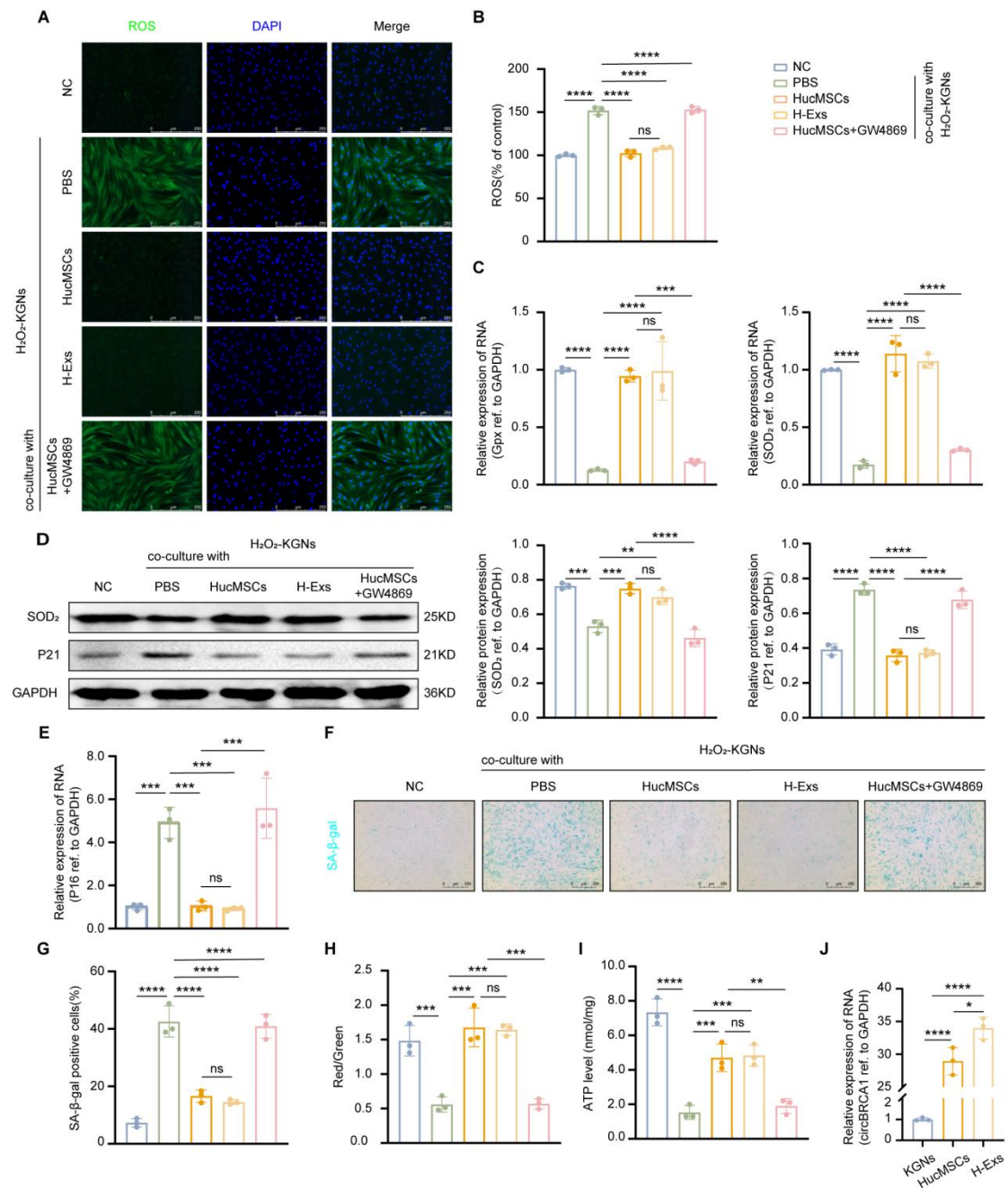
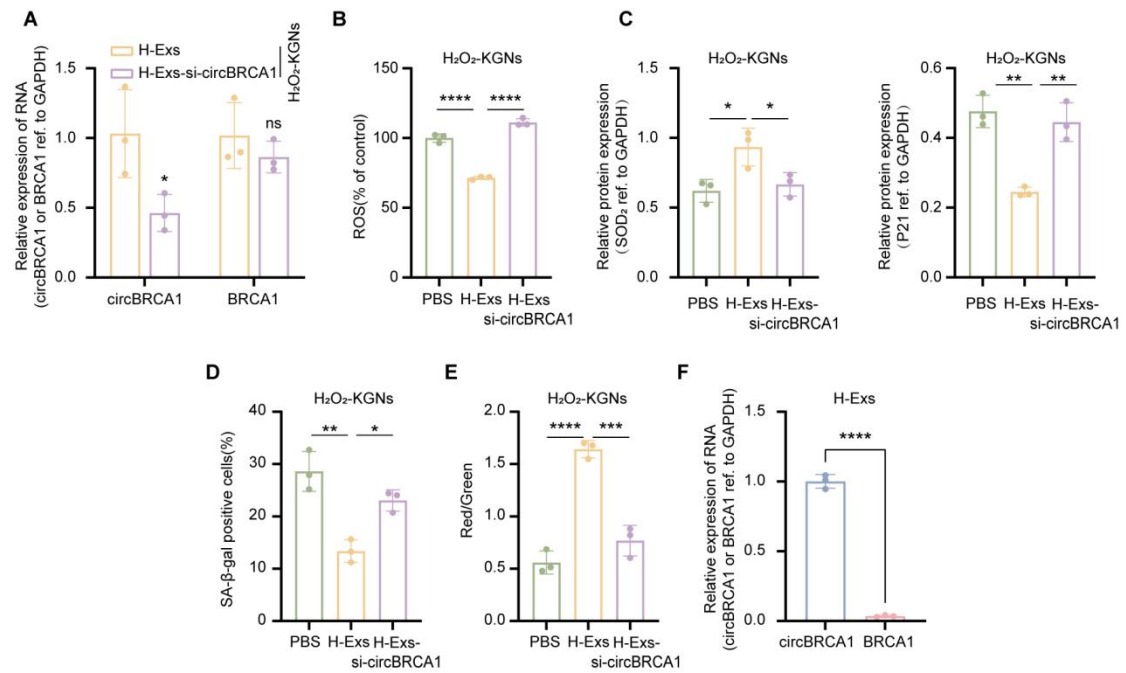


