THE ROLE OF CELLULAR SENESCENCE IN CHEMOTHERAPY-INDUCED PRIMARY OVARIAN INSUFFICIENCY (POI)

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Abstract Body

Objective: Recent studies elucidated pivotal roles of cellular senescence, a phenomenon characterized by the permanent cell growth arrest, in various pathology of disease. Moreover, several promising senolytics, which induce apoptosis of senescent cells, are developing. With the improvements in survival rates and the rise in the incidence of cancer, young female cancer patients were faced with chemotherapy-induced POI, which leads to infertility. In the present study, we investigated whether cellular senescence is involved in cyclophosphamide (Cy)-induced POI and whether a senolytic rescues ovaries from damage induced by Cy.

Methods: The expression of cellular senescence markers was examined in the ovaries harvested from Cy-induced POI mice with or without a senolytic, Dasatinib/Quercetin (DQ) and in primary cultured human granulosa cells (GCs) treated with Cy with or without DQ, by immunohistochemistry and quantitative RT-PCR (qPCR) and by Western blotting, respectively. POI model mice were treated with DQ, then morphology of the ovaries and the response to superovulation were examined.

Results: The expression of cellular senescence markers, p16, p21, p53 and γH2AX, was up-regulated in granulosa cells of POI mice and in human GCs treated with Cy. In cultured human GCs, treatment with DQ abrogated the Cy-induced expression of these markers of cellular senescence. Administration of Cy decreased primordial and primary follicles, with a concomitant increase in secondary and preovulatory follicles. This phenomenon, so called 'Burn-out', was partially recovered by co-treatment with DQ. Moreover, treatment with DQ significantly improved the response to superovulation in POI mice after 6 weeks of administration of Cy, that exhibited significantly smaller numbers of ovulated oocytes than control mice.

Conclusion: DQ might serve as promising protective agents against Cy-induced damage in the ovary.