Scientists discover key step for regulating embryonic development

April 22 2010

Deleting a gene in mouse embryos caused cardiac defects and early death, leading researchers to identify a mechanism that turns developmental genes off and on as an embryo matures, a team led by a scientist at The University of Texas M. D. Anderson Cancer Center reported today in *Molecular Cell*.

"Our study focused on regulation of two genes that are critical to the healthy development of the heart, but many other genes are regulated in this way," said senior author Edward T.H. Yeh, M.D., professor and chair of M. D. Anderson's Department of Cardiology. "This novel pathway marks an advance in our understanding of how developmental genes are turned on and off."

All cells in an embryo contain the same DNA. Different genes are turned off and on in different cells at different times to form specific tissues and organs as the embryo develops. This gene regulation is accomplished by epigenetic processes that control gene expression without altering DNA. Instead, epigenetic processes attach chemical groups to genes or to histones, proteins that are intertwined with DNA to form chromosomes, to activate genes or to shut them down.

"Our findings provide a new window through which to look at epigenetic control," Yeh said, "and how epigenetics and development are unexpectedly tied together by the SUMO/SENP2 system."

The key actors are members of two tightly associated families of

proteins that Yeh and colleagues discovered and continue to study. The first, Small Ubiquitin-related Modifier, or SUMO, attaches to other proteins to modify their function or physically move them within the cell (SUMOylation). The second, Sentrin/SUMO-specific protease 2, or SENP2, snips SUMO off of proteins (de-SUMOylation).

This line of research started when Yeh and colleagues knocked SENP2 out of mouse DNA and found that the embryos died at about day 10. Their hearts had smaller chambers and thinner walls. Through a series of experiments, the team worked backward from this observation to show:

1. A group of proteins called the polycomb repressive complex 1 (PRC1) that silences genes must first bind to a particular methylated address on a histone and,

2. A key component of the complex must be SUMOylated to make this connection, which results in

3. the silencing of Gata4 and Gata6, genes that are essential for cardiac development.

4. In early development, SENP2 works as a switch to turn on Gata4 and Gata6

"When SENP2 is turned on, it peels SUMO off of PRC1, which then falls off the histone, and when that happens, the lock is removed and genes are transcribed," Yeh said. Gata4 and Gata6 are free to properly develop the heart.

In short, SUMO helps the PRC1 complex repress genes, and SENP2 reverses this repression, allowing gene transcription and expression.

"By understanding how development unfolds, we can better control this process, which includes cell proliferation and organ development," Yeh said. "This will help us to better understand cancer.

"SUMO and SENP are important in cancer development, neurological diseases and heart development. Everything under the sun can be regulated by this system," Yeh said. "Here we've established a new role for SUMOylation, mediating the interaction between protein and protein methylation in epigenetic regulation."

Provided by University of Texas M. D. Anderson Cancer Center