Fig.S1



**S1. H-Exs repair the oxidative damage in KGNs.** A-B The ROS levels were detected by DCFH-DA staining. Green: DCFH-DA staining; Blue: nuclear staining. (scale bar = 50  $\mu$ m) C Relative expression levels of SOD<sub>2</sub> and Gpx were determined by RT-qPCR. D Western blot analysis revealed the expression levels of SOD<sub>2</sub> and P21 in KGNs. E Relative expression levels of P16 were determined by RT-qPCR. F-G Senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) staining. Senescent cells were stained blue. (scale bar = 100  $\mu$ m) H Fluorescence intensity statistics of the JC-1 staining. I Statistical analysis of ATP level. J Relative expression level of circBRCA1 in H<sub>2</sub>O<sub>2</sub>-KGNs co-culture with PBS and H-Exs.

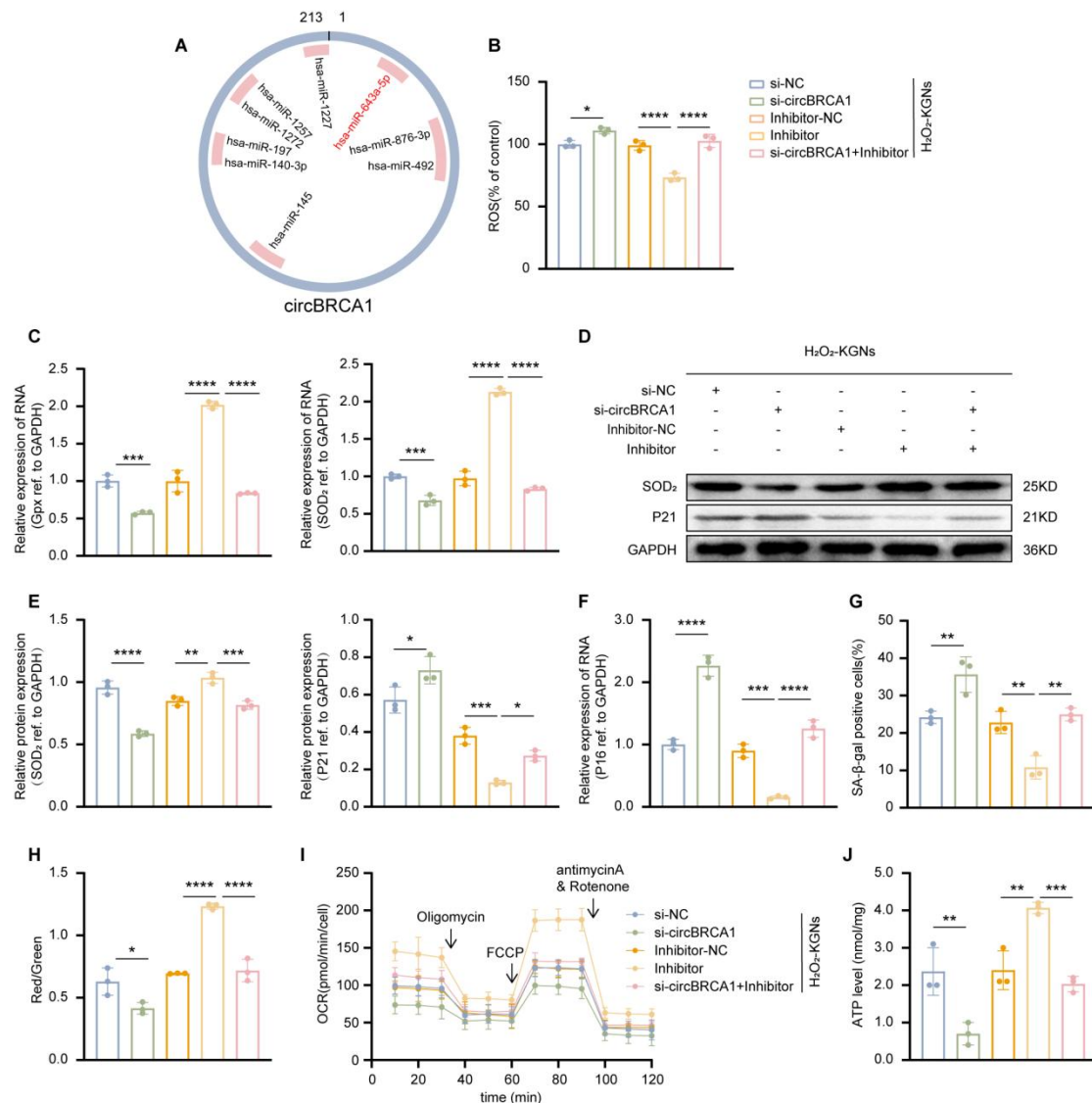
Fig.S2



## S2. H-Ex-released circBRCA1 is the key for repairing oxidatively damaged KGNs.

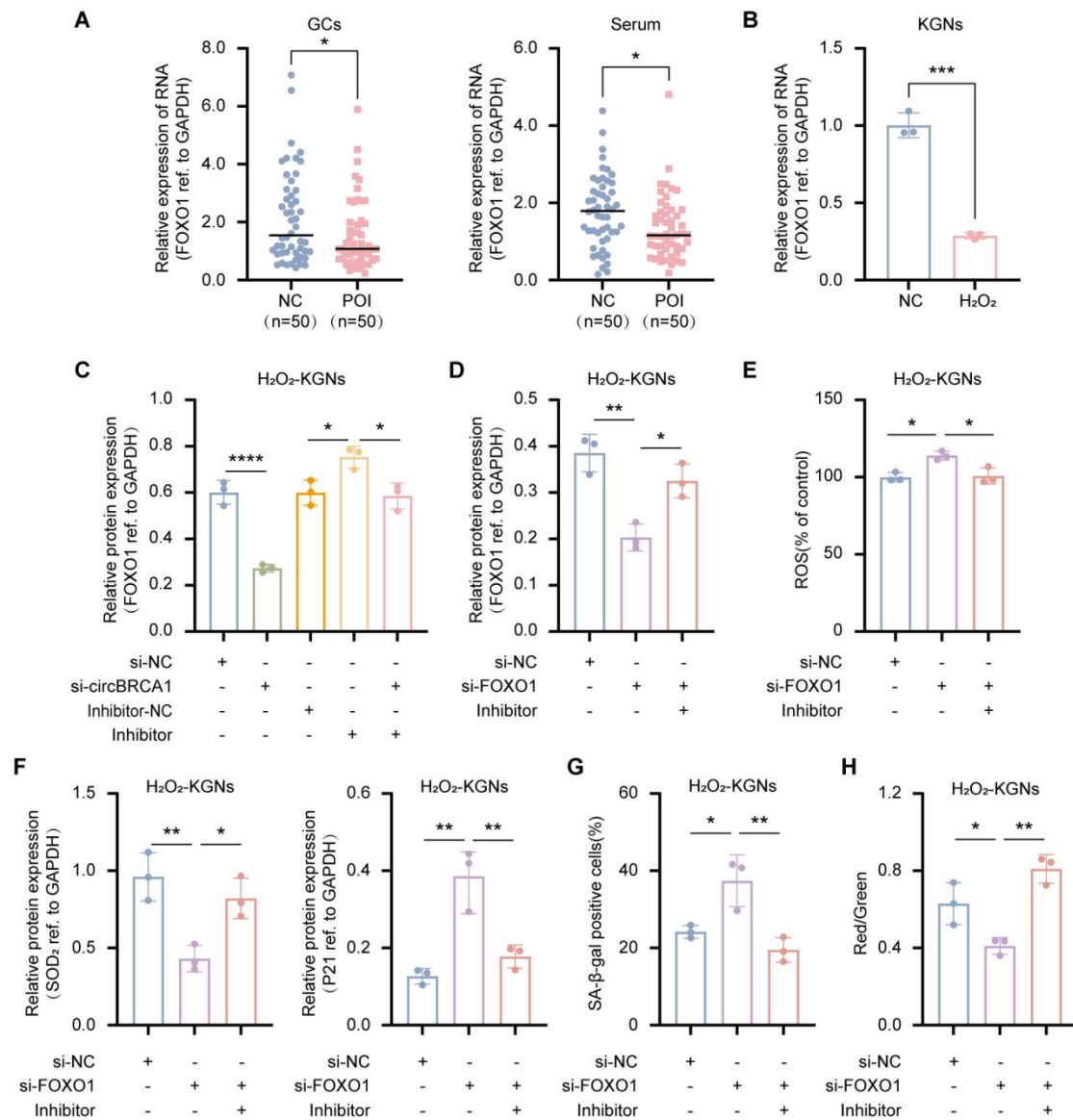
A Relative expression levels of circBRCA1 and BRCA1 in KGNs co-cultured with H-Exs and H-Exs-si-circBRCA1 were determined by RT-qPCR. B Fluorescence intensity statistics of DCFH-DA staining. C Statistical analysis of the western blot analysis. D SA-β-gal positive cell counts. E Fluorescence intensity statistics of the JC-1 staining. F Relative expression levels of circBRCA1 and BRCA1 in H-Exs were determined by RT-qPCR.

