SOUTHWESTERN NEWS

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EMBARGOED FOR NOON CST, OCT. 12, 2000

UT SOUTHWESTERN RESEARCHERS DISCOVER LINK BETWEEN REGULATORY PROTEIN AND INFERTILITY

DALLAS – Oct. 12, 2000 – The absence of the protein called heat shock factor 1 (HSF1) in females may contribute to infertility, researchers at UT Southwestern Medical Center at Dallas report in today's issue of *Nature*. They believe this may explain why a number of human in vitro fertilizations fail.

Drs. Ivor Benjamin and Elisabeth Christians, who use "knockout mice" – mice with a specific gene deleted, in this case HSF1 protein – in their collaborative research, investigated why females were infertile while the males were fertile. HSF1 is a regulatory protein and stress-response factor that controls the expression of several genes, termed heat shock proteins, and is required for the development of placenta in mice.

"Our rationale to create mice lacking the regulatory HSF1 was to develop an experimental model to assess the direct relationship involving the stress proteins and physiological health and pathological states," said Benjamin, associate professor of internal medicine. "We knew that it (HSF1) was involved in operating a family of genes called stress proteins especially after exposure to elevated temperatures or oxidative stress. What was not known was whether or not this factor was needed under nonstressed, or normal, physiological conditions."

These unknown factors triggered Benjamin and Christians, assistant professor of internal medicine, to determine the specific requirement of this protein in their study.

Using their knockout mice, Benjamin and Christians discovered that after fertilization, the embryos did not develop properly beyond the zygotic stage.

"The research provides the basis for what may cause infertility," Christians said.

In addition, the researchers discovered that the protein must be expressed in the female for normal development. Even if the male expressed two HSP1 proteins, development was altered, Benjamin said.

"It is essential that the female has at least one copy of the protein. In instances where two copies may come from the male, development is blocked or arrested soon thereafter," he said. "These results for the first time indicate that maternal HSF1 expression plays a novel role for reproductive success, and support the notion that this factor serves as a master regulator of multiple physiological events, many of which are not commonly viewed as 'stressful' conditions. The surprise was that this regulatory protein has multiple functions which are not directly related to the control of classical stress proteins."

In an earlier study published in the October 1999 issue of *The European Molecular Biology Organization Journal*, Benjamin and other investigators discovered that HSF1 was required for development of placenta in mice. The regulatory protein is also required during postnatal development and appears to play a role in the normal growth of an organism after birth, Benjamin said. Earlier tests also showed that the male offspring lacking HSF1 were fertile, and female mice lacking the protein were sterile.

The researchers hope that their findings will stimulate other researchers to explore abnormal HSF1 proteins as a possible cause of post-fertilization abnormalities.

Sylvia Thomas, research associate in internal medicine at UT Southwestern, and Alberta Davis of Alcon Laboratories also contributed to this study.

The National Institutes of Health and National Bank of Belgium funded the research.