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Follicle loss and PTEN/PI3K/mTOR signaling pathway activated in LepRb-mutated mice

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Context
Leptin and its receptors (LepR) play an important role in female reproduction. In the downstream pathways of LepR, phosphoinositol-3-kinase (PI3K)/protein kinase B (Akt)/ mammalian target of rapamycin (mTOR) took part in primordial follicle activation. The phosphatase and tensin homolog deleted on chromosome 10 in humans (PTEN) is a main negative regulator of PI3K pathway. A PTEN inhibitor and PI3K activator could activate primordial follicles from dormancy.
Objective
Female mice (Y123F) with substitution mutations introduced through homologous gene targeting, replacing the 3 tyrosine (Y) residues, Tyr985, Tyr1077 and Tyr1138 with phenylalanine (F), could induce infertility. This study aimed to describe the reproductive alteration in the LepR mutated mice and to explore its mechanism.
Methods
Mice?Patients?
Adult heterozygous male and female Y123F mice were raised in an animal care facility of Obstetrics and Gynecology Hospital, Fudan University.
Intervention(s)
Fetus mice were delivered, and the female ones were genotyped by PCR analysis of toe/tail-tip DNA at age 4 weeks, before grouped into homozygous (HOM) Y123F mice and WT littermates, each group being composed of 10.
Main Outcome Measure(s)
At age of 10 weeks, blood was collected for anti-mullerian hormone (AMH) detection before all mice were sacrificed. We compared the reproduction characteristics in the female Y123F HOM mice and WT littermates, analyzing the phosphorylation of downstream molecules of LepR, Akt/ mammalian target of mTOR, PTEN and insulin receptor substrate (IRS) in the ovaries.
Results
The results showed that 10-week old female Y123F HOM exhibited no reproductive periods, declined AMH levels in the serum and ovaries, reduced primordial follicles, primary follicles, secondary follicles, antral follicles and hardly no corpus lutea (all $P < 0.05$). The phosphorylation of downsream Akt, mTOR, p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E binding protein-1 (4E-BP1) of LepR were all elevated in the ovaries of the mutated female mice. They also presented a decreased phosphorylation of IRS-1, IRS-2, and PTEN, and a strengthened phosphorylation of Forkhead box O-3a (FOXO-3A) in the ovaries, when compared with WT mice.

Conclusions

LepRb mutation could result in follicle loss and activation of PTEN/PI3K/Akt/mTOR pathway in adult female mice, independent of the insulin signaling pathway.

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