Fig.S3



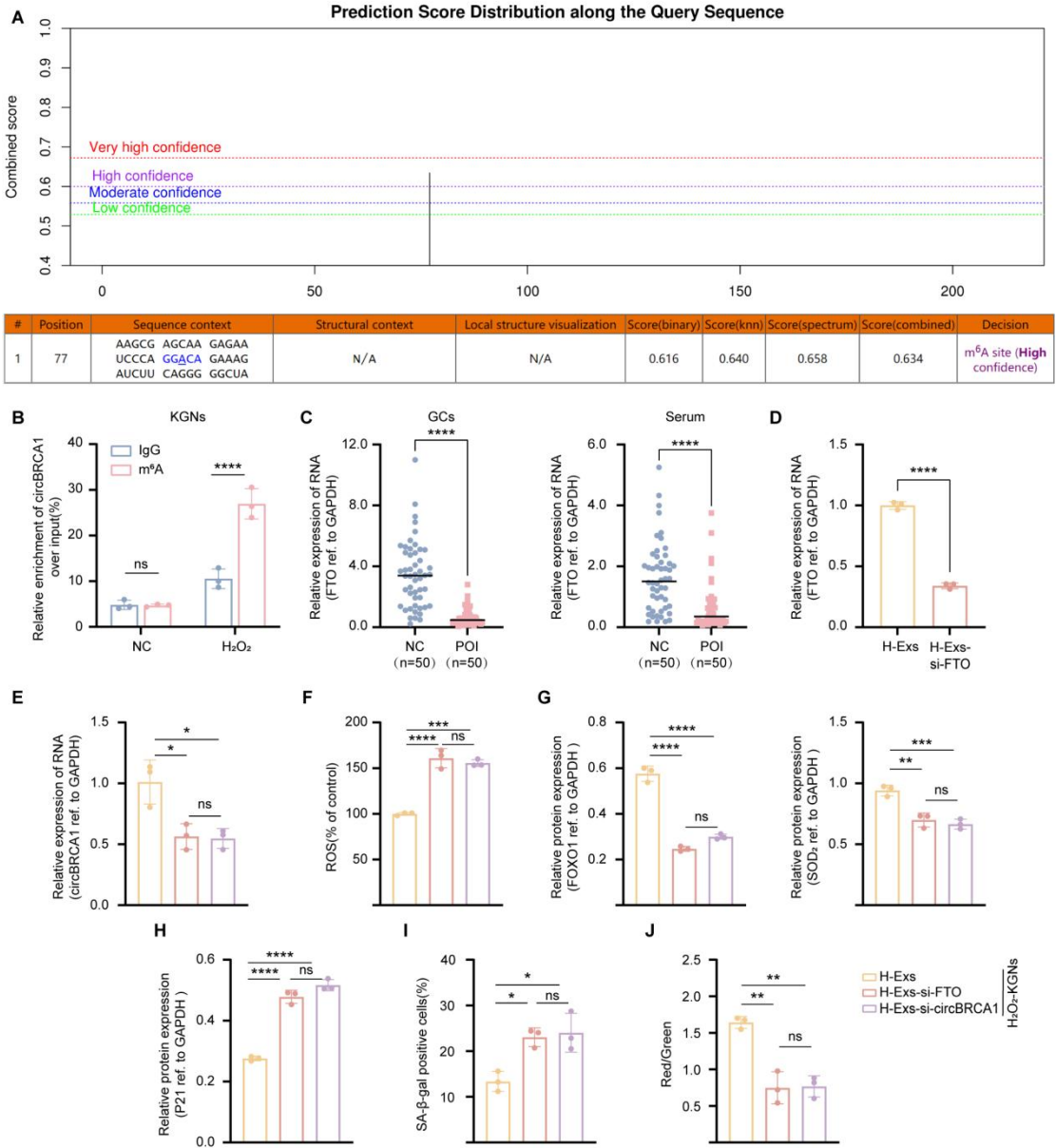
**S3.CircBRCA1 acts as a sponge for miR-642a-5p.** A The schematic drawing shows the putative binding sites for miRNAs associated with circBRCA1. B Fluorescence intensity statistics of DCFH-DA staining. C Relative expression levels of SOD<sub>2</sub> and Gpx were determined by RT-qPCR. D Western blot analysis revealed the expression levels of SOD<sub>2</sub> and P21 in KGNs. E Statistical analysis of the western blot analysis. F Relative expression levels of P16 were determined by RT-qPCR. G SA-β-gal positive cell counts. H Fluorescence intensity statistics of the JC-1 staining. I Oxygen consumption rate of KGNs. J Statistical analysis of ATP level.

Fig.S4



