Metabolism, Muscle, Oxygen & Work:

Molecules in Motion

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Did you know that a blue crab's backfin muscle grows in the same manner as human muscle? Muscle tissue grows by increasing the size of individual muscle cells rather than their number. This developmental pattern means that juvenile blue crabs have muscle cells that are very similar in size to those of a small child. However, as a blue crab grows to adulthood, its body mass increases more than 3,000 times. If humans grew like this, a 7-pound newborn would weigh 21,000 pounds as an adult! Since the crab's muscle fibers grow as it grows, adult blue crabs have muscle cells that are about 20 times larger than adult human muscle cells. This characteristic of blue crab muscles makes them important to studies that will ultimately aid our understanding of the function of cells in general, including human cell function.

My students and I in the department of biology and marine biology at UNCW are investigating the unique properties of muscles from marine organisms to better understand how processes at the biochemical, cellular, tissue and whole-animal level interact to affect animal function. What can the large muscle cells of blue crabs teach us about cell function in humans? To answer this question, we must first consider how molecules travel from place to place inside cells.

Molecules React, But They Move Around, Too

Most of what we know about biochemistry and cell function is derived from a century of carefully controlled laboratory experiments conducted using chemical solutions in test tubes. Research of this type has been extremely successful, yielding roadmaps of highly complex metabolic pathways, as well as contributing to our understanding of the molecular basis of many diseases.

Recent technological advances have allowed scientists to expand this approach. Today, noninvasive techniques allow researchers to study biochemistry in living cells. These approaches offer a more accurate picture of metabolism that is often quite different from the traditional view.

For example, the classical depiction of metabolic pathways is that of a series of molecules connected by arrows. The arrows represent the conversion of one molecule to the next in the pathway. This visualization represents test-tube biochemistry very well. However, to be true to living cell processes, the arrows need to also represent the movement of the molecules from place to place within the cell.

Molecules move about in cells by a process known as diffusion (one of Albert Einstein's theories). Like people walking through a forest in the dark, randomly changing direction every time they bump into a tree, so do diffusing molecules in a metabolic pathway "find" their way by bouncing off the cellular structures they encounter (which is why diffusion is sometimes referred to as a "random walk"). Therefore, a complete understanding of metabolism in living cells must include both the chemical conversion (reaction), as well as the movement of molecules to and from the reaction sites (diffusion). Accounting for both of these processes is known as a reaction-diffusion analysis, a familiar approach to chemical engineers but relatively new to biologists.

In the past, one of the difficulties of studying processes such as molecular motion in living cells is that it has been hard to measure intracellular events without disrupting the cells. Today, we can apply a host of methods in our research not available to us just a few years ago to look inside living cells (or even within living animals). Noninvasive techniques such as laser scanning confocal microscopy and nuclear magnetic resonance (NMR), which are a family of procedures that includes magnetic resonance imaging (MRI) are now widely available to biologists.

For example, using a special application of NMR, our lab demonstrated that the rate at which molecules move in living muscle depends on the direction of movement within the cylindrically shaped cells. This is important because muscle contraction depends on molecules moving across muscle cells, and it turns out that molecules move across muscle cells at about half the rate as they do when they move along their length.

Muscle Diversity in Marine Animals

To understand how properties of living cells, such as molecular motion, impact cell and organism function, we need to know the rules that govern cellular design. That is, why are cells built in the way that they are? And how might environmental factors and/or the presence of disease alter cellular design and function? August Krogh was a famous physiologist who developed the premise that for every biological question, there is an ideal organism for study. There-

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Undergraduate students in our lab work side-by-side with graduate students and doctoral (Ph.D.) candidates.

clockwise from bottom left: **Nicole Zane, Matt Weissenbach, Al Nyack, Dr. Steve Kinsey, Jeff Overton, Kristin Hardy, Jennifer Berting and Ana Jimenez.**

fore, in order to find answers to these questions, we apply "the August Krogh Principle," and we study marine animals.

Marine animals offer a tremendous diversity of muscle form. Studying the variety of muscle types in marine animals provides clues as to the diverse ways nature has solved problems common to all organisms. Since our research interest is molecular movement, it makes sense to examine cells where the movement of molecules is expected to be an important component of metabolism. And so, we return to the backfin muscle cells of the blue crab. More famous among humans for their culinary appeal, these muscle cells control the paddle-like legs that power the crab's sideways swimming behavior, making them metabolic machines critical to the crab's survival.

In an adult blue crab, the backfin muscle cells can exceed 1/32 inch in diameter and may be more than 1 inch long. That may not sound big, but, because of the random walk nature of diffusion, it takes a molecule 400 times longer to diffuse across a blue crab cell than across a human cell. Since the juvenile crab has cells of more humanly dimensions, we have a natural experiment. Monitoring muscle metabolic and contractile properties as the blue crabs grow (and cellular distances get larger), we can easily observe how cell design and function are impacted by molecular motion.

Of Mice and Men (and Women)

While blue crabs and other marine organisms can tell us a great deal about some of the basic rules that govern cell design, our ultimate goal is to be able to apply these rules to human physiology and health. To observe a closer parallel of human physiology, we also examine molecular motion in mice, the most studied animals in biomedical research.

Here, we take advantage of a genetic model of exercise performance first developed at UNCW by Dr. R. Dale McCall of the department of anthropology. Dr. McCall and his students discovered that in certain strains of mice, only two genes were principally responsible for dramatic differences in the capacity for endurance exercise. Significantly, these studies were conducted under conditions of simulated high altitude, where oxygen availability is drastically reduced and intake compromised.

Since poor oxygen supply is associated with many diseases, including heart disease, this research potentially has broad applications and benefits for human health and performance. Our reaction-diffusion analyses are very useful and applicable in understanding how oxygen gets from the atmosphere to the inside of the muscle cells where it can be used to generate energy. The work of Dr. McCall and his students is, therefore, highly relevant to our investigations.

Putting It All Together

The ultimate goal of our research is to be able to predict how cells will respond to different conditions. To accomplish this, we need mathematical simulation models of reaction-diffusion processes in cells. Our lab at UNCW is fortunate to have received grants from the National Science Foundation to work collaboratively with Dr. Bruce Locke of Florida State University's department of chemical and biomedical engineering to develop these models.

Dr. Locke and his students work with my students and me to develop computer models of the muscle cells that we study to compare measured data to theoretical predictions. If experiments agree with predictions, that probably means we have a good understanding of the metabolic process under examination. We have collaborated with Dr. Locke's lab for several years, and together we have been able to advance our research at both of our institutions and address questions that neither group could have done alone.

Our understanding of how metabolism works in living cells continues to grow, and we are frequently surprised by our findings. At times, those surprises have caused us to discard some dearly held hypotheses. It is these surprises, however, that force us to take up new paths that may lead to greater advances in the field. Finally, perhaps our greatest contribution to society is the ever-growing number of highly scientifically and technically trained students whom we graduate – their contributions when they leave UNCW are also products of our research.

FOR FURTHER READING OR RESEARCH ON THIS TOPIC:

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