00482 Passive smoking impairs protein phosphatase 2A activity in children with severe asthma

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Background: Exposure to parental smoking is known to worsen asthma symptoms in their children. As one of the molecular mechanisms, we recently reported that cigarette smoke-induced oxidative stress impairs histone deacetylase-2 (HDAC2) via phosphoinositide-3-kinase (PI3K) signalling activation, resulting in corticosteroid insensitivity in alveolar macrophages. Here we further investigated the involvement of protein phosphatase 2A (PP2A) in oxidative stress-mediated PI3K-Akt signalling activation.

Methods: To investigate passive smoking-dependent molecular abnormalities, bronchoalveolar lavage fluid (BALF) samples were obtained from 19 children with severe asthma (10 non-passive smoking and 9 passive smoking subjects). Immunoprecipitated PP2A/HDAC2 activities, PP2A/Akt phosphorylation levels, responsiveness to corticosteroid and PP2A/Akt association were evaluated in alveolar macrophages and PMA-differentiated macrophage-like U937 cells under oxidative stress.

Results: Passive smoking reduced PP2A activity with negative correlation to Akt phosphorylation level and with positive correlation to HDAC2 activity in alveolar macrophages. Also in PMA-U937 cells exposed to oxidative stress which can induce steroid insensitivity, PP2A activity was reduced with concomitant enhancement of Akt phosphorylation level and reduction of HDAC2 activity. Oxidative stress not only reduced PP2A activity, but also dissociated PP2A from Akt. Even more importantly, PP2A overexpression reduced Akt phosphorylation levels.

Conclusion: Passive smoking impaired PP2A function, which could contribute to Akt signal-dependent corticosteroid insensitivity in children with refractory asthma. PP2A appears to be a negative regulator of PI3K-Akt signalling and impaired PP2A may be a potential therapeutic target.