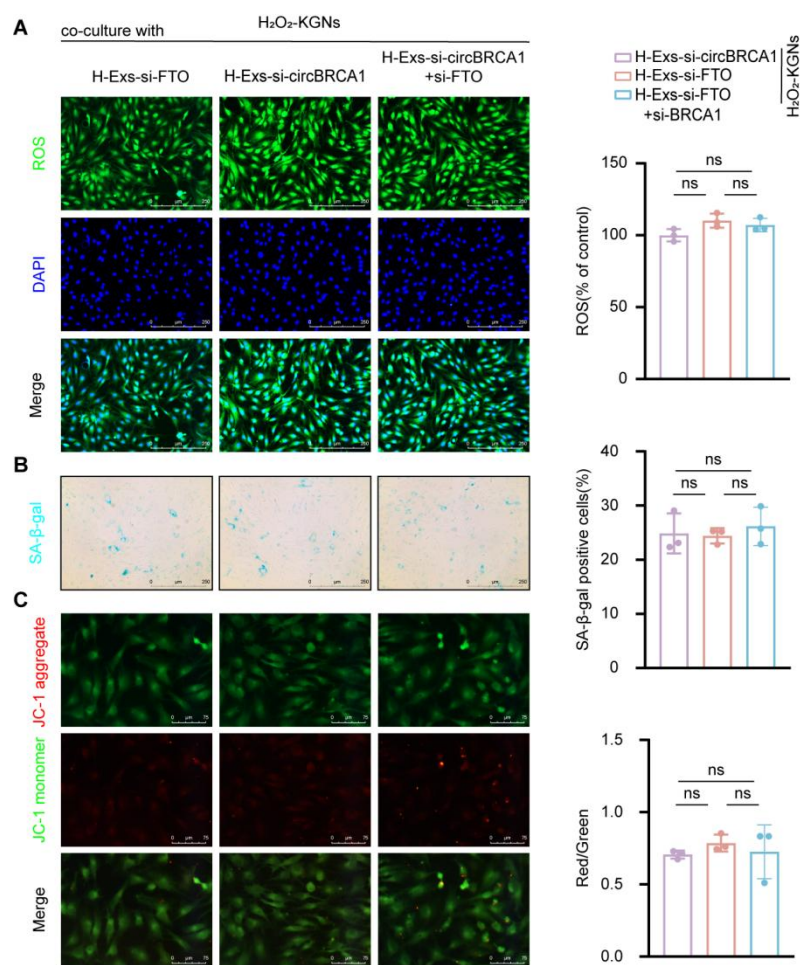
**S4. CircBRCA1 upregulates FOXO1 expression by sponging miR-642a-5p.** A Relative expression levels of FOXO1 in GCs and serum of patients with normal ovarian function (NC, n=50) and POI patients (POI, n=50) were determined by RT-qPCR. B Relative expression levels of FOXO1 in KGNs and H<sub>2</sub>O<sub>2</sub>-KGNs were determined by RT-qPCR. C-D Statistical analysis of the western blot analysis. E Fluorescence intensity statistics of DCFH-DA staining. F Statistical analysis of the western blot analysis. G SA-β-gal positive cell counts. H Fluorescence intensity statistics of the JC-1 staining.

