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MITOCHONDRIAL TRANSLATION IS THE PRIMARY DETERMINANT OF SECONDARY MITOCHONDRIAL COMPLEX I DEFICIENCIES

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Individual complexes of the mitochondrial oxidative phosphorylation system (OXPHOS) are not linked solely by their function; they also share dependencies at the maintenance/assembly level, where one complex depends on the presence of a different individual complex. Despite the relevance of this 'interdependence' behavior for mitochondrial diseases, its true nature remains elusive. To understand the mechanism that can explain this phenomenon, we examined the consequences of the aberration of different OXPHOS complexes in human cells. We demonstrate here that complete disruption of each of the OXPHOS complexes resulted in a perturbation in energy deficiency sensing pathways, including the integrated stress response (ISR) pathway. The secondary decrease of complex I (cI) level was triggered by both complex IV and complex V deficiency, and it was independent of ISR signaling. On the other hand, we identified the unifying mechanism behind cI downregulation in the downregulation of mitochondrial ribosomal proteins and, thus, mitochondrial translation. We conclude that the secondary cI defect is due to mitochondrial protein synthesis attenuation, while the responsible signaling pathways could differ based on the origin of the OXPHOS defect.

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