

Blocking cancer metastasis with TGF-beta antagonists

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Induction of epithelial-mesenchymal transition (EMT) has been shown to confer both metastatic and self-renewal properties to breast tumor cells resulting in drug resistance and tumor recurrence. TGF β is a potent inducer of EMT. We found that chemotherapeutic drug doxorubicin activates TGF β signaling in breast cancer cells. Doxorubicin induced EMT, promoted invasion and enhanced stem cell properties in the murine 4T1 breast cancer cells in vitro, which were inhibited by a TGF β type I receptor kinase inhibitor (T β RI-KI). These observations suggest that the adverse activation of TGF β pathway by chemotherapeutics in the cancer cells together with elevated TGF β levels in tumor microenvironment may lead to EMT and generation of cancer stem cells resulting in the resistance to the chemotherapy. We investigated the potential synergistic anti-tumor activity of T β RI-KI in combination with doxorubicin in animal models of metastatic breast cancer. Combination of Doxorubicin and T β RI-KI enhanced the efficacy of doxorubicin in reducing tumor growth and lung metastasis in the 4T1 orthotopic xenograft model in comparison to single treatments. Doxorubicin treatment alone enhanced metastasis to lung in the human breast cancer MDA-MB-231 orthotopic xenograft model and metastasis to bone in the 4T1 orthotopic xenograft model, which was significantly blocked when T β RI-KI was administered in combination with doxorubicin. Our results indicate that the combination treatment of doxorubicin with a TGF β inhibitor has the potential to reduce the dose and consequently the toxic side-effects of doxorubicin, and improve its efficacy in the inhibition of breast cancer growth and metastasis.

Biography

Dr. LuZhe Sun received his Ph.D. degree in Physiology from Rutgers-The State University of New Jersey and UMDNJ-Robert Wood Johnson Medical School in 1990 and obtained his postdoctoral training in Baylor College of Medicine in the US. He became an independent researcher in 1995 as Tenure-track Assistant Professor of Pharmacology in the University of Kentucky School of Medicine and is currently Professor of Cellular and Structural Biology, Dielmann Endowed Chair in Oncology, and Associate Director for Translational Research at the Cancer Treatment and Research Center in the University of Texas Health Science Center. Dr. Sun's main research interest is to elucidate the role of transforming growth factor beta (TGF β) signaling in tumor progression. He participated in the discovery of the tumor suppressor role of TGF β type II receptor in hereditary non-polyposis colorectal cancer and pioneered the use of a soluble TGF β type III receptor and the engineer of a soluble chimeric TGF β receptor for the inhibition of cancer growth, angiogenesis, and metastasis in various xenograft models of late stage human cancers. His research has been supported with multi-million dollar funding from National Institutes of Health, Department of Defense, the University of Texas Health Science Center, and other private foundations. He has co-authored more than sixty peer-reviewed publications, and serves regularly as scientific reviewer over the past decade for the National Institutes of Health and the Department of Defense in the US.