysteinemia (HHcy). (A) Methionine cycle is a source of homocysteine, which is further metabolized via transsulfuration and remethylation pathways. Around 50% homocysteine is cycled via transsulfuration pathway to produce cysteine, while the remaining 50% is re-methylated back to methionine via the folate 1-carbon cycle. (B) The range of homocysteine levels in healthy vs. disease states. (C) Major causes of hyperhomocysteinemia. (D) Management of hyperhomocysteinemic conditions via supplementation with vitamins B6, B9, and B12. CBS, cystathionine-β-synthase; CSE, cystathionine γ-lyase.

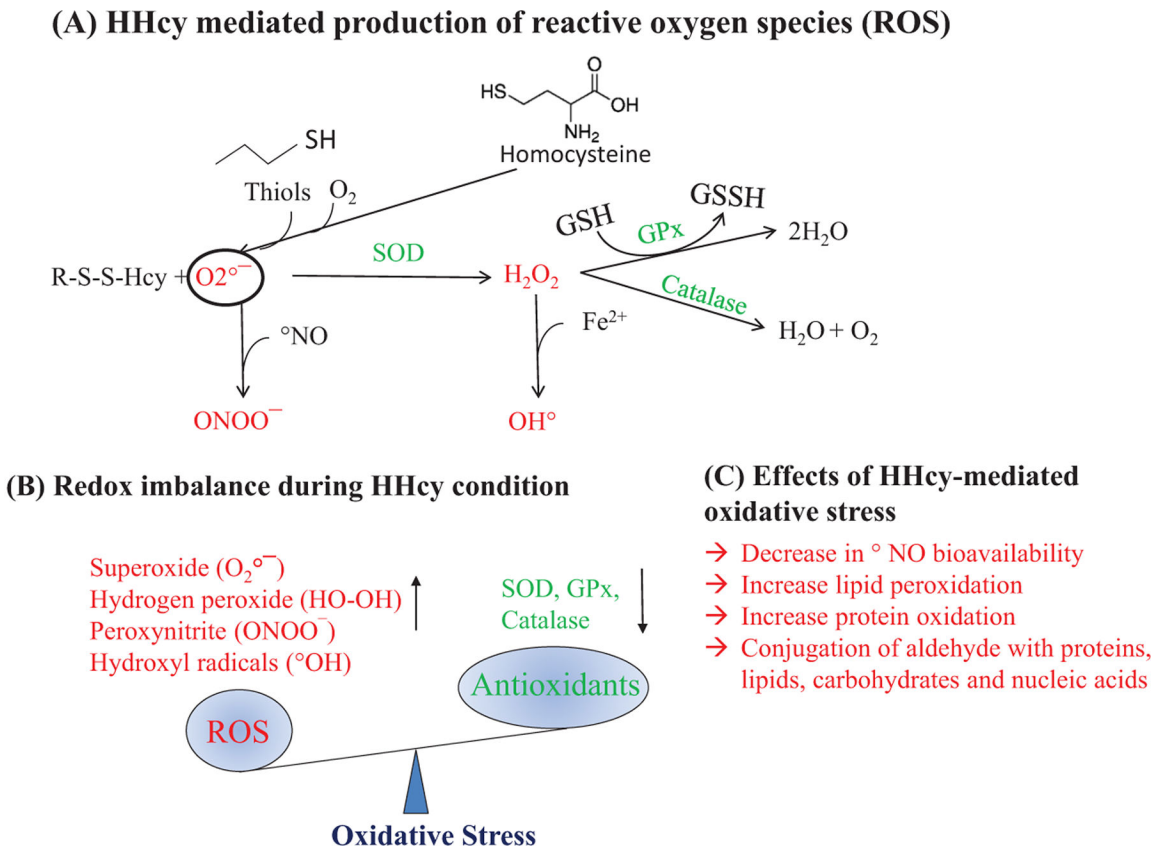

Fig. 2.

