Research team disputes evidence of new egg development in mammal ovaries

July 10 2012, by Bob Yirka

(Medical Xpress) -- Back in February, a team of researchers led by Jonathan Tilly published a paper in *Nature Medicine* describing new work that they said backed up research done in 2004 (resulting in a paper published in the journal *Nature*) that claimed to have debunked the "myth" that female mammals, including humans, produced all the eggs they ever would while still developing in the womb. Now, new research by another team, this one led by Kui Liu, claims that the results obtained by Tilly and associates was flawed and that there is still no evidence to suggest that women produce more eggs later on in life. In their paper published in the *Proceedings of the National Academy of Sciences*, the team says that the results of the research conducted by Tilly et al were wrong because the proteins they searched for on the surface of stem cells exist only inside the cells and thus couldn't be found by the method they used.

The whole argument has come about as research has shown that mammal ovaries have stem cells in them that many argue, should be able to develop into human embryos. Unfortunately, it's almost impossible to test this idea because to do so would involve harming ovaries in otherwise healthy women and dealing with the development of an actual egg that could potentially develop into a live human being simply for test purposes; something that cannot happen. Thus, researchers have been constrained by available test subjects and material. In their research, Tilly and his team were able to obtain whole ovaries from healthy women undergoing sex change operations. In performing research on those specimens, Tilly and his team report that they had found evidence

of stem cells growing into eggs. But there the research had to stop for ethical and/or moral issues.

In looking at the research done by the Tilly group, the new team said the technique they'd used (employing antibodies that recognize DDX4, a protein found in reproductive cells) wouldn't work because the proteins are believed to only exist inside of cells where the antibodies wouldn't be able to find them. So, instead they performed the same experiment as described by Tilly, et al, on a breed of mice that have reproductive cells that glow one color under normal conditions then change color if the DDX4 gene is switched on. They report that none of the cells divided or produced eggs.

In responding to the new research, Tilly has said that the DDX4 protein does in fact exist on the surface of cells and that he believes the findings he and his team reported still stand, leading observers to conclude that more research still needs to be done; first to determine if DDX4 does actually exist on the surface of stem cells found in mammalian ovaries, and then, if new eggs come about as a result. Until then, it would appear to be premature to declare one side right and the other wrong.

More information: Experimental evidence showing that no mitotically active female germline progenitors exist in postnatal mouse ovaries, *PNAS*, Published online before print July 9, 2012, doi: 10.1073/pnas.1206600109

Abstract
It has been generally accepted for more than half a century that, in most mammalian species, oocytes cannot renew themselves in postnatal or adult life, and that the number of oocytes is already fixed in fetal or neonatal ovaries. This assumption, however, has been challenged over the past decade. In this study, we have taken an endogenous genetic approach to this question and generated a multiple fluorescent

Rosa26rbw/+;Ddx4-Cre germline reporter mouse model for in vivo and in vitro tracing of the development of female germline cell lineage. Through live cell imaging and de novo folliculogenesis experiments, we show that the Ddx4-expressing cells from postnatal mouse ovaries did not enter mitosis, nor did they contribute to oocytes during de novo folliculogenesis. Our results provide evidence that supports the traditional view that no postnatal follicular renewal occurs in mammals, and no mitotically active Ddx4-expressing female germline progenitors exist in postnatal mouse ovaries.