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Title: Endoplasmic reticulum stress, COPD and lung cancer

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Body: Introduction: COPD is a risk factor for lung cancer (LC). The mechanisms for this association are unknown. Both diseases can present endoplasmic reticulum stress (ERS) that is characterised by an accumulation of misfolded and unfolded proteins in endoplasmic reticulum lumen, altering the cellular homeostasis. Hypothesis: The ERS could be a mechanism for LC in COPD patients. Aims: To compare, in smoking patients with/without COPD (with /without LC) and healthy non-smoking controls, different ERS markers. Population and methods: Fifty one subjects distributed in 5 groups according to the presence or not of COPD and LC. Clinical history, lung function tests and blood analysis were performed in all subjects. The most representatives markers for ERS (BIP, IRE, xBPS, PERK, CHOP, EIF and ATF6) were analysed by real-time polymerase chain reaction (RT-PCR). The values were normalised according to the GADPH. Results: Healthy controls, n=10 (3 men, 63± 6years); Smoking subjects with normal lung function without LC, n=11 (9 men, 57 ± 14 years, 37± 28 pack-year) ; COPD patients without LC, n=9 (9 men, 62 ± 10 years, 55± 20 pack-year, FEV1ref 77 ± 17 %, FEV1/FVC 59 ± 8%); Smoking subjects with normal lung function with LC, n=11 (11 men, 67 ± 9 years, 57 ± 37pack-year); COPD patients with LC, n=10 (10 men, 66 ± 7years, 61 ± 20pack-year, FEV1ref 70±14 %, FEV1/FVC 60 ± 9%). We found that BIP values (median and range) increased ($p<0.05$) in patients with LC with normal function text and patients with LC and COPD ((1.44 [1.28-1.99], 1.36 [0.97-1.64], respectively) compared with healthy controls (0.99 [0.70-1.19]). We found no differences in the other ERS markers. Conclusions: BIP is associated with LC independently of lung function.