Caspase-8 is involved in lung carcinogenesis in both humans and mice

M. Terlizzi[1], V.G. Di Crescenzo[2], G. Perillo[3], A. Galderisi[4], R. Sorrentino[1], A. Pinto[1]

[1]Dept of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, Fisciano, Salerno, 84084, Italy
[2]Dept of Medicine and Surgery University of Salerno, Fisciano, 84084, Salerno
[3]Struttura Complessa di Malattie dell'Apparato Respiratorio, A.O.U. San Giovanni di Dio e Ruggi D'Aragona, Salerno
[4]Endoscopia Bronchiale e Pneumologia Interventistica, A.O.U. San Giovanni di Dio e Ruggi D'Aragona, Salerno

Lung cancer is one of the leading cause of cancer death worldwide (Pinto et al., 2011). The conventional therapy still remains the main treatment with low percentage of success and higher risk for chemotherapy resistance. Caspase-8 is one of the upstream enzyme involved in cell death via apoptosis (Blander et al., 2014). However, it was also described as involved in inflammasome activation that lead to IL-1-like cytokine release with the ensuing inflammatory response (Gurung et al., 2014), that in the context of lung cancer can favor tumor proliferation. Therefore the aim of our study was to understand the role of caspase-8 in human lung carcinoma taking advantage of a mouse model of carcinogen-induced lung cancer. C57Bl/6 mice were intratracheally injected with N-Methyl N-Nitroso Urea (NMU), a well known carcinogen and mutagen agent (Karran et al., 1979; Lin et al., 2010) for three consecutive weeks, starting with a high dose of 50 μg/mouse (in 10 μl of saline) at first week followed by other two administrations of 10 μg/mouse at week 2 and 3; the mice were sacrificed at different time points (7 and 28 days) to study the involvement of caspase-8 during lung cancer development. Human samples of non-small cell lung cancer (NSCLC) patients, undergoing thoracic surgery, were used. Western blotting analysis showed that the active form of caspase-8 (22 kDa) was present in the lung of both NSCLC patients and tumor-bearing mice at both 7 days and 28 days compared to naive mice. The pharmacological inhibition of caspase-8 by means of z-IETD-FMK robustly reduced lung tumor growth compared to control mice, implying that caspase-8 activation is involved in lung tumor progression. Moreover, the administration of z-IETD-FMK significantly reduced the levels of IL-6, TNF-α, IL-18, but not IL-1β into the broncho-alveolar fluid (BAL) of tumor bearing mice compared to the control group. In addition, the levels of IL-1α and IL-33 in lung homogenates were significantly lower in z-IETD-FMK-treated than in control tumor-bearing mice. Although the pharmacological inhibition of caspase-8 diminishes the pro-inflammatory humoral pattern of lung tumor microenvironment, it does not interfere with the recruitment of immune cells to the lung of tumor-bearing mice, implying that its activation does not play a role during the tumor adaptive immunoediting. In addition, both mouse and human samples showed that the limiting step for caspase-8 activity in tumor progression was related to the presence of the short segment of cellular FLICE (FADD-like IL-1β-converting enzyme) inhibitory protein (c-FLIP).
In conclusion, our data demonstrate that caspase-8 is an important orchestrator of cancer–associated inflammatory process amplification and the presence of the short or long c-FLIP may represent the rheostat for caspase-8-induced tumor proliferation or tumor arrest/regression in the lung.