CROSSTALK

CrossTalk proposal: Skeletal muscle oxidative capacity is altered in patients with cystic fibrosis

Paula Rodriguez-Miguelez1, Melissa L. Erickson2, Kevin K. McCully2 and Ryan A. Harris1,3*

1 Georgia Prevention Institute, Department of Pediatrics, Augusta University, Augusta, GA, USA
2 Department of Kinesiology, University of Georgia, Athens, GA, USA
3 Sport and Exercise Science Research Institute, University of Ulster, Jordanstown, Northern Ireland, UK
Email: ryharris@augusta.edu

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which functions as an ATP-gated anion channel. Pulmonary dysfunction is the most common clinical manifestation of CF; however, there are many other systemic consequences that contribute to the shortened life expectancy in this population. Exercise intolerance has been shown to predict mortality in patients with CF independent of lung function. Despite the clinical importance for assessing exercise capacity, the mechanisms which lead to exercise intolerance in CF have yet to be elucidated. Although evidence suggests that the impaired expression of CFTR in skeletal muscle may be associated with abnormalities in muscle oxygenation and muscle metabolism, there are recent studies that have described a preserved muscle metabolism in patients with CF. Considering the available data, support of a dysfunctional skeletal muscle oxidative metabolism in patients with CF is briefly discussed.

Patients with CF exhibit intrinsic skeletal muscle limitations

Numerous studies have described that patients with CF exhibit intrinsic skeletal muscle defects, independently of muscle mass, lung function, or physical activity status (de Meer et al. 1995; Moser et al. 2000; Sahlberg et al. 2005; Rosenthal et al. 2009; Troosters et al. 2009; Lamhonwah et al. 2010). In fact, even patients with CF who are competitive athletes show reductions in muscle strength and power compared to apparently healthy control athletes (Selvadurai et al. 2003). The manifestation of these skeletal muscle impairments in patients with CF has been closely related with the abnormal function of the CFTR in muscle tissue (Divangahi et al. 2009; Lamhonwah et al. 2010). The aforementioned studies have related a dysfunctional CFTR channel with an anomalous response to cell membrane polarization (Divangahi et al. 2009). In fact, CFTR channel dysfunction contributes to disturbed ion transport (Guo et al. 2014), thereby resulting in a reduction in action potential magnitude and impairment in skeletal muscle function.

Patients with CF exhibit mitochondrial dysfunction

Prevailing data in the literature have described how the impaired function of the CFTR protein in CF skeletal muscle is associated with different anomalies that are not observed in other respiratory pathologies (Divangahi et al. 2009; Lamhonwah et al. 2010; Wells et al. 2011). Among them, the existence of mitochondrial dysfunction has been confirmed in cells from patients with CF (Feigal & Shapiro, 1979; Shapiro et al. 1979; Feigal et al. 1982; Valdivieso et al. 2012). Such mitochondrial impairments have been related with alterations in mitochondrial morphology (i.e. mitochondrial shape) and mitochondrial energetic metabolism (i.e. electron transport chain) (Feigal & Shapiro, 1979; Shapiro, 1989; Antigny et al. 2009). Indeed, more than two decades ago, several studies described the existence of different contributors to mitochondrial dysfunctions in CF; including impairments in calcium homeostasis and the existence of an altered respiratory system (Feigal & Shapiro, 1979; Shapiro et al. 1979; Feigal et al. 1982; Shapiro, 1989). More recently, these same impairments were confirmed in CF (Antigny et al. 2009; Divangahi et al. 2009; Wells et al. 2011; Valdivieso et al. 2012) providing strong evidence for the existence of an impaired bioenergetics metabolism in this patient population.

Patients with CF exhibit reduced skeletal muscle oxidative capacity

There is compelling evidence at the cellular level that oxidative metabolism is diminished in CF. In this regard, several groups have described that patients with CF exhibit lower resting concentrations of ATP (Divangahi et al. 2009; Lamhonwah et al. 2010), which have been linked to a dysfunctional CFTR (Tu et al. 2010). Lower resting ATP coupled with significant reductions in ATP production during exercise (de Meer et al. 1995)

