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The role of autophagy in chemotherapy resistance of cisplatin in ovarian cancer

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Introduction: Epithelial ovarian cancer is one of the most lethal oncogynecological diseases. Recent researches showed that autophagy induction contributes to the development of the resistance against anticancer drugs. In this work, we evaluated the contribution of the autophagy to cisplatin resistance in the ovarian cancer cell line OVCR8. Atg5 protein plays a critical role in the initiation and elongation stages of autophagy. Effective knockout for ATG5 blocks autophagy induction in the ovarian cancer cell lines, which is confirmed by the lower expression level of the LC-II.

Materials and methods: In this study, we knocked out *ATG-5* in the ovarian cell cancer OVCAR8 using doxycycline-inducible CRISPR-Cas9.

Results: After 6 days in the doxycycline containing media, the Atg-5 protein was effectively depleted. The western blot showed the absence of LC3-II (a marker of autophagy) in comparison with wild-type, which means that we successfully inhibited autophagy. We defined the cisplatin IC50 for *ATG5*-knockouted OVCAR8 (IC50= 2.14 mkM) and wild-type cell line (IC50=2.74 mkM). Fold Change (FC) = $IC50^{mut}$: $IC50^{w}$ = 0.78. We concluded that cells with inhibited autophagy are more sensitive to cisplatin than the wild type. Our data is similar to studies suggesting that autophagy can defend ovarian cancer-associated fibroblasts from oxidative stress. That means blocking autophagy can sensitize ovarian cancer-associated fibroblasts for chemotherapeutic drug cisplatin.

We evaluated the expression levels of autophagy markers (LC3-I, LC3-II, P62, Atg5), and anti-apoptotic protein (Bcl2).

The western blot showed non expression of LC3-II (a marker of autophagy) in comparison with wild-type. However other autophagy markers P62 and LC3-I were downregulated in Atg5-knockouted cell. The p62 depletion contradicts the published literature.

Conclusion: We are hypothesizing that in ovarian cancer cells, p62 level is regulated by uncharacterized signaling cascade that senses level of the autophagy. The exact mechanism of this process in autophagy- missing cells is not clear. In addition, in Atg5-knockouted cells, Bcl2 levels were higher than wild-type (p-value < 0.05*) and high level of Bcl2 inhibits apoptosis, and contributes to the resistance to chemotherapeutic drugs, which is consistent with earlier published Results. Autophagy is a promising therapeutic target and characterization of autophagy-mediated chemotherapeutic resistance will pave the way to better treatment of the ovarian cancers.

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