Redox imbalance during hyperhomocysteinemia (HHcy). (A) Homocysteine can homo/hetero-dimerize in the presence of transition metal catalysts and molecular oxygen to form superoxide radicals that are converted to H_2O_2 by superoxide dismutase (SOD) and which are in turn neutralized to H_2O and O_2 by glutathione peroxidase (GPx) and catalase. (B) HHcycauses redox imbalance via excessive production of reactive oxygen species (ROS) and dysregulation of oxidative defense mechanisms (SOD, GPx, and catalase). (C) Overall effects of oxidative stress in the cellular environment.

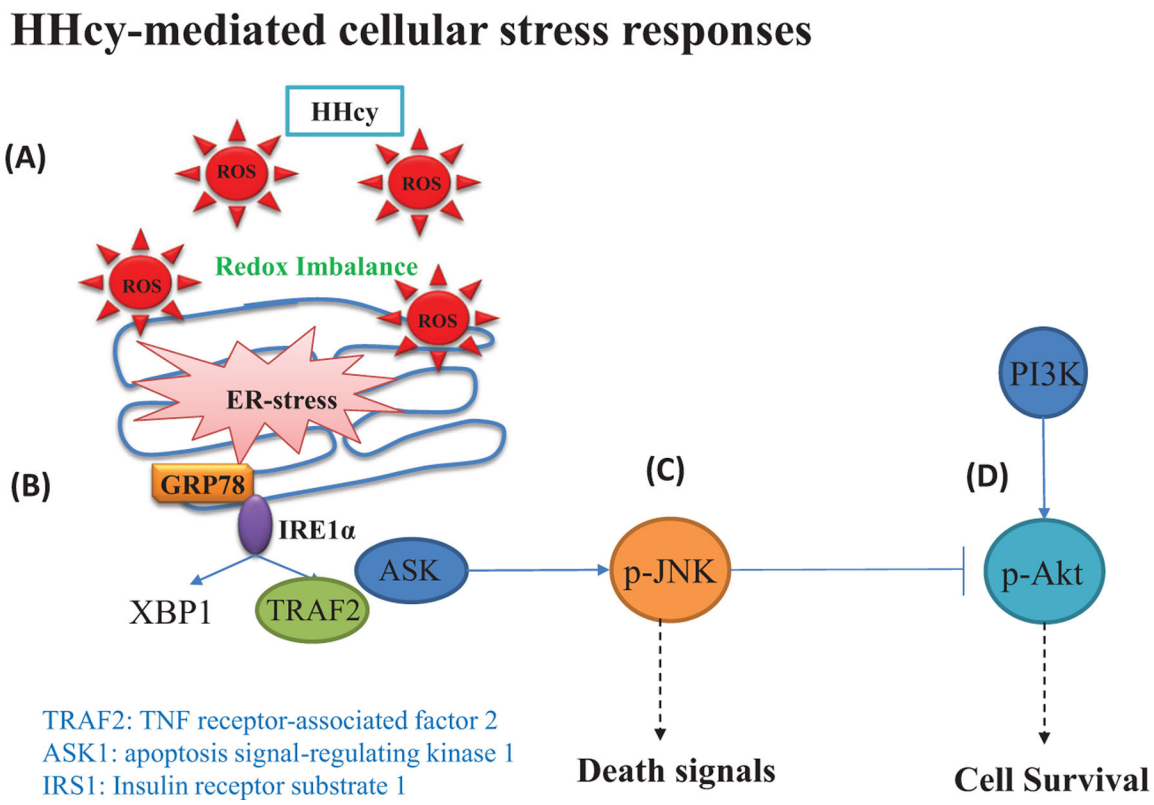

Fig. 3.

