A story about FXPOI: inclusions, poly-glycin, and ovulation

In case women cease menstruation before the age of 40, this is called premature ovarian insufficiency (POI). This happens to about 1% of the women in the normal population. For women that carry an FMR1 premutation this is 20%. In addition, a proportion of the women with a premutation still cycling show hormonal profiles indicative of ovarian dysfunction. These women have fragile X-associated primary ovarian insufficiency (FXPOI). The FMR1 premutation is a stretch of CGG repeats, which in unaffected individuals has an average of about 30 units. In case this stretch of CGG repeats expands to 55-200 units we name this a premutation. Although this premutation is the most common genetic cause of POI, very little is known about the underlying mechanisms involved.

The FMR1 premutation is also associated with the late-onset neurodegenerative disorder fragile X-associated tremor/ataxia syndrome (FXTAS). We have used our expertise in studying the effects of expanded CGG repeats related to this disorder, to further understand what might causing FXPOI.

For FXTAS the theory is that is caused by the presence of the CGG repeat in the RNA directly, or by the repetitive poly-glycine containing peptide/protein which is the product of this CGG RNA. This poly-glycine protein has only recently been identified and is found in inclusion bodies which are characteristic for FXTAS patients. These inclusion bodies containing the poly-glycine protein are found throughout the brain of FXTAS patients, but also in non-CNS tissues and organs. Therefore we assumed that these inclusion bodies with the poly-glycine protein might also be present in the ovaries of women with FXPOI. Indeed, we were able to identify those inclusion bodies in ovarian tissue of a woman with FXPOI. This suggest that the same mechanisms may play a role in FXPOI as in FXTAS.

We further studied FXPOI using a mouse model carrying an expanded premutation CGG repeat. Also the ovaries from these mice contain the inclusion bodies. Closer examination of these mouse ovaries showed that composition of the follicle pool is quite normal. At different stages of follicle development no obvious differences were found due to the presence of the expanded CGG repeat, except for a reduced amount of corpora lutea or yellow bodies, which are a sign of recent ovulation. It is often thought that women with FXPOI cease menstruating early because they have a smaller number of follicle to start with or that they’re reserve is exhausted quicker. Our results contradict these thoughts and point towards a problem in ovulation rather than problems with the follicle reserve or follicle maturation.

Our results also suggest that the cause of the problems with ovulation might be caused by something outside the ovaries. Ovulation is regulated by hormones produced elsewhere in the body, including the pituitary gland. We could show that both in our mice and in a human premutation pituitary samples the same poly-glycine positive inclusion bodies are present. Further research will have to resolve the question whether these inclusion bodies are the cause of the ovulatory problems and of FXPOI and what the exact role of the poly-glycin protein in this process

is.

In summary our study provide in two major new insight: 1) FXPOI seems to be caused by a problem in ovulation and 2) there seems to be a role for the poly-glycin protein.

Renate K. Hukema
Department of Clinical Genetics, Erasmus MC Rotterdam
The Netherlands

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