



# ATP Sensitive Potassium Channels in the Skeletal Muscle Function: Involvement of the *KCNJ11*(Kir6.2) Gene in the Determination of Mechanical Warner Bratzer Shear Force

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The ATP-sensitive K<sup>+</sup>-channels (KATP) are distributed in the tissues coupling metabolism with K<sup>+</sup> ions efflux. KATP subunits are encoded by *KCNJ8* (Kir6.1), *KCNJ11* (Kir6.2), *ABCC8* (SUR1), and *ABCC9* (SUR2) genes, alternative RNA splicing give rise to SUR variants that confer distinct physiological properties on the channel. An high expression/activity of the sarco-KATP channel is observed in various rat fast-twitch muscles, characterized by elevated muscle strength, while a low expression/activity is observed in the slow-twitch muscles characterized by reduced strength and frailty. Down-regulation of the KATP subunits of fast-twitch fibers is found in conditions characterized by weakness and frailty. *KCNJ11* gene knockout mice have reduced glycogen, lean phenotype, lower body fat, and weakness. KATP channel is also a sensor of muscle atrophy. The *KCNJ11* gene is located on BTA15, close to a QTL for meat tenderness, it has also a role in glycogen storage, a key mechanism of the postmortem transformation of muscle into meat. The role of *KCNJ11* gene in muscle function may underlie an effect of *KCNJ11* genotypes on meat tenderness, as recently reported. The fiber phenotype and genotype are important in livestock production science. Quantitative traits including meat production and quality are influenced both by environment and genes. Molecular markers can play an important role in the genetic improvement of animals through breeding strategies. Many factors influence the muscle Warner-Bratzler shear force including breed, age, feeding, the biochemical, and functional parameters. The role of *KCNJ11* gene and related genes on muscle tenderness will be discussed in the present review.

**Keywords:** meat tenderness, ATP sensitive K<sup>+</sup> channels, Warner-Bratzler shear force, skeletal muscle, gene polymorphisms

## INTRODUCTION

The ATP-sensitive K<sup>+</sup>-channels (KATP) are widely distributed in the tissues including neurons, vascular, pancreatic beta cells, cardiac, and skeletal muscles (Amoroso et al., 1990; Zhang and Bolton, 1996; Liss and Roeper, 2001; Cole and Clément-Chomienne, 2003; Flagg et al., 2010; Olson and Terzic, 2010). The multi-level regulation by membrane phospholipids (PIP<sub>2</sub>), fatty acids (LC-Acyl-CoA), protein kinases (PKA, PKC), creatin kinase shuttle, and glycolytic enzymes, pH, hypoxia, and intracellular nucleotides ensures complexity of metabolic sensing by KATP channels (Selivanov et al., 2004; Flagg et al., 2010; Mele et al., 2012; Mohammed Abdul et al., 2015). The main regulator of the KATP channel is the ATP/ADP ratio, an elevated ATP/ADP ratio leads to channel closure while the reduction of the ATP/ADP ratio in the presence of Mg<sup>2+</sup> ions determine the channel opening thereby sensing nucleotides changes (Flagg et al., 2010).

## Structure, Distribution, and Regulation of KATP Channels

The KATP channels are hetero-octameric complexes of pore-forming inwardly rectifier K<sup>+</sup> (Kir6) channel subunits associated with regulatory sulphonylureas receptor (SUR) subunits, members of the ATP binding cassette (ABC) family of membrane proteins. Two Kir6-encoding genes, *KCNJ8* (Kir6.1) and *KCNJ11* (Kir6.2), and two SUR genes, *ABCC8* (SUR1) and *ABCC9* (SUR2), encode mammalian KATP subunits, but alternative RNA splicing can give rise to multiple SUR protein variants (e.g., SUR2A and SUR2B) that confer distinct physiological and pharmacological properties on the channel complex (Inagaki et al., 1995, 1996; Chutkow et al., 1996; Babenko et al., 2000; Tricarico et al., 2006; Wheeler et al., 2008). The nucleotide inhibitory and stimulatory sites are located on the Kir6.2/Kir6.1 and on SURs subunits of the channel complex, respectively (Babenko et al., 2000; Flagg et al., 2010).

