Editors' comments and author responses

Kinase perturbations redirect mitochondrial function in cancer

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Editors

We suggest clarifying the sentence:
"For example, PKA, where is in the mitochondrial matrix, it has been shown to phosphorylate the NADH:ubiquinone oxidoreductase (Complex I, CI) and the cytochrome c oxidase (Complex IV, CIV)."

Authors

New sentence:
"For example, PKA, when it is localized at the mitochondrial matrix, has been shown to phosphorylate the NADH:ubiquinone oxidoreductase"

Editors

We suggest changing the following sentence for clarification and in accordance to MitoEAGLE (BEC 2020.1):
"AKT has been shown to compartmentalize with mitochondria and thus may phosphorylate elements of the ETS at the level of the ATP-synthase."
ATP synthase does not belong to the ETS, but to the phosphorylation system.

Authors

New sentence:
"AKT has been shown to be associated with mitochondria and may phosphorylate elements of the ATP-synthase."

Editors

Changes suggested in Figure 1 legend for clarification and in accordance to MitoEAGLE (BEC 2020.1):

(1) "The oxidative phosphorylation (OXPHOS) system comprises the ETS (electron transfer capacity, ET) and the ATP synthase where the reduced fuel substrates coming from the tricarboxylic acid cycle (TCA) and other metabolic pathways are oxidized by electron transfer, chemiosmotic coupling to the phosphorylation

of ADP to ATP and intrinsically uncoupling by proton leak, cation cycling and electron leak (LEAK, L)."

Suggestion to not mention the respiratory coupling states in the figure and figure legend since they are also not cited throughout the manuscript. Also, the OXPHOS system consists of the ETS and the phosphorylation system, and ATP synthase is a component of the phosphorylation system. The proton slip could also be mentioned since it can also be responsible for the uncoupling.

(2) "Electrons fuel from NADH-linked substrates to Complex I (CI) and from FADH2-linked substrates to CII converging at the Q-junction and transferred to CIII, cytochrome *c* (c) and CIV, where reduce a molecule of O_2 to produce H_2O."

Succinate is the substrate of Complex II, and not $FADH_2$. There are also other electron transfer pathways that converge at the Q-junction.

(3) "The protonmotive force generated is dissipated at the ATP synthase to generate ATP from ADP."

It would be better to mention that the energy from the proton motive force is used by the ATP synthase for the phosphorylation of ADP to ATP rather then dissipated.

Authors

New sentences:

(1) "The oxidative phosphorylation (OXPHOS) system comprises the ETS and the phosphorylation system (including ATP synthase [ATP syn]) where the reduced fuel substrates coming from the tricarboxylic acid cycle (TCA) and other metabolic pathways are oxidized by electron transfer, chemiosmotic coupling to the phosphorylation of ADP to ATP and intrinsically uncoupling by proton leak and slip, cation cycling, and electron leak."

(2) "Electrons fuel from NADH-linked substrates to Complex I (CI) and from succinate to CII. These and other electron transfer pathways converge at the Q-junction with further transfer to CIII, cytochrome *c* (c) and CIV, where electrons reduce O_2 producing H_2O."

(3) "The protonmotive force generated is utilized for the ATP synthase to phosphorylate ADP to ATP (Gnaiger et al 2020)."