Paula Rodriguez-Miguelez obtained her PhD with International Mention from the University of León and is now performing postdoctoral research at Augusta University. Her research focuses on understanding muscle and vascular contributions to exercise intolerance in cystic fibrosis. Melissa L. Erickson is currently a doctoral student in the Kinesiology Department at the University of Georgia. Her doctoral research focuses on the interaction of exercise and medication use on glucose levels in pre-diabetics. Kevin K. McCully is professor in the Department of Kinesiology and Director of the Exercise Muscle Physiology Laboratory at the University of Georgia. His research focuses on using non-invasive technologies to study skeletal muscle function in people with chronic injuries or illnesses. Ryan A. Harris is currently an associate professor in the Department of Pediatrics and Director of the Laboratory of Integrative Vascular and Exercise Physiology at Augusta University. His research focuses on exploring the interaction between vascular function, exercise capacity, and pulmonary function in CF.
may compromise muscle function and contribute to exercise intolerance. In turn, ATP depletion may also impact the opening–closing cycle and the stability of the CFTR channel (Quinton & Reddy, 1992; Hwang & Kirk, 2013). In addition, mitochondrial complex I, a key respiratory chain protein involved in the synthesis of ATP, is positively regulated by the CFTR protein and its expression is reduced in CF (Shapiro et al. 1979; Dechecchi et al. 1988; Valdivieso et al. 2007; Valdivieso et al. 2012). Additionally, downregulation of the mitochondrial protein CISD1, a modulator of the oxidative capacity of the cell, has been also reported in CF (Taminelli et al. 2008). Different methods have been employed to examine the functionality of mitochondria metabolism in vivo. 31P magnetic resonance spectroscopy (31P-MRS) has been widely used in different populations as a non-invasive technique to assess skeletal muscle oxidative capacity through monitoring the recovery rate after exercise of phosphocreatine (PCr). Evaluations of energetic metabolism with 31P-MRS have documented abnormalities in the PCr recovery time of patients with CF compared to controls (de Meer et al. 1995; Wells et al. 2011). In addition, our group has used near infrared spectroscopy (NIRS) to assess the rate of recovery of skeletal muscle oxidative metabolism of the vastus lateralis in patients with CF (Erickson et al. 2015). The NIRS technology is methodologically similar to 31P-MRS (Ryan et al. 2013), and validation studies have shown strong correlations between NIRS measured rate constants and 31P-MRS rate constants as well as with state 3 respiratory rates from muscle biopsies (Ryan et al. 2014). NIRS offers an accessible, inexpensive and reproducible evaluation of mitochondrial capacity (a combination of mitochondrial function and mitochondrial number). Our findings indicate that patients with CF exhibit a 15% reduction in skeletal muscle oxidative metabolism compared with apparently healthy, demographically matched controls (Erickson et al. 2015). Although the assessment of mitochondrial metabolism with NIRS does not allow the differentiation between a reduction in mitochondrial number and/or mitochondrial dysfunction, our data support previous reports of impaired mitochondrial bioenergetics in patients with CF. It is important to note that, possible vascular manifestations may impact the supply of oxygen to the exercising muscles. Despite the existence of both conduit (Poore et al. 2013) and microvascular (Rodriguez-Miguez et al. 2016) endothelial dysfunction in patients with CF, unpublished data from our lab indicates a similar NIRS response at rest providing evidence that NIRS is unaffected by vasculopathies.

The impact of disease severity on skeletal muscle function in patients with CF

Advancing age is often associated with disease severity and constitutes a key factor in the progression of the CF pathology. Reductions in muscle blood flow as well as changes in muscle fibre type towards an anaerobic metabolism have been closely associated with age-related exercise intolerance in other populations. Accordingly, our group identified a significant inverse relationship between age and skeletal muscle oxidative metabolism in patients with CF, which was not observed in control subjects (Erickson et al. 2015). Bearing in mind that muscle bioenergetics may be reduced in CF by approximately 2.5% per year and the impact that this drop may have on exercise capacity, it is important to consider the role of age in the evaluation of mitochondrial bioenergetics in this specific patient population.

Chronic inflammation, a common phenotype in patients with CF, has also been associated with mitochondrial dysfunction. In particular, the overexpression of the proinflammatory cytokine interleukin-1β, commonly elevated in patients with CF, seems to be involved in both modulation of CFTR expression (Cafferata et al. 2000) and reduction of the mitochondrial complex 1 activity (Lopez-Armada et al. 2006). Although no spontaneous inflammation in CF has been described previously (Becker et al. 2004; Stoltz et al. 2010), prevailing data indicate that an impaired CFTR protein upregulates the expression of nuclear factor κB, which is also directly involved in the reduction of oxidative metabolism with an overall reduction in cellular energy (Remels et al. 2013).

The elevated levels of reactive oxygen species (ROS), a common phenotype observed in patients with CF, also directly impact mitochondrial function. An excessive production of ROS promotes damage in the mitochondrial DNA and disturbs homeostasis within the electron transport chain homeostasis, thereby disrupting oxidative phosphorylation metabolism (Escames et al. 2012). In addition, CFTR knockout mice show a decrease in the expression of peroxiredoxin 6, an antioxidant enzyme also involved in the control of mitochondrial oxidative metabolism (Trudel et al. 2009). Oxidative damage and the associated mitochondrial dysfunction may also result in a disturbed autophagy mechanism: a natural regulatory process to recycle unnecessary or dysfunctional cellular components. In fact, CFTR dysfunction seems to alter autophagy regulation (Luciani et al. 2010), which appears to mediate an important role in the maintenance of mitochondrial oxidative metabolism (Guo et al. 2011).

In summary, data from multiple in vitro and in vivo studies provide compelling evidence to support the existence of mitochondrial dysfunction, impaired mitochondrial bioenergetics and altered skeletal muscle oxidative capacity in patients with cystic fibrosis. The dysfunctional CFTR as well as the elevated oxidative stress and systemic inflammation seem to contribute to the impaired muscle function, all of which may significantly impact exercise capacity and quality of life in CF.

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References


**Additional information**

**Competing interests**

None declared.

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