The SUR subunits carry the binding sites for the KATP channel blockers used as insulin releasing agents, and for the KATP channel openers used as cardioprotective and vasodilating drugs (Babenko et al., 2000; Tricarico et al., 2008a, 2012). These drugs are also effective on the skeletal muscle KATP channels (Table 1).

As in cardiac muscle, skeletal muscle KATP channels (sarco-KATP) remain closed at rest and do not contribute to electrical activity unless the muscle is stressed. Channel regulation by intracellular nucleotide, metabolic enzymes, and ATP-ase pumps are similar to that in cardiac muscle, but the intracellular acidification is a potent activator of the skeletal muscle subtype (Tricarico et al., 1997a, 2003, 2012).

The properties of the sarco-KATP channels are age dependent in rat fibers. The activity recorded in excised patches from fast-twitch fibers is low at 5–6 days of postnatal life, increases to a plateau at 12–13 days, then declines toward adult values after 37 days. Two distinct types of the KATP channel complex can be distinguished. The early developmental period (5–6 days) is dominated by a KATP channel having a conductance of 66 pS, a high open probability of 0.602 which is determined by a reduced mean close time as compared to that recorded in the adult fibers,

and an IC<sub>50</sub> for ATP and glibenclamide of 123.1 and 3.97 μM, respectively. The later developmental period (from 56 days) is dominated by a KATP channel having a 71 pS conductance, but a low open probability of 0.222. This adult channel is also 3.2 and 73.5 times more sensitive to ATP and glibenclamide than the juvenile channel, respectively (Tricarico et al., 1997b).

The molecular composition of the sarco-KATP channels has been clarified in adult rat muscle fibers. Hybrid KATP channel complexes composed of Kir6.2, SUR2A, SUR1, and SUR2B subunits contribute to functional channels in different muscle phenotypes (Tricarico et al., 2006). A high expression/activity of the Kir6.2-SUR2A and Kir6.2-SUR1 channel subunits is observed in type IIA fast-twitch muscles, characterized by elevated strength. A low expression/activity of the sarco-KATP channel is observed in the slow-twitch muscle of the rat characterized by reduced strength and frailty being more susceptible to mechanical and chemical insults, and the Kir6.2-SUR2B subunits contribute to the functional channel in this muscle phenotype (Table 1). The sarco-KATP channel activity declines with aging in fast-twitch rat fibers showing surface channel subtypes characterized by low open probability and current density (Tricarico and Camerino, 1994).

The age-dependent changes of the KATP channels subtypes may reflect the different metabolic needs of the muscles during development and aging.

## Role of KATP Channels in Skeletal Muscle Homeostasis and Fatigue

The role of the sarco-KATP channels in the muscle fatigue has been extensively investigated. Muscle fatigue is the decline in force production during prolonged and repetitive stimulation and many biochemical mechanisms have been proposed to contribute to this process. One possible mechanism is that activation of KATP channels, in response to reduction of ATP/ADP ratio, might underlie a decrease in action potential duration and hence twitch force. The activation of sarco-KATP channels after fatigue has developed, helps to preserve a polarized membrane potential and rise of tension that is observed in Kir6.2<sup>-/-</sup> muscles that are exposed to fatiguing stimuli (Gramolini and Renaud, 1997; Gong et al., 2000, 2003; Cifelli et al., 2007, 2008). KATP channels play a role in Ca<sup>2+</sup> handling and maintaining fiber integrity during exercise. Abolishing KATP channel activity in fast-twitch muscle fibers leads to a decrease in peak Ca<sup>2+</sup> and tetanic force, increases in resting unstimulated Ca<sup>2+</sup> ions with faster fatigue rate (Cifelli et al., 2007). The observation that there is extensive fiber damage in Kir6.2<sup>-/-</sup> subjected to training protocols corroborates the conclusion that KATP channel activation is a physiologically relevant myoprotective mechanism *in vivo* (Kane et al., 2004; Thabet et al., 2005). These findings accounts for the observation that the rate and extent of post-fatigue recovery are decreased in Kir6.2<sup>-/-</sup> animals. A similar phenotype has been found in SUR2<sup>-/-</sup> mice, that show impaired exercise performance and extensive fiber damage following exercise (Stoller et al., 2009).

