

PERSPECTIVES

The phosphocreatine–creatine kinase system helps to shape muscle cells and keep them healthy and alive

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An article by O'Connor *et al.* (2008) in this issue of *The Journal of Physiology* significantly expands our knowledge of the role of the phosphocreatine (PCr)–creatine kinase (CK) system in muscle cells. The role of this system in muscle, brain and other tissue with high energy requirements and fluxes has been intensively studied and debated during the last four decades. The main results and current state of art of these studies were recently summarized in a number of chapters of three almost simultaneously published books (Vial, 2006; Wallimann *et al.* 2007; Dzeja *et al.* 2007; Saks *et al.* 2007; Wyss & Salomon, 2007). These studies helped to develop the new paradigm of bioenergetic studies – molecular system bioenergetics, a part of systems biology (Saks *et al.* 2006, 2007).

The important role of the PCr–CK system is based on the metabolic compartmentation of adenine nucleotides and modular organization of energy metabolism – both are system level properties not predictable from properties of isolated components of the cell (Weiss *et al.* 2006; Saks *et al.* 2007). Abundant experimental evidence shows the existence of distinct cellular ATP microdomains (compartments) localized in mitochondria and at the sites of ATP utilization. These are connected by phosphotransfer networks, notably via the PCr–creatine kinase pathway (reviewed by Wallimann *et al.* 2007; Dzeja *et al.* 2007; Saks *et al.* 2007; Wyss & Salomon, 2007). These networks function to bypass and overcome local restrictions on ATP or ADP diffusion and thus perform the important

tasks of both energy supply and metabolic feedback regulation of respiration (Saks *et al.* 2006). This explains many classical observations that while all kinds of cellular work is based on the use of ATP, the total content of ATP in cells has no diagnostic value – contractile function of muscle cells and action potential duration decrease in pathological conditions (hypoxia, ischaemia) at an almost constant total level of ATP but follow changes in PCr; and ATP content itself can be changed by 70% by deoxyglucose treatment of perfused aerobic hearts without changes in contractile function if the PCr–CK system is intact and functional (data reviewed by Saks *et al.* 2007).

This general phenomenon – dissociation of total content of ATP from cell function – is again clearly demonstrated by O'Connor *et al.* (2008). The authors show that it is the PCr–CK system which sustains localized ATP-dependent reactions during actin polymerization in myoblast fusion. Myoblasts treated with exogenous creatine showed enhanced intracellular PCr stores without any effect on ATP levels. This increase in PCr induced myoblast fusion and myotube formation during the initial 24 h of myogenesis. Interestingly, during this time CK-BB became localized and after 36 and 48 h was found to be close to the ends of myotubes. Actin polymerization is critical for myoblast fusion and occurs with involvement of ATP during both the addition of actin monomers to the growing ends of filaments and the dissociation of monomers at the tail (O'Connor *et al.* 2008). It is this localized ATP which is rapidly regenerated by CK-BB at the expense of PCr, and it seems that the formation of these ATP microdomains is a dynamic process during actin cytoskeleton remodelling. O'Connor *et al.* (2008) showed also that local injection of creatine into injured skeletal muscle increased growth of regenerating myofibres from satellite cells via differentiation and fusion of myoblasts. All these results add new insight into the functioning of the PCr–CK system in muscle cells, showing its new role in energy supply for cytoskeletal remodelling. These results may help to better explain the therapeutic effects of creatine supplementation (Wallimann *et al.* 2007;

Brosnan & Brosnan, 2007; Wyss & Salomon, 2007).

The vital importance of ATP in functional microdomains (compartments) connected to the PCr–CK system was also recently well documented in clinical studies by Neubauer's group in Oxford on a large number of patients with heart disease – dilated cardiomyopathy – involving a follow-up study using nuclear magnetic resonance spectroscopy to record the ³¹P-NMR spectra in the heart (Neubauer, 2007). While again almost no differences were seen in ATP content in the healthy control and cardiomyopathic hearts, the mortality rate of patient during the follow-up period correlated with a decrease in the PCr/ATP ratio below 1.6 (Neubauer, 2007). Low PCr/ATP ratios mean decreased regeneration of ATP by the PCr–CK system in microdomains (compartments) which are critically important for function of the heart. These microdomains are localized in myofibrils, near the sarcolemma and the membrane of sarcoplasmic reticulum (Wallimann *et al.* 2007; Saks *et al.* 2006, 2007).

There is now a general consensus among the researchers in muscle and brain energy metabolism that the next challenge and most urgent need is to develop better bioprobes to image metabolic microdomains of ATP, and functional proteomics to identify physical interactions between key proteins responsible for their formation (Weiss *et al.* 2006; Neubauer, 2007; Wallimann *et al.* 2007; Saks *et al.* 2006, 2007). The article by O'Connor *et al.* (2008) published in this issue of *The Journal of Physiology* emphasizes further the importance of this new perspective for research in cellular physiology and bioenergetics.

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