SOUTHWESTERN NEWS

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UT SOUTHWESTERN SCIENTIST HELPS IDENTIFY GENE THAT MAY LEAD TO TREATMENTS FOR SLEEP DISORDERS

DALLAS – Nov. 21, 2002 – A researcher at UT Southwestern Medical Center at Dallas has helped uncover key information in the treatment of sleep disorders by identifying a gene that controls the rhythmic behavior of animals.

Dr. Jin Jiang, assistant professor in the Center for Developmental Biology and of pharmacology at UT Southwestern, and researchers from Rutgers University have learned through studying fruit flies (*Drosophila melanogaster)* that the gene *slimb* is a vital component in the regulation of the circadian clock – the brain's day-night mechanism that allows humans and other organisms to anticipate daily environmental changes and then tailor behavior like sleeping, waking and eating to the appropriate time of day.

"*Slimb* is one of the newest clock genes being identified, and we believe it is also involved in human clock regulation," said Jiang, co-author of the study, published today in *Nature*. "We've only demonstrated the clock regulation in insects so far, but given the conservation in core clock mechanisms between insects and humans, I'm confident this gene is important in human clock regulation."

Researchers previously have identified genes in the brain that drive the circadian clocks in humans, fruit flies, mice and other species. Fruit flies have long been used as a model organism to uncover the molecular basis of the circadian clock. Researchers isolated the first identified clock gene, *period (per*), about 30 years ago. Jiang identified *slimb* about five years ago while screening genes that control fruit flies' physical development.

"You would think the genomes of fruit flies and humans are totally different, but in the regions that control metabolism, behavior, organ development and other functions, they are quite similar," said Jiang. "Almost 70 percent of human-disease genes have counterparts in fruit flies – including the clock genes in the brain."

Clock genes oscillate in a 24-hour cycle that ultimately leads to the day-night change of behaviors. It has been known for years that *per* protein level goes up and down each cycle, but how the leveling is regulated was unknown.

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The new study, Jiang said, demonstrates that *slimb* acts in conjunction with another clock gene, *doubletime (dbt)*, to control the oscillation of *per*. By altering the activity of *slimb* in the fruit fly brain, the circadian clock can be accelerated, decreased or disarrayed, he said. When *slimb* activity is reduced, the circadian clock is lengthened, and vice versa. If *slimb* activity is eliminated, the clock operates at random because there is no oscillation.

Dr. Luis F. Parada, director of the Center for Developmental Biology and professor of cell biology, said Jiang's research helps in the overall understanding of genetic disorders and cancers.

"This research exemplifies the power of using a primitive organism like a fruit fly in dissecting signaling pathways that are relevant and related to the genes in human beings and that we know are involved in both the developmental biology of human beings as well as in cancer," said Parada, who also is director of the Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration.

"These signaling pathways are like a switch on a wall. You might assume it turns on a light, but it might also turn on a fan, turn off a heater or turn on an intercom. Between *Drosophila* and humans, what is between the switch and the output is conserved, even if the output is not. In this particular case, however, Jiang and colleagues provide a compelling example of what may turn out to be not only conservation of the wiring but also of the outcome."

This discovery may lead to the development of drugs that speed up or slow down the circadian clock, Parada predicted. Sleep disorders affect 70 million Americans, according to the National Center on Sleep Disorders Research.

"It's a long process from basic research to clinical applications, but each step definitely helps," said Jiang. "We need to have a complete picture of how the circadian clock works by identifying every single molecule involved."

Jiang collaborated with two Rutgers University researchers: Hyuk Wan Ko, principal investigator, and Dr. Isaac Edery, senior author.

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