The sarco-KATP channels regulate glucose homeostasis. The *in vitro* pharmacological blockade of sarco-KATP channels in

TABLE 1 | Molecular composition and functions of KATP channel subunits in skeletal muscles.

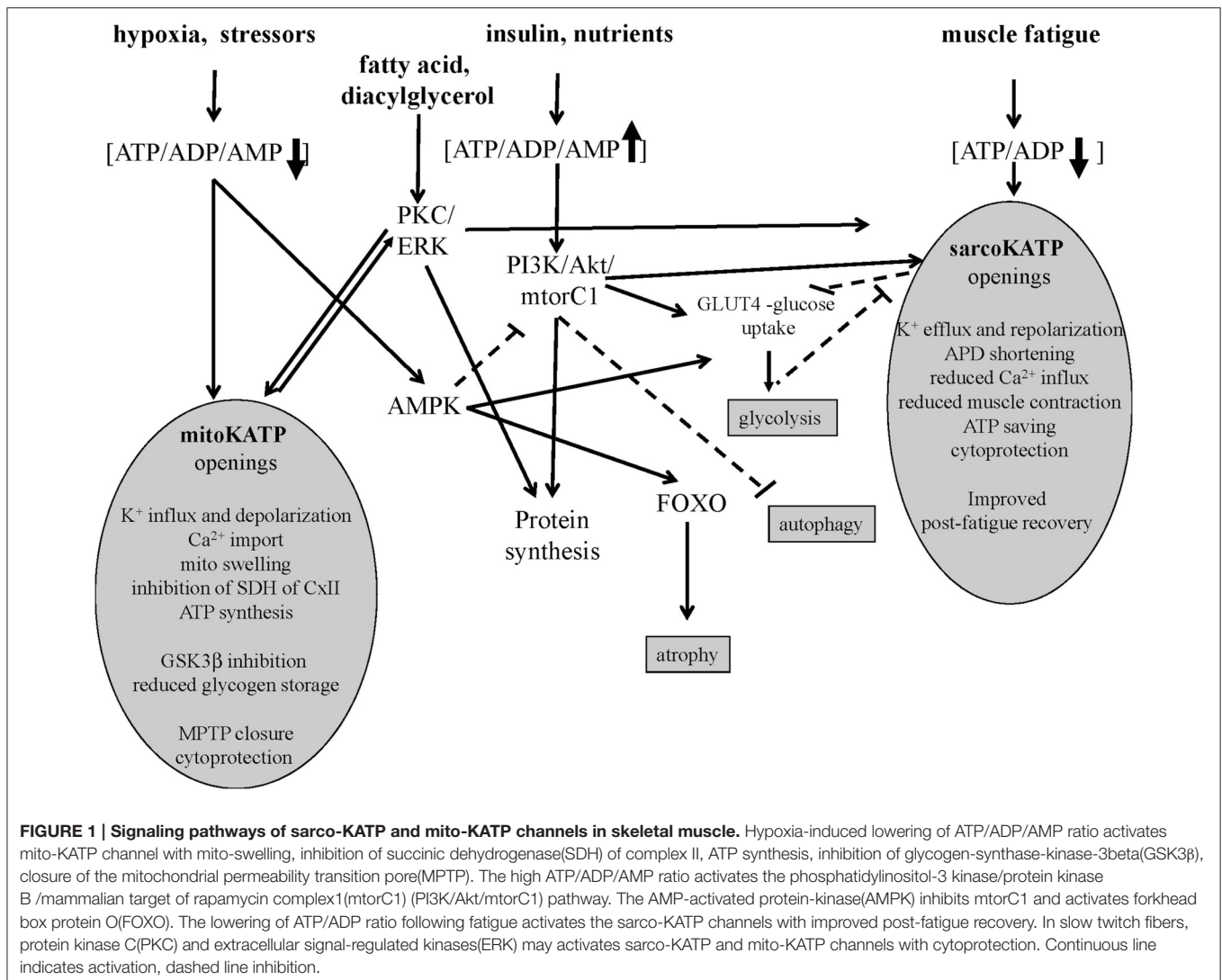
Fiber types and properties	Molecular composition of sarco KATP channels	Functions	Pharmacology
<b>Fast-twitch muscles</b> type IIB glycolytic fibers, show low mitochondria density, are resistant to mechanical stress, fatigue sensitive, are involved in the short term intense explosive exercise (min).	Kir6.2/SUR2A> Kir6.2/SUR2B>> Kir6.2/SUR1	Elevated expression/activity. Partial cytoprotection against disuse related atrophy and staurosporine induced atrophy. Upregulation of SUR2A in response to hypoxia. Downregulation of Kir6.2/SUR2A in response to hypokalemia with weakness. Reduced activity with aging.	Responsive to openers and blockers. Rank order of efficacy of the KATP openers: benzoxazine analogs>>cromakalim=minoxidil=pinacidil> diazoxide Rank order of efficacy of the KATP blockers: glimepiride>glibenclamide> repaglinide> nateglinide> tolbutamide
Type IIA glycolitic-oxidative fibers, show low sensitivity to fatigue, are involved in the moderate intensity exercise, and resistance to elevated mechanical stress. Type IIX fibers with intermediate properties between type IIB and IIA fibers.	Kir6.2/SUR2A> Kir6.2/SUR1>> Kir6.2/SUR2B	Full cytoprotection against muscle disuse and staurosporine induced atrophy. Downregulation of Kir6.2/SUR2A in response to hypokalemia with weakness. Reduced activity with aging.	Rank order of efficacy of the KATP openers: benzoxazine analogs >>cromakalim=minoxidil=pinacidil = diazoxide Rank order of efficacy of the KATP blockers: glibenclamide>repaglinide> nateglinide>glimepiride> tolbutamide
<b>Slow twitch muscles</b> Type I oxidative fibers show high mitochondria density, elevated frailty, fatigue resistance, and recruited following low intensity and long lasting exercise (hours).	Kir6.2/SUR2A> Kir6.2/SUR2B> Kir6.2/SUR1	Reduced expression/activity. Enhanced susceptibility to atrophic stressors. Downregulation of Kir6.2/SUR2B; SUR1 in response to muscle disuse and staurosporine induced atrophy. In the short term upregulation of Kir6.2/SUR2B/SUR1 with cytoprotection against staurosporine insults.	Less responsive to openers and blockers. Rank order of efficacy of the KATP openers: cromakalim > diazoxide Rank order of efficacy of the blockers: repaglinide>glibenclamide> nateglinide>tolbutamide> glimepiride

