MIRNAS INVOLVEMENT IN CYCLOPHOSPHAMIDE-INDUCED GROWING FOLLICULAR DAMAGE IN MICE

Authors

Alexandri, Chrysanthi, Author, Stamatopoulos, Basile, Co-Author, Demeestere, Isabelle, Co-Author

Abstract Body

Cancer treatments as cyclophosphamide and its active metabolite, 4-hydroxycyclophosphamide can cause primordial follicle activation, follicular apoptosis and ovarian reserve depletion. As these therapies negatively influence the ovarian function, fertility preservation is recommended. While oocytes or embryo vitrification and ovarian tissue cryopreservation are usually offered, innovative options aiming to reduce ovarian damage during oncological treatments appear to be very attractive.MiRNAs are small non-coding molecules which offer new promising approaches in the fertility preservation, as they have a key role in follicular growth, activation and atresia. Hence, this study aims to identify miRNAs that are involved in DNA damage response of growing follicles and in the mechanisms of primordial follicles activation during exposure to 4-hydroxycyclophosphamide using mouse model. Moreover, we identified the targets of selected miRNAs which are differentially expressed after exposure to cyclophosphamide metabolite in granulosa cells.Preantral follicles were isolated from mouse ovaries and were further cultured under two main conditions: control and exposure to 4-hydroxycyclophosphamide. The miRNA expression profiles in the granulosa cell samples were determined by TaqMan Low Density Cards. The expression level of each miRNA, was estimated by the comparative Ct method (ΔΔCt) and the fold change was calculated. A significant number of miRNAs (35) was found to be up and down regulated between the different conditions and a set of miRNAs was selected for further validation by QPCR. MiRNA targets were identified by miRTarBase database while the pathway enrichment analysis was performed by DAVID database. We have highlighted a subset of miRNAs, among them: Mir34a, Mir15a and Mir-let7 family genes which according to the computational analysis and to the literature, are involved in apoptosis and in follicular activation pathways. We believe that investigating the functions of miRNA-gene signalling networks will lead to an improved understanding of how follicles alter their biological processes under chemotherapy exposure.