Hyperhomocysteinemia (HHcy) is a non-inducer of cellular stress responses. (A) During oxidative stress conditions, the biogenesis as well as protein folding process are severely compromised leading to unfolded protein response (UPR). (B) Activation of inositol-requiring enzyme-1α (IRE1α) during endoplasmic reticulum (ER) stress response causes X-box binding protein-1 (XBP1) mRNA splicing (induces the production of chaperon proteins) and during severe ER stress condition it recruits TNF receptor-associated factor-2 (TRAF2) along with apoptosis signal-regulating kinase-1 (ASK1), which further leads to activation of c-Jun N-terminal kinase (JNK). (C) Activated-JNK phosphorylates c-Jun (Ser63 and 73 residues) that leads to the recruitment of activator protein-1 (AP-1) to the promoter sequences of various pro-apoptotic genes, and induce apoptosis. (D) JNK is also involved in the phosphorylation of IRS-1 at Ser^{307} which in turn inhibits IRS-1 signaling thus impairing the PI3K/AKT survival axis.

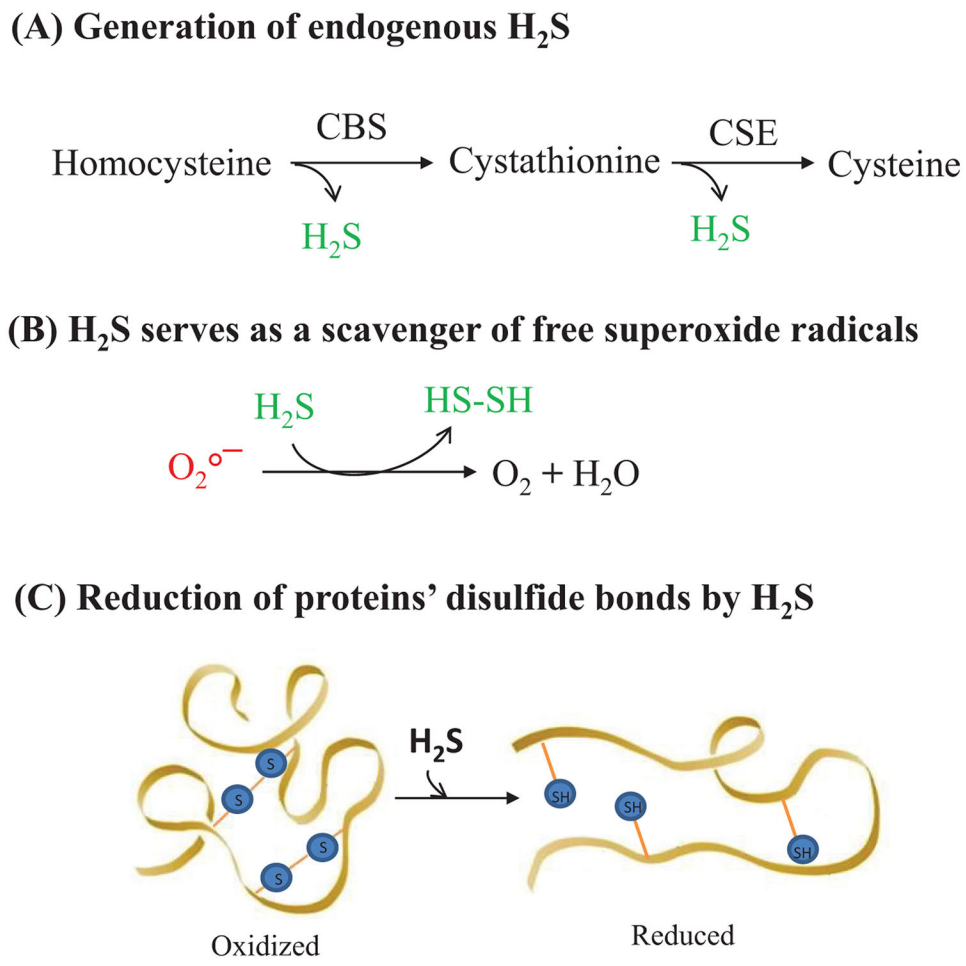

Fig. 4.

