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Role of nuclear pore protein NUP62 in ovarian cancer cisplatin Chemoresistance

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Objective: While not the most common of the gynecologic malignancies, ovarian cancer is the number one cause of death from gynecologic cancer in American women. Ovarian cancers high mortality rate is a result of: i) pathogenesis being incompletely understood; ii) early-stage disease being asymptomatic, iii) lack of a cost-effective screening test, and iv) most patients while showing initial good response to surgery & chemotherapy, eventually develop chemoresistance and disease recurrence. We have previously reported that altered NUP62 induces dormancy in ovarian cancer cell lines, and confers resistance to cisplatin. We have explored the chemoresistance mechanism further.

Materials & Methods: Ovarian cancer cell lines A2780 (cisplatin sensitive) and CP70 (cisplatin resistant) were used for in vitro experiments. Activated form of proline-rich tyrosine kinase (PYK2) was assessed via antibody to phosphoY402 site (Cell Signaling Technology). Colony forming assays used PYK2 inhibitor PF-562271 (Selleckchem). Tyrosine phosphatase inhibitor pervanadate was used to assess subcellular distribution of phosphorylated Y422 NUP62 via immunofluorescence microscopy. The work on human tumors was approved by the Institutional Review Board. Tissue microarrays (TMAs) were created by taking four needle-core biopsies sized at 0.6 mm, from each paraffin-embedded tissue block guided by the hematoxylin-eosin-stained (H&E) slide. The cases were collected from the Surgical Pathology Archives at The Icahn (at Mount Sinai) School of Medicine. Three-micron thick slices were cut from the TMA blocks, placed on 3-aminopropyltriethoxysilane-coated slides to enhance adhesion. Slides were subjected to manual deparaffination and rehydrated. Immunohistochemistry was performed using anti- phosphorylated tyrosine 422 residue (Y422) of the NUP62 protein according to standard procedures. Samples were analyzed by scoring each case for intensity of staining (0, 1+ =mild staining, 2+=moderate staining, or 3+=strong staining), extent of staining (0, 25%, 50%, 75%, 100%), and distribution of staining (cytoplasmic, nuclear / nuclear membrane). Kaplan Meier analysis was performed.

Results: In vitro assays with cisplatin showed greater activated PYK2 in CP70 cells than A2780 cells, which redistributed to the nucleus after 18 hours in culture. When exposed to cisplatin in the presence of PYK2 inhibitor PF-562271, regrowth of remnant CP70 cells was diminished. Treatment of cultured cells with protein tyrosine phosphatase inhibitor pervanadate resulted in movement of phosphorylated NUP62 from the nuclear membrane into the cytoplasm. TMA results: Eighty-nine patients' cases met selection criteria. Of these, average patient age was 59 years old, 81% were Caucasian, 86% had optimal cytoreduction, 54% showed platinum resistance, 67% experienced tumor recurrence, 24.9% showed 5-year progression free survival, and 50.6% showed 5-year overall survival. Histologically, 80% of cases were serous carcinomas, and 88% were high-grade malignancies. Tumors with nuclear distribution of phospho-Y422-NUP62 showed greater progression-free survival than those with cytoplasmic NUP (P=0.0069).

Conclusions: Redistribution of activated PYK2 to the nucleus may contribute to cisplatin resistance. Redistribution of PYK2 may contribute to the growth recovery of quiescent cisplatin resistant cells. Activation and translocation of PYK2 induces phosphorylation of NUP62 at Y422 and its release into the cytoplasm. In vitro results are mirrored by TMA studies in human samples and suggest that PYK2 signals promote resistance to platinum treatment and regrowth of tumor cells.

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