Graduate Studies

Department of Physiology
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Skeletal muscle energetics and remodeling

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Skeletal muscle is a major sink for metabolic fuels and its proper function is energy homeostasis. Alterations in muscle phenotype (mass or composition) are associated with diabetes, cardiovascular disease and obesity. My laboratory is primarily interested in cellular energetics and its regulation. We are focused on how metabolism adapts due to metabolic stress particularly as it relates to metabolic deficiencies and disease states. In these areas there are several broad problems that have not been fully understood.

How is mitochondrial function integrated into cell function and regulated by changes in energy demands? How do cells adapt to changes in functional demands (alter phenotype) over extended time periods? Which cellular processes signal the maintenance and/or transition in adult muscle cell phenotypes? How do muscle stem cells (satellite cells) respond to mechanical and/or metabolic stress?

These questions relate to physiologic signaling of gene expression changes in both healthy and diseased skeletal muscle. Research goals are directed towards understanding cell plasticity and gene expression related to chronic changes in energy requirements (i.e. metabolic substrate availability, altered levels of physical activity) and thus directly applicable to chronic metabolic diseases (diabetes, cardiovascular disease). The preparations primarily used are isolated muscles from transgenic mice where metabolic deficiencies can be created through knocking out enzymes responsible for maintaining ATP free energy. However, in addition a range of other cell systems from cells in culture to intact animals and even human subjects are used. To address these questions a broad range of biophysical techniques including magnetic resonance and optical imaging, molecular biology, DNA array analysis, and viral transfection methods are employed. To date several funded projects are underway in our laboratory including magnetic resonance studies of cellular energetics in cultured insulinoma cells (Fig 1) and fluorescence studies of calcium handling properties in isolated muscle (Fig 2). Finally we use fluorescently tagged muscle stem cells to investigate the role of these cells in muscle during stress induced remodeling (Fig. 3). Because the nature of such studies is highly collaborative, in 2001, the department of Physiology, together with Radiology, entered into the formation of a Molecular Imaging Research Center (MIRC) designed to foster research in the growing field of molecular imaging. Investigators from both departments share common use equipment including 5 magnetic resonance imaging spectrometers (3 for clinical use), computerized tomographs (including a microCT for animals), and optical imaging using near infrared surface tomography. An epifluorescence microscope is available with both imaging and spectrometric capabilities to study cells in culture or isolated preparations.

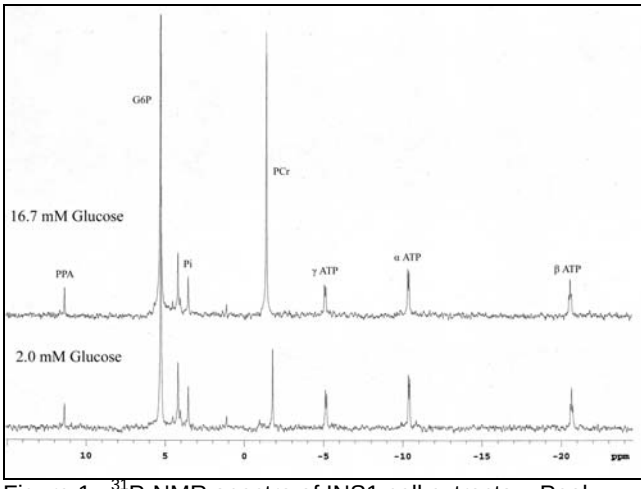

Figure 1. ^{31}P-NMR spectra of INS1 cell extracts. Peak resonances are labeled and are proportional to chemical content.

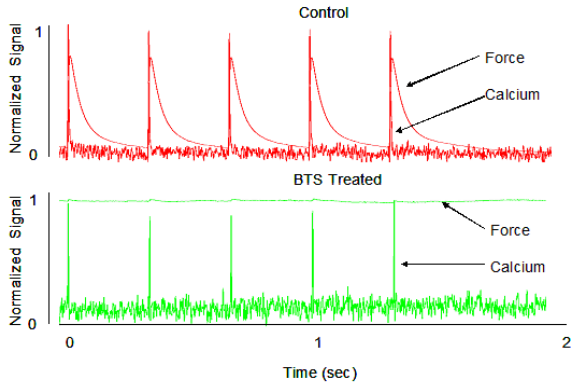

Figure 2. Calcium and force measurements in isolated mouse muscles in absence and presence of a crossbridge inhibitor (BTS). Note loss of muscle force in lower panel.

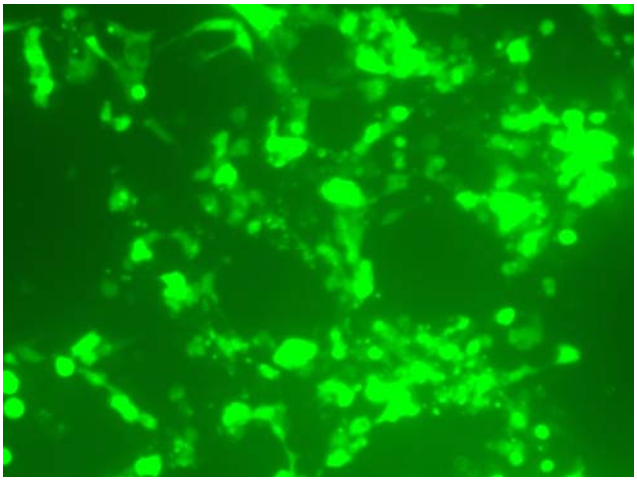

Figure 3. Green fluorescent protein labeled cells for transplantation studies. Cells are transfected with adenoassociated virus.