Reprogramming of cellular metabolism: driver for airway remodelling in COPD?

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Mitochondrial dysfunction and metabolic changes contribute to inflammation and tissue remodelling in COPD http://ow.ly/hgsm30gARnv

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Mitochondrial dysfunction, in particular decreased oxidative phosphorylation and increased production of mitochondrial reactive oxidant species (ROS), and changes in cellular metabolism are increasingly recognised as important events in the pathogenesis of a range of lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension and lung cancer [1, 2]. We are beginning to understand how dysfunction of the mitochondria is linked to the altered use of metabolic pathways and how this impacts cellular function. This switch in use of different metabolic pathways is often referred to as metabolic reprogramming, repatterning or rewiring. Mitochondrial dysfunction and metabolic reprogramming are important for understanding cancer, immunity and inflammation, but studies focused on tissue remodelling have also revealed a regulatory role of these mechanisms [1, 2].

Glycolysis followed by oxidative phosphorylation within mitochondria is a very efficient way to generate ATP. However, cells can also generate ATP independent of mitochondrial function using anaerobic glycolysis, which is, however, much less efficient. Studies by Warburg have shown that tumour cells can also switch to glycolysis independent of cellular oxygen levels, and similar mechanisms may be operational in proliferating non-transformed cells [3]. This flexibility in the use of various metabolic pathways is important for the ability of cells to respond to triggers in the cellular micro-environment, as well as to adapt to intracellular changes in function of organelles such as mitochondria. Indeed, in cancer, enhanced glycolysis is associated with both enhanced growth demands and adaptation to altered mitochondrial function [3, 4]. Importantly, inflammation and cigarette smoke exposure have been shown to result in mitochondrial dysfunction, including decreased oxidative phosphorylation and increased production of mitochondrial ROS [1]. In lung cancer cells, KRAS mutations may drive mitochondrial dysfunction and subsequent glycolysis, as well as an increased delivery of glucose-derived metabolites into the tricarboxylic acid (TCA) cycle and glutathione biosynthesis [4, 5]. Collectively, these findings indicate that mitochondrial dysfunction may also drive metabolic reprogramming and increase antioxidant defences through glutathione synthesis in COPD. Previous studies have demonstrated mitochondrial dysfunction in various cell types in COPD, including airway smooth muscle cells (ASMC) [6]. Metabolic reprogramming resulting from mitochondrial dysfunction may affect nucleotide and amino acid synthesis, as well as maintenance of the cellular redox balance by, for example, increasing synthesis of glutathione. The outcome of these changes may result in enhanced cellular proliferation.

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Energy metabolism and changes herein possibly affecting local inflammatory responses and tissue repair are a relatively unexplored area in (chronic) lung diseases, and harbour potential important therapeutic targets. In this issue of the *European Respiratory Journal*, Michaeloudes *et al.* [7] build on their previous findings of mitochondrial dysfunction and metabolic reprogramming in a study that provides evidence that metabolic changes in glycolysis, glutamine and fatty acid metabolism may contribute to hyper-proliferation of ASMC in COPD through an increase in biosynthesis and anti-oxidant defences. This hyper-proliferation of ASMC is thought to be an important contributor to small airway remodelling, which is a feature of COPD, together with inflammation and destruction of parenchymal tissue. Airway remodelling contributes to lung function impairment, and it is therefore essential to understand crucial events herein for unravelling COPD disease pathogenesis and development of novel therapeutics. The authors used cultures of ASMC collected from endobronchial biopsies and airway tissue obtained during lung resection surgery from non-smokers, smokers without airflow limitation and COPD patients. They studied the metabolic profile of these cells at baseline conditions and following growth stimulation by treatment with transforming growth factor (TGF)-β and foetal bovine serum using a state-of-the-art unbiased metabolomics approach and advanced bioinformatics tools. The authors demonstrate an increase in glycolysis, glutamine accumulation, and alterations in fatty acid metabolism in cells derived from COPD patients. In addition, they demonstrate a higher ratio of reduced-to-oxidised glutathione and less formation of reactive oxygen species in the mitochondria in these cultured cells (figure 1). This is in apparent contrast to the oxidant-induced tissue injury reported in COPD, and indicates that *in vivo* these increased anti-oxidant defences may not suffice to prevent oxidant-induced injury. They conclude that these differences in COPD ASMC may underlie the observed cellular hyper-proliferation as well as affect redox balance, collectively supporting the growth of ASMC in COPD.

