Assembly defects induce oxidative stress in inherited mitochondrial complex I deficiency

Titre	Assembly defects induce oxidative stress in inherited mitochondrial complex I deficiency
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Mots-clés	Mitochondria; Mitochondrial diseases; Complex I; FMN site; Oxidative stress; Assembly defects [17]
Résumé en anglais	Complex I (CI) deficiency is the most common respiratory chain defect representing more than 30% of mitochondrial diseases. CI is an L-shaped multi-subunit complex with a peripheral arm protruding into the mitochondrial matrix and a membrane arm. CI sequentially assembled into main assembly intermediates: the P (pumping), Q (Quinone) and N (NADH dehydrogenase) modules. In this study, we analyzed 11 fibroblast cell lines derived from patients with inherited CI deficiency resulting from mutations in the nuclear or mitochondrial DNA and impacting these different modules. In patient cells carrying a mutation located in the matrix arm of CI, blue native-polyacrylamide gel electrophoresis (BN-PAGE) revealed a significant reduction of fully assembled CI enzyme and an accumulation of intermediates of the N module. In these cell lines with an assembly defect, NADH dehydrogenase activity was partly functional, even though CI was not fully assembled. We further demonstrated that this functional N module was responsible for ROS production through the reduced flavin mononucleotide. Due to the assembly defect, the FMN site was not re-oxidized leading to a significant oxidative stress in cell lines with an assembly defect. These findings not only highlight the relationship between CI assembly and oxidative stress, but also show the suitability of BN-PAGE analysis in evaluating the consequences of CI dysfunction. Moreover, these data suggest that the use of antioxidants may be particularly relevant for patients displaying a CI assembly defect.

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