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Title: Smoking during pregnancy induces early lung senescence in neonates

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Body: Background and Aim. In utero smoke exposure is associated to altered lung growth and airflow limitation in early adult life, which may predispose to chronic respiratory diseases such as COPD. As accelerated lung aging has been demonstrated as a key pathogenic mechanism of COPD, the aim of our study was to demonstrate the induction of early lung senescence by in utero exposure to cigarette smoke (CS). Methods. Female mice were cyclically exposed to CS during their pregnancy, while control females were exposed in same conditions to air. Body growth, lung volume, and lung function were measured in pups. Lung expression of genes controlling senescence and apoptosis was analyzed in pups at birth, and at 21 days of postnatal age. Results. When compared to control litters, in utero smoke exposure induced lower birth weight ($p<0.001$), lower lung volume at 21 days ($p<0.05$), and decrease lung compliance ($p<0.01$). Lung expression of Bax, p16, and p21 significantly differed between groups at birth, and lung expression of p16 was still significantly higher at day 21 in pups exposed to CS in utero.

	Birth			Day 21		
Gene	Control	CS exposure	p value	Control	CS exposure	p value
Bax	0.99±0.05	1.33±0.06	<0.001	0.90±0.10	1.15±0.07	NS
p53	1.17±0.12	1.25±0.06	NS	0.62±0.14	0.83±0.11	NS
p21	0.88±0.17	1.44±0.11	<0.01	0.65±0.10	1.02±0.15	NS
p16	2.33±0.56	0.17±0.03	<0.0001	3.66±0.71	10.2±2.08	<0.05

Conclusion. In our mouse model, in utero smoke exposure reproduced growth alterations observed in humans. We demonstrated the induction of early lung cellular senescence, associated to permanent impairment in respiratory function. These molecular abnormalities may induce susceptibility to the development of COPD in adults.