



3^o Meeting

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STEBICEF-UNIPA



UNIVERSITÀ
DEGLI STUDI
DI PALERMO

BIOINFORMATICA IMMUNOLOGIA
MALATTIE APPARATO RESPIRATORIO
MALATTIE METABOLICHE
MICROORGANISMI NELLE BIOTECNOLOGIE
NANOTECNOLOGIE NEUROSCIENZE
ONCOLOGIA SVILUPPO E DIFFERENZIAMENTO

LIBRO degli ABSTRACT

 **PALERMO 17-18 DICEMBRE 2015**

Area della Ricerca di Palermo Via Ugo La Malfa 153

Progetto grafico:
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chronic Cigarette smoke extract (CSE) exposure on the expression of DAB2IP and EZH2 using *ex vivo* and *in vitro* studies to identify their involvement in the progression of COPD toward lung cancer. In *ex vivo* studies, EZH2 and DAB2IP expression was assessed by immunohistochemistry in bronchial epithelial cells of surgical specimens from COPD patients and healthy control subjects (HC). In *in vitro* studies, we created a chronic model using CSE; EZH2 and DAB2IP expression was studied by western blot and real time methods in bronchial epithelial cell line (16HBE) and in lung cancer cell lines (A549 and H292) stimulated with CSE. We tested the effect of GSK343, an EZH2 inhibitor, on the expression of DAB2IP and analyzed apoptosis by annexin test, and proliferation in the cell lines. *Ex vivo*, DAB2IP immunoreactivity was statistically significant lower while EZH2 was higher in bronchial epithelial cells (positive cells/mm²) from COPD patients compared to HC subjects. Furthermore, DAB2IP and EZH2 expression was correlated with bronchial epithelial metaplasia in COPD. *In vitro*, DAB2IP was statistically significant downregulated while EZH2 increased in the cell lines CSE treated. The use of GSK343 restored the DAB2IP expression and promotes apoptosis in cells stimulated for 14 days with 20% CSE in combination with EZH2 inhibitor. Chronic inflammation due to cigarette smoke might play a critic role on the alteration of DAB2IP/EZH2 genes expression in COPD, promoting lung cancer progression toward lung carcinoma.

The cytotoxic effect exerted by parthenolide and DMAPT on breast cancer stem-like cells

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Triple-negative breast cancers (TNBCs) are aggressive forms of breast carcinoma associated with a high rate of recidivism. It is known that a small proportion of tumour cells, termed cancer stem cells (CSCs), is responsible for tumour formation, progression and recurrence. The sesquiterpene lactone parthenolide (PN) was identified as the first small molecule capable of killing CSCs.¹ Previously we have shown² that PN and its soluble analogue DMAPT induce a strong cytotoxic effect in MDA-MB231 cells, the most studied line of TNBCs. In the present research we investigated about the effects exerted by both PN and DMAPT on breast cancer stem-like cells derived from three lines of TNBCs (MDA-MB231, BT20 and MDA-MB436). The two compounds inhibited both the production of mammospheres from the three lines of cells and the viability of breast cancer stem-like cells derived from dissociation of mammospheres. This effect was suppressed by NAC, while z-VAD, a general inhibitor of caspase activity, was ineffective. PN and DMAPT induced in stem-like cells, in the first hours of treatment, a strong production of hydrogen peroxide. Prolonging the time of treatment (12-24h) the levels of both superoxide anion and hROS (hydroxyl radicals and peroxynitrite) increased in concomitance with down-regulation of MnSOD and catalase, dissipation of mitochondrial membrane potential and cell necrosis. It is noteworthy that treatment with PN and DMAPT also caused a rapid and remarkable decrement of the level of Nrf-2, which is a critical regulator of the intracellular antioxidant response. In conclusion PN and DMAPT markedly inhibited viability of stem-like cells derived from three lines of TNBCs by inducing ROS generation, mitochondrial dysfunction and cell necrosis.

[1] *Drug Discov Today* 2013; **18**: 894-905.

[2] *Cell Death Dis* 2013; **4**: e891.



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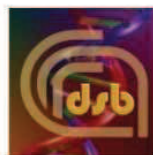
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