Fig.S5



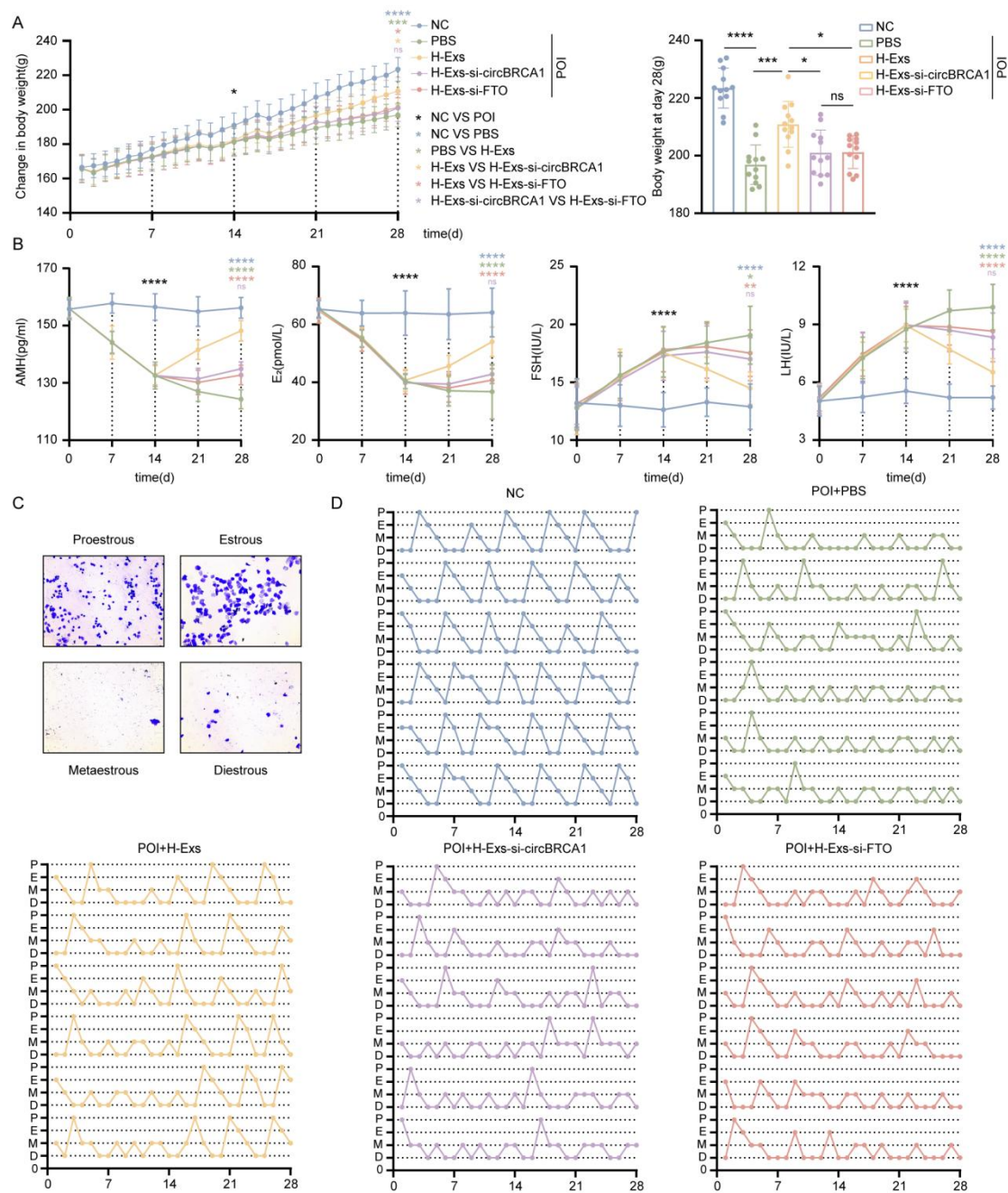
**S5. FTO-mediated m<sup>6</sup>A demethylation regulates circBRCA1 stability and expression.** A Bioinformatics analysis showed that there was a m<sup>6</sup>A modification site in circBRCA1. B M<sup>6</sup>A RIP assay was performed to detect the enrichment rate of circBRCA1 in KGNs and H<sub>2</sub>O<sub>2</sub>-KGNs. C Relative expression levels of FTO in GCs and serum of patients with normal ovarian function (NC, n=50) and POI patients (POI, n=50) were determined by RT-qPCR. D Relative expression levels of FTO in H<sub>2</sub>O<sub>2</sub>-KGNs co-culture with H-Exs and H-Exs-si-FTO were determined by RT-qPCR. E Relative expression levels of circBRCA1 in H<sub>2</sub>O<sub>2</sub>-KGNs co-culture with H-Exs, H-Exs-si-FTO and H-Exs-si-circBRCA1 were determined by RT-qPCR. F Fluorescence intensity statistics of DCFH-DA staining. G-H Statistical analysis of the western blot analysis. I SA-β-gal positive cell counts. J Fluorescence intensity statistics of the JC-1 staining.

