

Identification and mechanistic exploration of VentX as a novel tumor suppressor in lymphocytic leukemia

Hong Gao¹, Xiaoming Wu², Leslie Silberstein³ and Zhenglun Zhu²

¹Department of Medicine, North Shore Hospital

²Brigham and Women's Hospital

³Children's Hospital, Harvard Medical School, USA

The canonical Wnt/beta-catenin signaling has been viewed as a major oncogenic pathway, implicated in both solid and hematological malignancies. Wnt regulation is a target of intensive investigation for its potential application in cancer prevention and treatment. During our recent studies, we identified VentX, a human homologue of the *Xenopus* homeobox gene *Xom* of the BMP4 signaling pathway, as a novel Wnt antagonist and a putative tumor suppressor in lymphocytic leukemia.

To further define the mechanism underlying tumor suppressor function of VentX, we performed a target screen to determine the potential effects of VentX on the expression of cell cycle regulators. We found that VentX activates the expression of genes involved in cellular senescence, such as the p53/p21 and Rb/p16. Combined approaches of biochemical and cellular studies showed that VentX is a direct activator of senescence pathway by binding to the promoters of p53 and p16. While, ectopic expression of VentX induce senescence phenotype in stable leukemic cell lines, inhibition of VentX induction by chemotherapeutic agents lead to chemo-resistance of leukemia cells.

In summary, using methods of reverse genetics, we have identified VentX as a novel tumor suppressor. Our data showed that VentX is an antagonist of the oncogenic Wnt signaling and a direct activator of the senescence pathways of tumor suppression. As such, we propose that VentX functions as a pivotal link between oncogenic and tumor suppressing pathways and represents a novel target of intervention in the management of neoplastic diseases.

Biography

Dr. Zhu is an Associate Physician at the Brigham and Women's Hospital and Assistant Professor of Medicine at Harvard Medical School. Dr. Zhu's research focuses on the molecular mechanisms in cell fate determination during early embryogenesis and its potential translation in cancer diagnosis and treatment. Well recognized for his contribution in the field of development and cancer biology, Dr. Zhu is an elected member of the American Society of Clinical Investigation.

zzhu@partners.org