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Aerosol therapy for the treatment of osteosarcoma lung metastases. Implications of the FAS/FASL apoptotic pathway and autophagy

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Lung metastasis constitutes the main cause of death in patients with osteosarcoma (OS).Despite aggressive chemotherapy and successful control of primary tumor, survival has remained stagnant for the past 20 years.

We demonstrated that Fas plays an important role in the metastatic potential of OS. We hypothesized that Fas is an early defense mechanism to clear invading tumor cells to the lung. Constitutive FasL in the lung microenvironment allows Fas positive tumor cells to get cleared while Fas negative cells survive and give rise to the tumor. Treatment of OS lung metastases with aerosol Gemcitabine or liposomal 9-Nitrocamptothecin upregulates Fas expression and causes tumor regression. Blocking the Fas pathway decreases aerosol therapeutic efficacy. In the absence of FasL in the lung, therapeutic effect of aerosolized therapy is completely abolished. These results demonstrate the importance of an intact Fas pathway in the therapeutic efficacy of these agents. A phase I trial of aerosol Gemcitabine will be initiated at MD Anderson.

Despite the significant therapeutic efficacy of aerosolized therapy, a subset of cells failed to respond to GCB resulting in persistent small isolated lung metastases.Autophagy, a catabolic process involved in cellular homeostasis, can either be protective or promote cell death. Our *in vitro* and *in vivo* studies demonstrated that autophagyplays a role in OSresponse to GCB. GCB induces autophagy in several different OS cell lines including the human LM7 and CCH-OS-D. Blocking autophagy using Hydroxychloroquine and/or the downregulation of Beclin 1increased the sensitivity of LM7 cells to GCB but decreased the sensitivity of CCH-OS-D cells. This dual role of autophagy has been described in other tumor types. However, predicting whether blocking autophagy will increase or decrease drug-sensitivity has not been described. We found that the induction of phosphorylated heat shock protein 27 (pHsp27) following drug exposure with camptothecin or GCB correlated with the role of autophagy in drug sensitivity. Blocking autophagy in cells whose pHsp27 was increased following chemotherapy resulted in enhanced drug sensitivity whereas blocking autophagy in cells where pHsp27 was decreased resulted in reduced drug sensitivity. In conclusion, induction of pHsp27 following chemotherapy predicts whether blocking autophagy will increase or decrease drug sensitivity.

Understanding the molecular pathways and characteristics that determine how autophagy contributes to drug-induced resistance or responsewill allow translational studies incorporating autophagy inhibitors or autophagy stimulators into specific treatment regimens using either chemotherapy, pathway specific blocking agents or immunotherapy.

Biography:

Dr. Nancy Gordon was born and raised in Caracas, Venezuela. She received her MD title in 1993. In 1995, she moved to the United States. She completed her Residency in Pediatrics at Driscoll Children's Hospital, Corpus Christi, TX in 2001 and her Hematology/Oncology fellowship at UT MD Anderson Cancer Center in 2005. In 2009 she completed three years of a post-doctoral fellowship. Thereafter she became an Instructor and 6 months later an Assistant Professor. Dr. Gordon is an established investigator at MD Anderson whose main focus has been in understanding the biology of bone tumors, specifically Osteosarcoma and the microenvironment as well as mechanisms implicated in tumor cells resistance to chemotherapy. More recently Dr. Gordon has been studying the process of autophagy and its implications in tumor response to therapy.