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Remembering those 'lazy' days – imprinting memory in our satellite cells

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Cellular memory or environmental imprinting is visible across numerous cell types in a variety of conditions. Specifically the *ex vivo* behaviour of isolated cells often replicates aspects of their *in vivo* environment. In other words, if the cells were exposed to a pathological condition *in vivo* they often will continue to present aspects of this condition *in vitro*. Cellular memory is now commonly termed imprinting or, more broadly, epigenetics, in which effects from the environment are transiently marked on the genome and impact the overall phenotype of the cell.

From an experimental perspective, investigators have taken advantage of cellular memory for years, without necessarily understanding that the mechanism was likely to be some form of epigenetics. The epigenetic phenomenon is an extremely powerful effect that allows researchers studying humans to utilize mechanistic and/or reductionist based approaches. An often-overlooked consideration is that isolating satellite cells from a muscle biopsy allows the investigator to take a small sample ($\sim$100 μg) that often yields only a few measures and expand the satellite cells in culture to allow for numerous different measures. However, the critical caveat that is necessary for this expansion-based approach is that the satellite cells resemble their *in vivo* phenotype when differentiated into myotubes. Dr. Joe Houmard and colleagues have elegantly shown that by isolating satellite cells from muscle biopsies it is possible to assess the inherent metabolic programme of cells from lean and severely obese patients (Boyle *et al.* 2012; Houmard *et al.* 2012). Specifically, they have demonstrated that myotubes from severely (BMI $>$ 50) obese individuals exhibit insulin resistance and reduced fatty acid oxidation compared to myotubes from lean subjects, regardless of which muscle was biopsied (Houmard *et al.* 2012). Most importantly this recapitulates what this group found *in vivo*. Collectively, the data derived from this approach demonstrates a powerful way to address metabolic aspects of skeletal muscle, independent of neural or endocrine influence, from a wide array of subjects.

In this issue of *The Journal of Physiology*, Green *et al.* (2013) describe a similar approach in which satellite cells were isolated from sedentary or physically active individuals. Myotubes derived from these satellite cells were characterized by their metabolic response to *in vitro* palmitate (PA) exposure, a method known to induce powerful metabolic insults to any cultured cell. Intramyocellular lipid (IMCL) concentrations of the myotubes increased in response to the PA treatment in both groups, but other metabolic responses differed between groups. For example, the myotubes from the active group exhibited indications of being more insulin sensitive after PA exposure than the cells isolated from the sedentary group (Green *et al.* 2013). Further, the IMCL accumulation was associated with altered responses in acetyl co-carboxylase (ACC) in the active group but not the sedentary group. This is interesting as ACC is a critical regulator of lipid utilization via its ability to allosterically regulate fatty acid movement into the mitochondria. Which raises the question of whether palmitate oxidation and mitochondrial function differ between groups? PA treatment also induced a measurable increase in serine phosphorylation of insulin receptor substrate-1, independent of an inflammatory response in the sedentary group, suggesting that an inflammatory response is not obligatory for a lipid-based induction of insulin resistance. In obesity models, it is often difficult to determine whether insulin resistance is the direct result of the lipid exposure or a result of corresponding inflammation as these effects often occur simultaneously. Finally, another fascinating concept to consider is that the subjects in the sedentary group were relatively healthy with average fitness, while the active group presented with above-average (but not elite) fitness. Thus, even moderate differences in fitness translated into significant differences in the metabolic responses of the differentiated satellite cells. It is interesting to note that the effects of physical fitness are evident (or remembered) in the isolated cells on a culture dish.

Although the *ex vivo* expansion and use of satellite cells is a powerful experimental model, it is not without weaknesses that should be considered by the investigator. For example, it is often forgotten that myotubes express an overall phenotype that is more consistent with developing muscle than it is with adult muscle. Myotubes are dominated by embryonic myosin expression instead of adult myosin (Beylkin *et al.* 2006), and the insulin-induced glucose response of cultured myotubes lacks the equivalent magnitude seen in adult muscle. This does not preclude an investigator from using the approach; it just means that the investigator must consider the unique differences that are inherent in these approaches when addressing the outcomes of the experiment.

Using this model has allowed Green *et al* to provide intriguing evidence that the fitness status of a subject from which the cells are derived will affect the cells' behaviour in culture. Specifically, myotubes from active individuals were better protected from the lipo-toxic challenges with PA than myotubes isolated from sedentary subjects. Although, the utilization of this single fatty acid exposure is not something typically seen *in vivo*, the data nonetheless suggest that regular physical activity enables cells to retain a 'memory' that protects them from lipid-based exposures. Thus, these investigators have reported an important finding indicating that it is critical to include physical activity status as a key aspect of the environment, even after removing the cells from the subject.

References

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