

Intracellular Sphingosine-1-Phosphate Receptor 3 Contributes to Lung Tumor Cell Proliferation

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Abstract : Sphingosine-1-phosphate (S1P) is a membrane-derived bioactive phospholipid exerting a multitude of effects on respiratory cell physiology and pathology through five S1P receptors (S1PR1-5). Higher levels of S1P have been registered in a broad range of respiratory diseases, including inflammatory disorders and cancer, although its exact role is still elusive. Based on our previous study in which we found that S1P/S1PR3 is involved in an inflammatory pattern via the activation of Toll-like Receptor 9 (TLR9), highly expressed on lung cancer cells, the main goal of the current study was to better understand the involvement of S1P/S1PR3 pathway/signaling during lung carcinogenesis, taking advantage of a mouse model of first-hand smoke exposure and of carcinogen-induced lung cancer. We used human samples of Non-Small Cell Lung Cancer (NSCLC), a mouse model of first-hand smoking, and of Benzo(a)pyrene (BaP)-induced tumor-bearing mice and A549 lung adenocarcinoma cells. We found that the intranuclear, but not the membrane, localization of S1PR3 was associated to the proliferation of lung adenocarcinoma cells, the mechanism that was correlated to human and mouse samples of smoke-exposure and carcinogen-induced lung cancer, which were characterized by higher utilization of S1P. Indeed, the inhibition of the membrane S1PR3 did not alter tumor cell proliferation after TLR9 activation. Instead, according to the nuclear localization of sphingosine kinase (SPHK) II, the enzyme responsible for the catalysis of the S1P last step synthesis, the inhibition of the kinase completely blocked the endogenous S1P-induced tumor cell proliferation. These results prove that the endogenous TLR9-induced S1P can on one side favor pro-inflammatory mechanisms in the tumor microenvironment via the activation of cell surface receptors, but on the other tumor progression via the nuclear S1PR3/SPHK II axis, highlighting a novel molecular mechanism that identifies S1P as one of the crucial mediators for lung carcinogenesis-associated inflammatory processes and that could provide differential therapeutic approaches especially in non-responsive lung cancer patients.

Keywords : sphingosine-1-phosphate (S1P), S1P Receptor 3 (S1PR3), smoking-mice, lung inflammation, lung cancer

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