The gene expression of the KATP channel subunits and the sarcolemma KATP channels (sarco-KATP) activity have been evaluated, respectively, by RT-PCR experiments in muscles and in excised macropatch experiments performed on enzymatically isolated native rat fibers. The drug effects on the channel currents were evaluated in symmetrical concentrations of K<sup>+</sup> ions on both side of the membrane patches, at -60 mV(Vm), in the absence of internal ATP and channel blockers or in the presence of internal ATP (100 10<sup>-6</sup> M) and channel openers.

cell line as well as the down-regulation of the subunits increases basal or insulin-dependent glucose uptake as observed in KATP deficient Kir6.2<sup>-/-</sup> and SUR2<sup>-/-</sup> animals (Tsiani et al., 1995; Chutkow et al., 2001; Wasada et al., 2001). In these mice there is enhanced glucose uptake, consistent with an inhibitory effect of sarco-KATP activity on glucose uptake (Wasada, 2002). *KCNJ11* gene knockout mice (Kir6.2<sup>-/-</sup>) also have reduced glycogen storage, lean phenotype, lower body fat, and severe muscle weakness (Alekseev et al., 2010; **Figure 1**). Down-regulation of Kir6.2/SUR2A subunits in skeletal muscle is associated with abnormal insulin response with severe hypokalemia and hypoglycaemia in rats (Tricarico et al., 2003, 2008b). It may be possible that the abnormally enhanced KATP channel activity as occurring in neonatal diabetes will affect also glucose uptake into skeletal muscle, thereby exacerbating the hyperglycaemia (Ellard et al., 2007; McTaggart et al., 2010). Similarly, in obesity an accumulation of fatty acyl-CoA intermediates, by activating KATP channels will exacerbate insulin resistance (Wasada et al., 2001; Wasada, 2002).

