The mitochondrial Uncoupling Protein 2 UCP2 is a member of the mitochondrial carrier family and belongs to the UCP subfamily. It is widely expressed in tissues. In immune cells, UCP2 has a regulatory function through its effect on the production of reactive oxygen species and MAPK signalling. Ucp2<sup>−/−</sup> mice are resistant to infection by parasites and intracellular bacteria but are more sensitive to chronic inflammation and experimental neurodegeneration. We found that autoimmune diabetes was strongly uncouples respiration from ATP synthesis is still debated. Ucp2 hyperinsulinism in patients. The question of whether UCP2 fully agreement with the known inhibitory role of UCP2 on insulin toward non-respiratory oxygen-dependent targets.

It is widely expressed in tissues. In immune cells, UCP2 has a regulatory function through its effect on the production of reactive oxygen species and MAPK signalling. Ucp2<sup>−/−</sup> mice are resistant to infection by parasites and intracellular bacteria but are more sensitive to chronic inflammation and experimental neurodegeneration. We found that autoimmune diabetes was strongly accelerated in Ucp2<sup>−/−</sup> mice compared to Ucp2<sup>+/+</sup> mice with increased intra-islet lymphocytic infiltration. These data highlight UCP2 as a new player in autoimmune diabetes. In addition, in agreement with the known inhibitory role of UCP2 on insulin secretion, loss of function of UCP2 contributes to congenital hyperinsulinism in patients. The question of whether UCP2 fully uncouples respiration from ATP synthesis is still debated. Ucp2<sup>−/−</sup> cells display enhanced proliferation associated with a metabolic switch from fatty acid oxidation to glucose metabolism. This metabolic switch requires the unrestricted availability of glucose, and Ucp2<sup>−/−</sup> cells more readily activate autophagy than wild-type cells when deprived of glucose. Altogether, these results suggest that UCP2 promotes mitochondrial fatty acid oxidation while limiting mitochondrial catabolism of pyruvate. UCP2 expression is also required for efficient oxidation of glutamine in macrophages. This role of UCP2 in glutamine metabolism appears independent from its uncoupling activity.

Our results demonstrate that NO acts not only as a physiological regulator of cell respiration but also as a signalling agent in the mitochondria and a controller of the distribution of available oxygen. Such mechanisms may also be involved in the initiation of pathophysiology.

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