Salubrious effects of H_2S on cellular biochemistry. (A) Being an important antioxidant molecule H_2S helps synthesize cysteine, which gets converted into GSH via cystathionine-β-synthase (CBS) and cystathionine γ-lyase (CSE) enzymatic pathways. (B) H_2S is a potent scavenger for a variety of reactive oxygen species (ROS). (C) H_2S is known to reduce disulfide bonds in proteins, thereby reversing the homocysteinylation of proteins during hyperhomocysteinemia conditions.

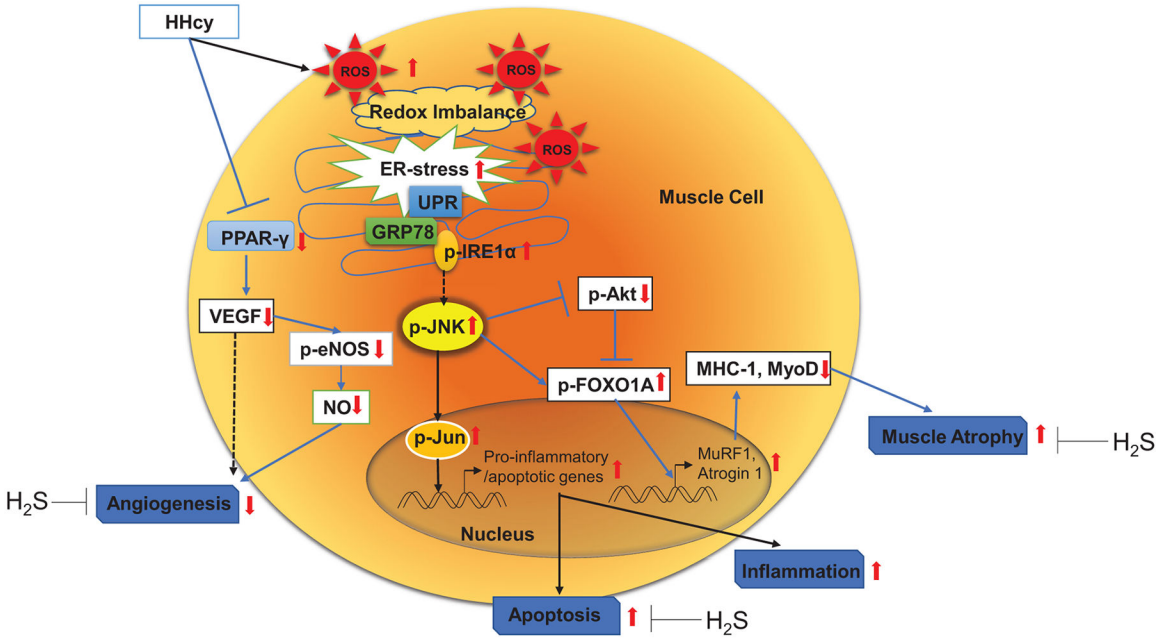

Fig. 5.

Schematic diagram highlighting hyperhomocysteinemia (HHcy)-mediated skeletal muscle dysfunction via induction of apoptosis, endoplasmic reticulum (ER), oxidative stress responses, and inhibition of angiogenesis that can lead to skeletal muscle atrophy as a result of JNK-activation and concurrent impairment of PI3K/AKT survival axis. H_2S, by virtue of it multi-farious beneficial properties, could mitigate these harmful effects successfully. eNOS, endothelial nitric oxide synthase; FOXO, forkhead box protein O; IRE1α, inositol-requiring enzyme-1α; JNK, c-Jun N-terminal kinase; MuRF1, muscle RING-finger protein-1; PPAR-γ, peroxisome proliferator-activated receptor-γ; UPR, unfolded protein response; VEGF, vascular endothelial growth factor.