Calorie Restriction Activates the Biosynthesis of Cardiolipin and its Distribution between Membranes

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Calorie restriction (CR) is a dietary regime that has been demonstrated experimentally to increase the lifespan in several organisms. A common metabolic feature in CR organisms is the enhancement in mitochondrial metabolism through a still unknown mechanism. Little attention has been focused to date on phospholipid or membrane homeostasis in this diet. Such studies are of importance given that mitochondrial function has a strict dependence on the protonmotive force across the inner membrane. Cardiolipin (CL) is the main anionic phospholipid present in mitochondrial membranes and plays a key role in the correct function of mitochondria. Moreover, it has diverse roles in cellular responses to environmental stress and acts as a signaling molecule. To elucidate the effect that CR exerts on the biosynthesis of CL, phospholipids were isolated from rat liver mitochondria under a CR or *ad libitum* diets and the content of CL together with the expression levels of the enzymes involved in its biosynthesis and remodeling were quantified. We found that mitochondria from *ad libitum* animals presented an increased content of lipoperoxides in addition to a higher activity of phospholipase A2, which hydrolyzes oxidatively-damaged acyl chains. Moreover, the expression of several enzymes involved in the biosynthesis of cardiolipin is upregulated in CR animals. Interestingly, when mitochondrial membranes were fractionated, the outer membrane presented a higher content of CL, indicating that it is redistributed between membranes: first between the inner-membranes leaflets by a scramblase and then by the contact sites between membranes. Moreover, we found that CR upregulates the enzymes of the CL biosynthetic pathway, thus increasing the total concentration of CL. Interestingly, to avoid an over-accumulation of this phospholipid in the inner membrane, it is actively redistributed between membranes. Finally, we demonstrate that CR promotes the biosynthesis of CL which contributes to the proper function of mitochondria.

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