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Crucial role of fatty acid oxidation in asthmatic bronchial smooth muscle remodelling

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Metabolic remodelling towards mitochondrial fatty acid metabolism increases ATP production in asthmatic bronchial smooth muscle cells. Fatty acid metabolism inhibition decreases asthmatic bronchial smooth muscle cell proliferation. https://bit.ly/3fyx6Ft

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Abstract

Background Bronchial smooth muscle (BSM) remodelling in asthma is related to an increased mitochondrial biogenesis and enhanced BSM cell proliferation in asthma. Since mitochondria produce the highest levels of cellular energy and fatty acid β-oxidation is the most powerful way to produce ATP, we hypothesised that, in asthmatic BSM cells, energetic metabolism is shifted towards the β-oxidation of fatty acids.

Objectives We aimed to characterise BSM cell metabolism in asthma both *in vitro* and *ex vivo* to identify a novel target for reducing BSM cell proliferation.

Methods 21 asthmatic and 31 non-asthmatic patients were enrolled. We used metabolomic and proteomic approaches to study BSM cells. Oxidative stress, ATP synthesis, fatty acid endocytosis, metabolite production, metabolic capabilities, mitochondrial networks, cell proliferation and apoptosis were assessed on BSM cells. Fatty acid content was assessed *in vivo* using matrix-assisted laser desorption/ionisation spectrometry imaging.

Results Asthmatic BSM cells were characterised by an increased rate of mitochondrial respiration with a stimulated ATP production and mitochondrial β-oxidation. Fatty acid consumption was increased in asthmatic BSM both *in vitro* and *ex vivo*. Proteome remodelling of asthmatic BSM occurred *via* two canonical mitochondrial pathways. The levels of carnitine palmitoyl transferase (CPT)2 and low-density lipoprotein (LDL) receptor, which internalise fatty acids through mitochondrial and cell membranes, respectively, were both increased in asthmatic BSM cells. Blocking CPT2 or LDL receptor drastically and specifically reduced asthmatic BSM cell proliferation.

Conclusion This study demonstrates a metabolic switch towards mitochondrial β-oxidation in asthmatic BSM and identifies fatty acid metabolism as a new key target to reduce BSM remodelling in asthma.