How can these observations be used to develop novel therapies for COPD? Since mitochondrial dysfunction appears to be a central event in COPD, therapeutic targeting of mitochondrial dysfunction may be an interesting approach [1, 2, 8]. Strategies may include the use of mitochondria-targeted anti-oxidants, stimulating mitochondrial biogenesis and regulation of mitophagy (a special from of autophagy that targets mitochondria). Recently, mesenchymal stromal cells (MSC) have emerged as a potential novel therapy for COPD. Following successful application of these cells in animal models of COPD, the first clinical trials have now also been reported [9]. MSC may modulate inflammation and tissue repair in COPD through a variety of mechanisms, including cell–cell contact, secretion of soluble mediators, exosomes and mitochondrial transfer. This latter mechanism was found to contribute to the

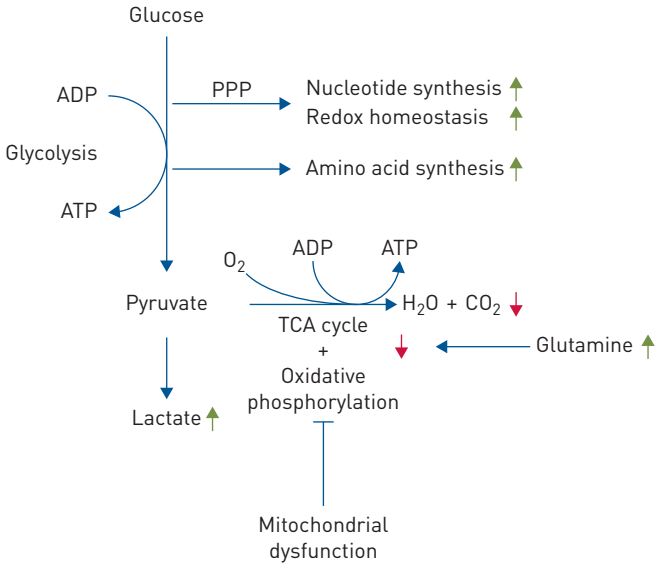

FIGURE 1 Mitochondrial dysfunction and metabolic reprogramming. Glucose is metabolised to pyruvate by glycolysis, and in presence of oxygen this pyruvate is converted to water, carbon dioxide and ATP in the mitochondria by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. In absence of oxygen or case of mitochondrial dysfunction, pyruvate is (largely) converted to lactate. In addition, glycolysis-derived carbons now also feed into several other pathways that direct offshoots of glycolysis, such as the pentose phosphate pathway (PPP; generating riboses and NADPH), and those leading to amino acid (alanine) synthesis. Furthermore, mitochondrial dysfunction also inhibits glutaminolysis resulting in the accumulation of glutamine. A green arrow indicates changes in chronic obstructive pulmonary disease airway smooth muscle cells reported by Michaeloudes *et al.* [7].

protective effect of MSC towards alveoli in acute lung injury models [10]. Interestingly, the authors of the article in the present issue of the *European Respiratory Journal* very recently also reported that MSC may limit oxidative stress-induced mitochondrial dysfunction in human ASMC and in an oxidant-induced mouse model of COPD; this protection appeared to involve transfer of mitochondria from the MSC to the airway smooth muscle cells [11]. It will be important to investigate whether this approach also reverses metabolic reprogramming and affects growth of COPD ASMC. Finally, it is also important to consider the interaction of the microbiota with metabolic processes of the host. This was for instance demonstrated to be likely important in the gut, where products derived from bacterial fermentation of dietary fibres were found to affect gut cell proliferation and gene expression dependent on the presence of the Warburg effect [12]. Similar mechanisms may also be relevant in the lung.

In summary, the study by Michaeloudes *et al.* [7] underscores the increasing relevance of delineating local and systemic metabolic changes for understanding diseases of the lung. This may provide relevant targets for new therapeutic interventions to counteract inflammation, tissue remodelling and possibly to promote tissue repair.

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