The phenotype-dependent KATP activity therefore leads to a better use of glucose among muscles in proportion to their metabolic needs. The enhanced expression/activity of the sarco-KATP channels reduces the glucose uptake in low energetic demand fast-twitch muscles, while making glucose available to slow-twitch muscles which are characterized by a high glucose demand during contraction and reduced expression/activity of the sarco-KATP channels (Bonen et al., 1981; Megeney et al., 1993; Tricarico et al., 2006). This mechanism may contribute to the action of the KATP channels in regulating the rate and extent of post-fatigue recovery.

The observed differences in KATP channel properties among muscles in terms of expression/activity and composition of channel subunits can be related to their specific functions in rat (Tricarico et al., 2006). The KATP channels of *flexor digitorum brevis* (*FDB*) are indeed composed of SUR1 and SUR2 subunits, whereas KATP channels of *tibialis anterioris* (*TA*), *extensor digitorum longus* (*EDL*), and *soleus* (*SOL*) muscles are composed of SUR2 subunits which are more responsive to metabolic stresses



compared with channel complexes of SUR1. The *TA*, *EDL*, and *SOL* muscles are exposed more often to hypoxia and fatigue than *FDB* muscle, which shows a different morphology and function (Table 1).

## KATP Channel Subunits Regulate Apoptosis and Cell Viability

The *in vivo* down-regulation of KATP channel subunits or the *in vitro* long term exposure of the channels to channel blockers (>24 h) are coupled to apoptosis and atrophic signaling in isolated fibers (Tricarico et al., 2010; Cetrone et al., 2014; Mele et al., 2014a,b). The atrophic effects of the channel blockers and of the apoptotic agent staurosporine are muscle type dependent and are related with the sarco-KATP channel density. For instance, the KATP channel blockers induces atrophy after 24 h of incubation time of fast-twitch fibers that are characterized by elevated sarco-KATP channels expression/activity, while the apoptotic agent staurosporine induce atrophy within 6 h of incubation time affecting slow-twitch fibers that are characterized by low sarco-KATP channel expression/activity. These findings corroborate the idea that the high/expression activity of the sarco-KATP channel subunits is a protective factor against insults (Cetrone et al., 2014; Mele et al., 2014a).

Emerging evidences suggest that in skeletal and cardiac muscles the sarco-KATP and mitochondria KATP (mito-KATP) channels are coupled to the insulin/IGF1-PI3K-Akt-mTOR signaling and/or PKC/ERK pathway (Figure 1). The SUR2A gene is upregulated by Akt following hypoxia and exerts cytoprotective action saving intracellular ATP/ADP/AMP ratio which is critical in regulating the Akt-mTOR pathway (Vadlakonda et al., 2013; Mohammed Abdul et al., 2015). The Akt-mTORC1 pathway determines protein synthesis also inhibiting FOXO atrophic signaling in fast-twitch skeletal muscle (Bonaldo and Sandri, 2013).

The sarco-KATP and mito-KATP channels are modulated by PKC phosphorylation in cardiomyocyte and in cell line expressing the recombinant channels (Light et al., 2000). PKC is coupled to ERK in skeletal muscle (Ronda et al., 2010). The fact that the unselective PKC inhibitor staurosporine induces atrophy of slow fibers which is prevented by diazoxide, suggests that PKC/ERK plays a role in this muscle phenotype in regulating protein synthesis (Mele et al., 2014a).

Diazoxide activates mito-KATP, potentiates PKC $\epsilon$ , and PI3K/Akt/mTORC1 pathways (Kim et al., 2006; Kwon et al., 2006; Chen et al., 2016). While, the mito-KATP channel blocker 5-hydroxydecanoate (5HD) and the sulphonylureas show opposite actions (Khanfar et al., 2013; Mele et al., 2014b).

The opening of mito-KATP channel following low ATP levels induces mitochondrial swelling of the inner membrane regulating ATP synthesis (Wojtovich et al., 2013). The mito-KATP channel was initially identified into the SUR1/Kir6.1 complex that recapitulated mito-KATP channel activity, including diazoxide activation and 5-hydroxydecanoate inhibition (Ardehali et al., 2004). Recently, a role for ROMK2 (Kir1) subunit in generating the mito-KATP channel has been proposed (Foster et al., 2012). Openings of the mito-KATP

channel blocks the mito-permeability transition pore reducing cytochrome C release in different cells. The mito-KATP channel is also coupled to the glycogen-synthase-kinase 3 $\beta$  (GSK-3 $\beta$ ) and connexin 43 (Cx43) so that the GSK-3 $\beta$  downregulation transfers cytoprotective signaling through mitochondrial Cx43 onto mito-KATP channels openings (Rottlaender et al., 2012; Figure 1).

