Nano-strategy of Targeting at Embryonic Trophoblast Cells Using CuO Nanoparticles for Female Contraception

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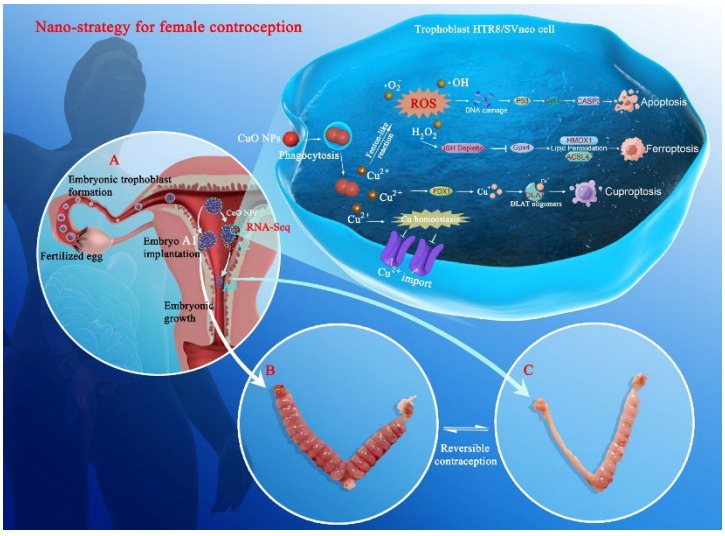
Effective contraceptives have been comprehensively adopted by women to prevent the negative consequences of unintended pregnancy for women, families, and societies. With great contributions of traditional hormonal drugs and Intra-Uterine Devices (IUDs) to effective female contraception by inhibiting ovulation and deactivating sperm, their long-standing side effects on hormonal homeostasis and reproductive organs for females remain concerns. Herein, we proposed a nano-strategy for female contraceptive, inducing embryonic trophoblast cell death using nanoparticles to prevent embryo implantation. Cupric oxide nanoparticles (CuO NPs) were adopted in this work to verify the feasibility of the nano-strategy and its contraceptive efficacy. We carried out the in vitro assessment on the interaction of CuO NPs with trophoblast cells using the HTR8/SVneo cell line. The results showed that the CuO NPs were able to be preferably uptake into cells and induced cell damage via a variety of pathways including oxidative stress, mitochondrial damage, DNA damage, and cell cycle arrest to induce cell death of apoptosis, ferroptosis, and cuproptosis. Moreover, the key regulatory processes and the key genes for cell damage and cell death caused by CuO NPs were revealed by RNA-Seq. We also conducted in vivo experiments using a rat model to examine the contraceptive efficacy of both the bare CuO NPs and the CuO/thermosensitive hydrogel nanocomposite. The results demonstrated that the CuO NPs were highly effective for contraceptive. There was no sign of disrupting the homeostasis of copper and hormone, or causing inflammation and organ damage in vivo. In all, this nano-strategy exhibited huge potential for contraceptive development with high biosafety, efficacy, clinical translation and non-hormonal style and on-demand for women.



Schematic illustration of a nano-strategy for female contraception. (A) A smooth pregnancy includes the fertilized egg, embryonic trophoblast formation, embryo implantation (A1), and embryonic growth (B). A contraceptive nano-strategy was proposed to interrupt the pregnancy process: nanomaterials mediate trophoblast cell death to prevent embryo implantation (A2), and the embryo falls off naturally (A3), achieving contraception without negative effects on the body (C). (A2) CuO NPs, as an example nanomaterial to verify the feasibility of the nano-strategy, were revealed by RNA-Seq to mediate trophoblast cell death through three mechanisms (apoptosis, ferroptosis, and cuproptosis).