Fig.S6



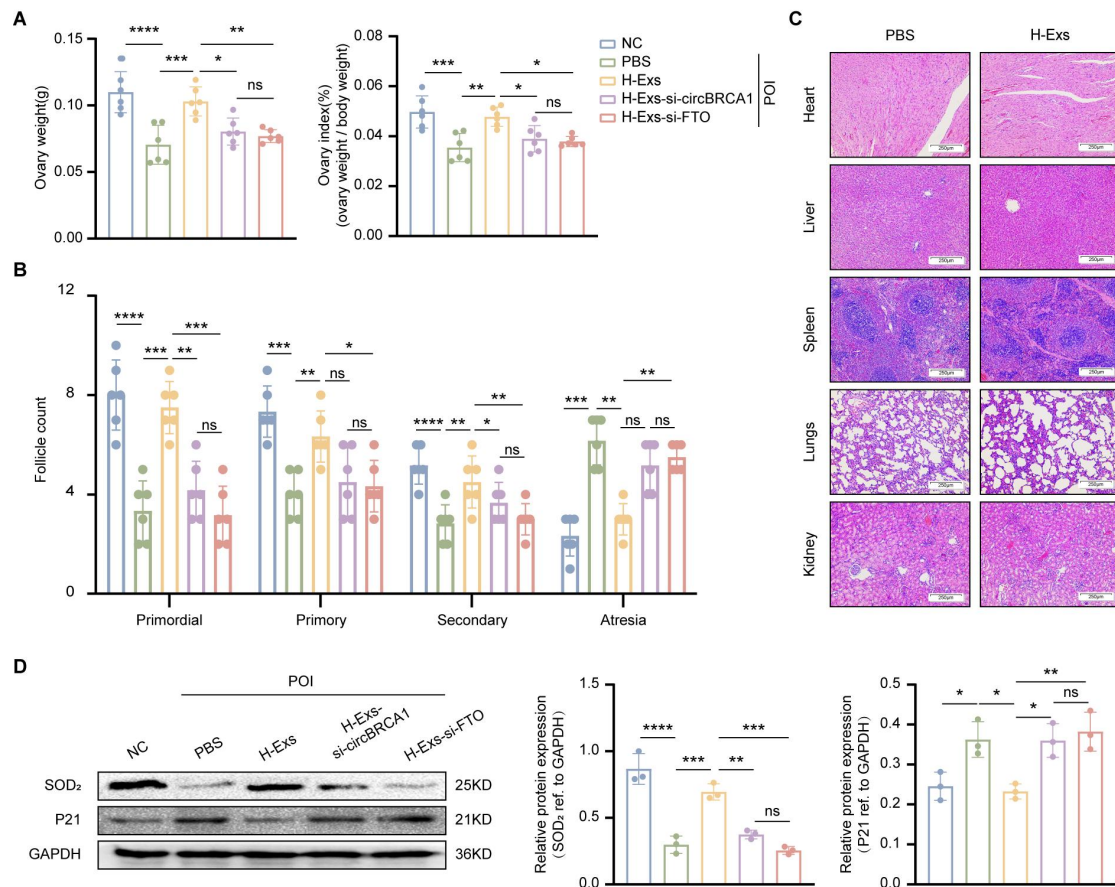
**S6. FTO-mediated m<sup>6</sup>A demethylation regulates circBRCA1 stability and expression.** A The ROS levels were detected by DCFH-DA staining. (scale bar = 50  $\mu$ m) B SA- $\beta$ -gal staining. (scale bar = 100  $\mu$ m) C JC-1 staining was used to detect the changes of MMP. (scale bar = 75 $\mu$ m)