## KATP Channelopathies

The KATP channels are involved in rare genetic diseases associated with insulin/glucose dis-metabolism, cardiomyopathy, weakness, and dysmorphisms.

Mutations in the *KCNJ11* and *ABCC8* genes are now well-understood to underlie neonatal diabetes mellitus and congenital hyperinsulinism (Ellard et al., 2007; Flanagan et al., 2007; Arnoux et al., 2010; McTaggart et al., 2010). Activating mutations in the *KCNJ11* gene encoding for the Kir6.2 subunit is associated with severe neuro-muscular weakness in permanent neonatal diabetes (Gloyn et al., 2004).

The SUR1 and SUR2A/B subunits are involved in neuroprotection following ischemia, and in neurodegenerative diseases such as Parkinson or Alzheimer's diseases and aging (Liss and Roeper, 2001; Zeng et al., 2007; Nelson et al., 2015). Gain of function and loss of function mutations in the *KCNJ8* gene is associated with the J-wave phenomenon and early repolarization of the hearth, and with the sudden infant death syndrome, respectively (Kane et al., 2005; Nichols et al., 2013). Loss-of-function mutations of the *ABCC9* gene were found in patients affected by long-standing atrial fibrillation originating in the vein of Marshall and in patients with dilated cardiomyopathy (Kane et al., 2005; Nichols et al., 2013).

Down regulation of the KATP channel subunits of fast-twitching fibers is associated with hypokalemic periodic paralysis. This disorder is characterized by attacks of weakness induced by insulin-glucose infusion and lowering of serum K<sup>+</sup> ions (Tricarico et al., 1998, 1999, 2008b).

Gain of function mutations in the *ABCC9* gene encoding for the cardiac, skeletal and smooth muscles SUR2A/B subunits of the KATP channel is responsible for the Cantu' syndrome, a distinctive multi-organ disease characterized by hypertrichosis, osteochondrodysplasia, cardiomegaly, and musculo-skeletal abnormalities (Harakalova et al., 2012).

## Involvement of the *KCNJ11*(Kir6.2) Gene in the Determination of the Meat Tenderness

Several polymorphisms were detected at *KCNJ11* locus in a sample of Nellore cattle (Tizioto et al., 2013). Among them, only two SNPs were used to investigate a possible association with meat tenderness of meat by using the Warner-Bratzler shear force (WBSF). The first polymorphism, c.1526C>T (NCBL\_ss#537718973) is a synonymous mutation located in the coding region; the second one, c.2342T>C (NCBL\_ss#537718995) is located in the 3'UTR region. The SNP c.2342T>C showed an additive effect on WBSF measured 24 h after slaughter and after 7 days of cold-chamber aging, with the T allele being associate with reduced WBSF. No effect of the haplotype was observed (Tizioto et al., 2013).

The *KCNJ11* gene is located on bovine chromosome 15, near a quantitative trait locus (QTL) for meat tenderness thereby indicating the involvement of this gene in regulating this muscle parameter in bovine species (Rexroad et al., 2001; Tizioto et al., 2013).

These findings suggest that the expression/activity of the KATP channel subunits may have relevance in determining the WBSF in muscles also under different nutritional status (De Palo et al., 2012). Meat tenderness is affected by breed, gender, and nutritional status. Biochemical and functional analysis showed that lower shear force values were associated with more tender meat. Muscles in the highest tenderness cluster had the lowest total and insoluble collagen contents, the highest mitochondrial enzyme activity (isocitrate dehydrogenase), the highest proportion of slow oxidative fibers, the lowest proportion of fast-glycolytic fibers, the lowest average muscle fiber cross-sectional area and showing intramuscular fat (Chriki et al., 2012).

