Zebrafish to shed light on human mitochondrial diseases

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Zebrafish can now be used to study COX deficiencies in humans, a discovery that gives scientists an unprecedented window to view the earliest stages of mitochondrial impairments that lead to potentially fatal metabolic disorders, according to researchers at the University of Oregon.

COX deficiencies refer to a breakdown of cytochrome coxidase, an enzyme located in the mitochondrion of every cell. Mitochondria are crucial cellular workhorses that provide chemical energy. Research of the deficiency has been stymied by a lack of model organisms, with mice being introduced as the first model by Japanese researchers just seven years ago.

COX involves multiple proteins and assembly factors, and deficiencies of any one of them can negatively affect metabolic tissues, including the brain, muscle and eyes. Deficiencies during the prenatal period are considered to be a potential cause of miscarriages and have been led to prenatal screenings, but scientists still don't understand the metabolic requirements of tissues and organs during early development.

The case for zebrafish (Danio rerio) as an alternative research model is described in a paper posted online ahead of regular publication by the *Journal of Biological Chemistry*. The comprehensive UO study, led by doctoral student Katrina N. Baden, could speed research and point to specific targets to test potential drug therapies, said co-author Karen Guillemin, a professor of molecular biology and member of the UO

Institute of Molecular Biology.

"Mitochondrial impairments are emerging as important in many human diseases, but there have been few models for understanding exactly what is happening during the early development of the diseases," Guillemin said. "The use of mice is limited, because knocking out protein expression in mice mitochondria to mimic human-disease states results in large numbers of deaths in utero. Therefore, the symptoms that researchers have wanted to study have not been assessable in mice."

Baden, a veterinarian, performed several experiments, using RNA-blocking reagents known as morpholinos to reduce gene expression of both a critical COX subunit and Surf1, an assembly-factor protein that when mutated can lead to Leigh syndrome, a severe neurological disorder. She targeted a variety of proteins, alone and in combination, and then added back components to rescue each deficiency. Normal COX activity declined as much as 50 percent in the experimental conditions and resulted in developmental defects in endodermal tissue, cardiac function and swimming behavior in the zebrafish.

"The unique characteristics of zebrafish make them an ideal model for studying the effects of mitochondrial deficiencies on early development," said Baden, who earned her doctorate in July and is now the veterinarian at the UO-based Zebrafish International Resource Center. "Because they develop outside of a uterus and are transparent in early stages, I was able to visualize the effects that molecular alterations have on cell biology, nervous system development, cardiac function and fish behavior."

The external and transparent embryo, Guillemin said, will allow scientists to create specific deficits that mirror those in humans. "The transparency of the embryo will let us see primary defects, what happens in the earliest stages, rather than having to settle for seeing secondary

downstream defects later in the disease state," she said.

"Different tissues respond differently to specific losses in mitochondria."

Baden and Guillemin said that the use of zebrafish will improve scientific understanding of the mechanisms of mitochondrial associated pathology in people and speed the identification of new treatments for mitochondrial diseases.

Source: University of Oregon

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