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LIMD2: A novel therapeutic target for metastatic papillary thyroid carcinoma

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Abstract

Although the papillary thyroid cancer (PTC) has a good prognosis, the metastatic disease negatively impacts the survival rate. Recent data have been postulated that the cellular reprograming verified during the metastasis can lead to cancer-stem cells (CSCs) formation, which are related to the therapy failure. In this sense, we identified that the LIMD2 gene is differentially expressed in PTC and, overexpressed in lymph node metastasis of patients carrying the BRAF V600E mutation, suggesting that this gene can be involved in CSC formation and, therefore, in therapeutic resistance. In order to investigate this hypothesis, we promoted the LIMD2 knockout in two cell lines from PTC (BCPAP – BRAF V600E and TPC1 – RET/ PTC) using the CRISPR/Cas9 system. Following validate the LIMD2 editing by TIDE and immunoassays, we analysed the expression CSC-related hallmarkers (SOX-2, OCT-3/4, NANOG, ALDH1A1 and CD44) using proteome profiler array, flow cytometry and High-Content Screening, the expression levels of thyroid-specific genes (FOXE1, NKX2, PAX8, TG and TPO) by qRT-PCR and multidrug resistance protein (MRP1) by Western blot. Results showed that the LIMD2 knockout promoted the down regulation of all CSC-related hallmarks, as well as MRP1 especially in BCPAP edit cells, suggesting that LIMD2 can be associated to the drug efflux. However, we observed an up regulation in the expression levels of all thyroidspecific genes in BCPAP edit cells, suggesting that LIMD2 is related to the CSC formation in PTC. We also analysed the LIMD2 involvement in drug resistance mechanisms. For this, we treated both parental and edit cells with acid hydrolysis extract of Agave sisalana (AHEAS), which cytotoxic activity was previously demonstrated. Results showed that the LIMD2 knockout increased the number of apoptotic/necrotic cells in both edit cell lines. Altogether, these data strongly suggest that LIMD2 expression can contribute with therapy failure by increasing the MRP1 expression through CSC formation dependent manner.

Biography

Prof. Dr. Rodrigo Pinheiro Araldi has completed his PhD in Biotechnology (Oncogenetics) at Universidade de São Paulo (USP, Brazil) and postdoctoral studies at Escola Paulista de Medicina – Universidade Federal de São Paulo (UNIFESP, Brazil). He was visiting researcher at Pathology Department of Naples University Federico II (Italy) and currently is researcher from Department of Morphology and Genetics of UNIFESP and professor at Bioscience Post-graduation Program of Universidade Federal da Integração Latino-Americana (UNILA, Brazil). He has over 30 publication in reputed journals that had been cited over 470 times and, his publication H-index is 12 and has serving as an editorial board member of reputed Journals.

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