Fig.S7



**S7. The therapeutic efficacy of exosomal circBRCA1 in treating POI in vivo.** A Changes in body weight of rats. B Serum concentrations of AMH, E<sub>2</sub>, FSH and LH. C Crystal violet staining of vaginal smears. D The estrous cycle of rats.

Fig.S8



**S8. The therapeutic efficacy of exosomal circBRCA1 in treating POI in vivo.** A Ovarian weight and ovarian index. B Quantitation of follicle count. C Histopathology of heart, liver, spleen, lung, kidney from rat treated by H-Exs. D Western blot analysis revealed the expression levels of SOD<sub>2</sub> and P21 in ovaries.

**Tab.S1 Patients information for this study**

| Parameters               | NC (n=50)    | POI (n=50)  | <i>P</i> value  |
|--------------------------|--------------|-------------|-----------------|
| Age (years)              | 31.50±5.50   | 33.00±5.00  | <i>P</i> =0.458 |
| BMI (kg/m <sup>2</sup> ) | 21.10±2.84   | 21.53±2.57  | <i>P</i> =0.513 |
| AMH (ng/mL)              | 4.94±3.90    | 0.50±0.49   | <i>P</i> <0.001 |
| E <sub>2</sub> (pmol/L)  | 181.00±91.00 | 80.50±67.50 | <i>P</i> <0.001 |
| FSH (IU/L)               | 6.26±3.68    | 32.19±7.11  | <i>P</i> <0.001 |
| LH (IU/L)                | 6.58±4.33    | 22.55±11.52 | <i>P</i> <0.001 |
| AFC                      | 12.50±5.50   | 3.00±2.00   | <i>P</i> <0.001 |

**Tab. S2 Primers names and sequences**

| Gene               | Forward                        | Reverse                       |
|--------------------|--------------------------------|-------------------------------|
| CircBRCA1          | 5'-GCTTCTGTGGTGAAGGAGCT-3'     | 5'-TCTTGCTCGCTTTGGACCTT-3'    |
| Divergent primers  | 5'-TGGTGCTTCTGTGGTGAAGG-3'     | 5'-CTCTTGCTCGCTTTGGACCT-3'    |
| Convergent primers | 5'-TGAAGTCAGAGGAGATGTGGTCA-3'  | 5'-GTGCCAAGGGTGAATGATGA-3'    |
| BRCA1              | 5'-GCCAAAGTAGCTGATGTATTGG-3'   | 5'-CAGTTACATGGCTTAAGTTGGG-3'  |
| miR-642a-5p        | 5'-ACGTCCCTCTCCAAATGTGTCTTG-3' | 5'-ATCCAGTGCAGGGICCGAGG-3'    |
| FOXO1              | 5'-TGTCCTACGCCGACCTCATCAC-3'   | 5'-GCACGCTCTTGACCATCCACTC-3'  |
| FTO                | 5'- GTTCACAACCTCGGTTTAGTTC-3'  | 5'- CATCATCATTGTCCACATCGTC-3' |
| SOD <sub>2</sub>   | 5'-CGCCCTGGAACCTCACATCAAC-3'   | 5'-AACGCCTCCTGGTACTTCTCCTC-3' |
| Gpx                | 5'-AAAGAACTCCTGTCCTCCACCTC-3'  | 5'-CCAGCGGATGTCGTGAACCTTC-3'  |
| P16                | 5'-GTTACGGTCGGAGGCCG-3'        | 5'-GTGAGAGTGGCGGGGTC-3'       |
| GAPDH              | 5'-CAGGAGGCATTGCTGATGAT-3'     | 5'-GAAGGCIGGGGCICATT-3'       |
| U6                 | 5'-AGAGAAGATTAGCATGGCCCCTG-3'  | 5'-ATCCAGTGCAGGGICCGAGG-3'    |