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Dysregulation of prostaglandin metabolism and action in the progression of Lymphangioleiomyomatosis (LAM)

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Lymphangioleiomyomatosis (LAM) is a female predominant and devastating pulmonary disease, characterized by diffusely infiltrated smooth muscle like cells that carry mutations in the tuberous sclerosis complex (*TSC*) genes. *TSC1, TSC2* and *TBC1D7* interact and inhibit the mammalian target of rapamycin complex 1 (mTORC1). The reasons that LAM exclusively affects women and how TSC1 or TSC2 deficiency contributes to the pathogenesis of LAM are not yet fully understood. We previously discovered that estrogen promotes the survival and lung metastases of tuberin-deficient. Recently, we reported that estrogen and mTORC2 coordinate to enhance prostaglandin biosynthesis and tumorigenesis in LAM. Prostaglandins are lipid mediators that participate in tumor survival, growth, invasion, and inflammation. Phospholipase A2 (PLA2), Cyclooxygenase-2 (COX-2) and prostacyclin synthase (PTGIS) are critical enzymes responsible for the production of prostaglandins. Prostaglandin receptors (EPs) mediate the biological function of prostaglandins. We performed bioinformatics analysis of public expression arrays and found a rapamycin-insensitive upregulation of prostaglandin biosynthesis genes including *PLA2, COX-2, PTGIS*, and *EP3*, in TSC2-deficient LAM patient-derived cells compared to TSC2-addback cells. We validated the enhanced expression of *PLA2, COX-2, PTGIS* and *EP3* in TSC2-deficient cells using real-time RT-PCR, immunoblotting and immunohistochemistry in cell cultures, preclinical models and clinical samples. Interestingly, PGE_2 specifically stimulated the growth of TSC2-deficient LAM patient-derived cells compared to TSC2-addback cells. Importantly, treatment of TSC2-deficient LAM patient-derived cells with inhibitors specific to *PLA2 COX-2*, or *EP3* resulted in dose-dependent reduction of cells growth. Our data documents that loss of TSC2 leads to the aberrant expression and accumulation of prostaglandin biosynthesis regulators, thereby enhancing prostaglandin production and promoting TSC2-deficient cell growth and tumor development. Our data supports the potential application of prostaglandin metabolites as biomarkers of disease severity and the development of prostaglandin biosynthesis inhibitors as alternative therapeutic options for LAM patients and in other gender-specific diseases.

Biography

Jane Yu has completed her PhD from the Graduate School and University Center of the City University of New York and Postdoctoral training from Fox Chase Cancer Center. She was an Assistant Professor of Medicine at the Brigham and Women's Hospital-Harvard Medical School. She is an Associate Professor at the Pulmonary Critical Care and Sleep Medicine at University of Cincinnati College of Medicine. Her research focuses are to study mechanisms through tumor suppressor proteins hamartin (TSC1) and tuberin (TSC2) regulate cellular metabolism and cell survival, identify potential biomarkers for tuberous sclerosis complex (TSC) and rare pulmonary disease lymphangioleiomyomatosis (LAM), establish preclinical models for TSC and LAM for translational research, perform bioinformatics and network analyses, conduct high-throughput drug screens, and develop pathway targeted therapies for TSC, LAM and cancers. She has published more than 30 papers in reputed journals.

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