Gene and proteomic analysis identified several gene pathways associated with tenderness, among these the heat shock proteins, the calpain/calpastatin and apoptotic genes, the energy and metabolic genes, and fatty acid related genes pathways have attracted the attention of several investigators (Hocquette et al., 2012; Picard et al., 2014). However, it is not always possible to extrapolate the relevance of these markers to all bovine population.

Moreover, a significant relationship between the *KCNJ11* gene expression level and the WBSF after 7 days of cold-chamber aging was found, without a significant influence of the investigated SNPs on gene expression levels (Tizioto et al., 2013). Although, the *KCNJ11* gene encodes for a K<sup>+</sup> channels Tizioto and coworkers reported no significant association between the two considered SNPs and the K<sup>+</sup> content in the meat obtained by Nellore cattle in Brazil. However, as these authors state, they did not distinguish between intracellular and extracellular K<sup>+</sup> content, being impossible to detect the regulation of K<sup>+</sup> flow (Tizioto et al., 2014). So, to further investigate all these concerns also in other breeds, genetically distant from Nellore, could be an interesting perspective.

The role of K<sup>+</sup> ions content on meat tenderness is controversial. It seems that higher levels of K<sup>+</sup> ions are related to meat tenderness, instrumentally evaluated through trained panel test (Mateescu et al., 2013). The addition of K-lactate in fresh bovine chuck muscles confers more tenderness to meat (Walsh et al., 2010). Furthermore, the substitution of Na<sup>+</sup> with K<sup>+</sup> ions brought to a higher tenderness of the product evaluating sensorial profile modifications through panel test (Greiff et al., 2015). Although, mechanical and instrumental meat tenderness determination is not strictly correlated to sensorial evaluation of the same qualitative pattern, different authors recently found a positive correlation between meat tenderness and K<sup>+</sup> ions

concentration. Similar results obtained with different tenderness evaluation techniques represent a strong confirmation of results. Actually scientific community is discussing on the best way for evaluating this important qualitative pattern of meat sensorial profile, comparing and correlating results obtained by human based analysis (consumer and panel tests), mechanical analysis (WBSF and Meullenet–Owens razor shear) and spectroscopy (visible and near-infrared; Yancey et al., 2010; Emerson et al., 2013). Besides, some found in Angus breed a heritability rate of K<sup>+</sup> ions concentration indicating also an important role of genetics in this aspect (Mateescu et al., 2013). Knock outs mice of K<sup>+</sup> channel gene subunits other than KATP subunits show a similar phenotype (muscle weakness, small size) supporting the role of K<sup>+</sup> ions as a factor involved in the muscle tenderness. Low intracellular K<sup>+</sup> content may activates K-dependent proteolysis effectors such as caspases with a potential role in the muscle tenderness (Nolin et al., 2016). Moreover, muscle-specific signaling pathways coupled to the splicing forms of the KATP channels may play a role (Figure 1).

## CONCLUSIONS

Several critical questions remain open for instance the role and distribution of *KCNJ11* gene polymorphisms and related genes in the Italian cattle breeds which has never been investigated. The effects of the c.2342T>C and c.1526C>T SNPs at *KCNJ11* locus on the expression/activity of the sarco-KATP channel subunits in *ex vivo* experiments as well as the cellular phenotype changes associated with the *KCNJ11* gene down-regulation in the muscles and in different native cell types of cattle are not known.

The correlation of the fiber phenotypes using biochemical and histological analysis of the muscle in terms of fiber composition, fat and collagen contents, qualitative and chromatic aspects with gene expression, and polymorphisms is another point of interest (Martin et al., 1985; Schiaffino et al., 1989; Picard et al., 1998; Duris et al., 2002; Tateo et al., 2007).

Genetic prediction of beef tenderness in bovine breeds represents an important topic useful to widen knowledge on the complex phenomena related to mechanical and sensorial properties of fresh and cured meat, but it could be a fundamental tool necessary for genetic improvement of meat producing animals, and of beef at first.

## AUTHOR CONTRIBUTIONS

DT, wrote the manuscript. AL, Revision of the manuscript. PI, Editing. AC, AM Cellular experiments. NZ, GP, Pathology. MS, CD, Genetists. PD, MS, Wrote the manuscript. AT, PC, PD, Quality control. GC, Molecular biology.

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