EFFECT OF PI3K/AKT ACTIVATORS AND INHIBITOR ON HUMAN PRIMORDIAL FOLLICLES ACTIVATION

Authors

Grosbois, Johanne, Author, Demeestere, Isabelle, Author

Abstract Body

Introduction: The ovarian cortex contains numerous primordial follicles that can be cryopreserved before gonadotoxic therapies in young patients. PI3K/Akt pathway was identified as a major regulator of primordial follicles activation. For patients facing ovarian insufficiency, Akt activators were used to recruit residual follicles, but concern rises about the quality of generated follicles. We studied the regulation of in vitro follicles activation and analyzed the ability of generated follicles to develop after exposure to PI3K/Akt activators or inhibitors. **Methods**: Cryopreserved ovarian cortex were obtained from patients between 19 and 25 years-old. After thawing, tissue slices (4x2x1mm) were exposed to DMSO (control vehicle), évérolimus (inhibitor) or bpV(HOpic) and 740Y-P (activators) during 24h. Media were then replaced with control medium and all tissues cultured for 5 additional days. **Findings**: At day 0, 90% of the follicles were quiescent. After 6 days of culture, 80% of the follicles were activated in both control and DMSO groups. The exposure to activators triggered an additional significant drop of the percentage of primordial follicles compared with control (11,0% vs 19,6% primordial follicles at day 6 respectively, $p<0,001$), whereas culture with inhibitor partially reduced quiescent follicles recruitment (24,6% vs 19,6% primordial follicles, $p<0,01$). Immunostainings for apoptosis or DNA breaks were similar whatever the groups. Granulosa cells from growing follicles were strongly stained for Ki67 and oocytes from primordial to secondary follicles expressed GDF9 although morphological irregularities were observed in all groups. These defects may be due to the rapid growth, as in vitro folliculogenesis is highly accelerated compared to in vivo physiology. **Conclusion**: PI3K activators accelerated follicular growth initiation whereas évérolimus partially safeguarded the follicular reserve, but did not improve follicular morphology. In vitro grown follicles expressed markers of healthy follicular development but still presented structural flaws, underlining the importance of respectful biological development timing on follicles integrity.