O2k brief Cancer
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High-resolution respirometry: cancer

OXPHOS remodeling in high-grade prostate cancer involves mtDNA mutations and increased succinate oxidation

nature communications

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High-resolution respirometry of prostate tissue samples

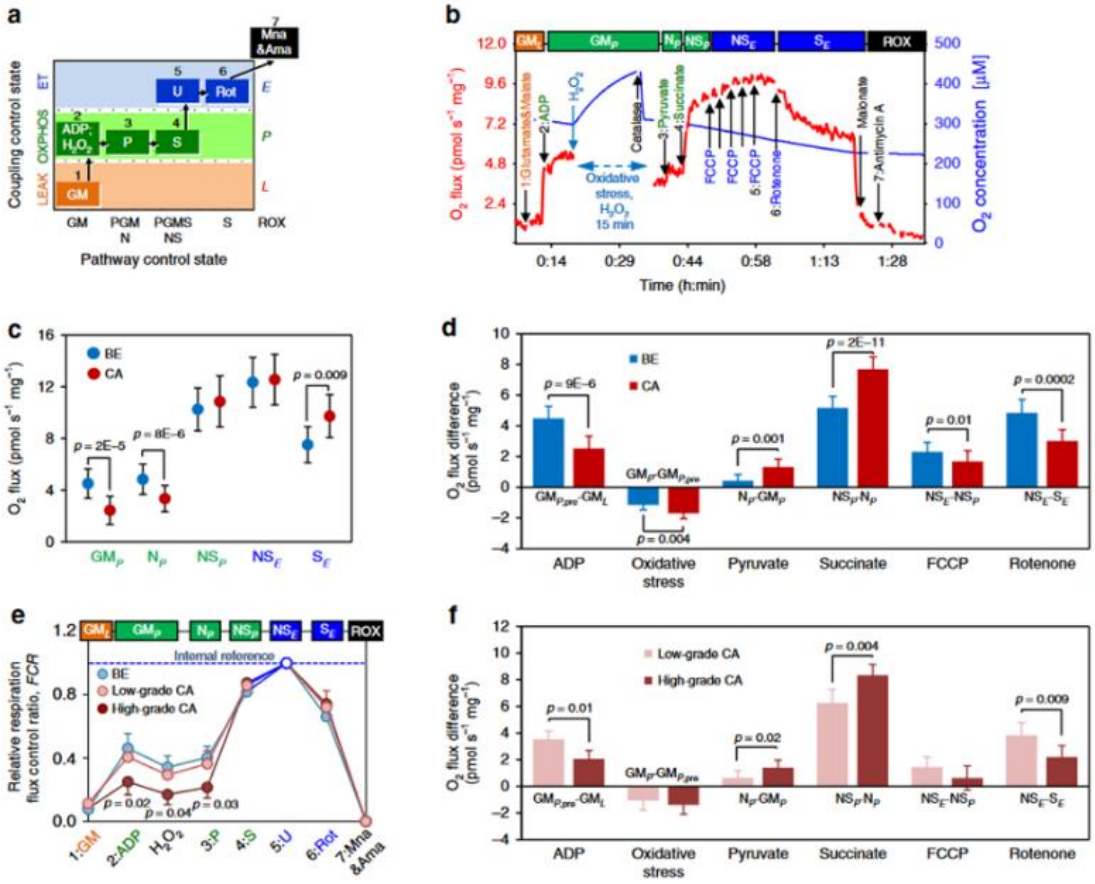

Figure 1. (a) Coupling/pathway control diagram showing the sequential steps in the substrate-uncoupler-inhibitor titration (SUIT) protocol with different coupling states. **(b)** Representative HRR traces with permeabilized tissue. Red line (left *Y*-axis): wet mass-specific O_2 flux. Blue line (right *Y*-axis): O_2 concentration. Substrate-uncoupler-inhibitor titrations are indicated by arrows. Different coupling/pathway control states are indicated in boxes: LEAK (orange); OXPHOS (green); ET (blue); ROX (black). **(c)** Respiratory capacity in benign (blue, $N = 50$) versus malignant (red, $N = 50$) tissue samples: OXPHOS-capacity (GM_P, N_P and NS_P) and ET-capacity (NS_E and S_E). **(d)** Effects of substrates GM, pyruvate, succinate, oxidative stress, uncoupler FCCP, and CI inhibitor rotenone on O_2 flux in benign (blue, $N = 50$) and malignant (red, $N = 50$) tissue samples. **(e)** Normalized respiratory capacities of high-grade tumor (Gleason > 7; dark red; $N = 10$) and low-grade tumor (Gleason ≤ 7, light red, $N = 40$) compared to benign samples (blue, $N = 50$). **(f)** Effects of substrates, oxidative stress, uncoupler, and CI inhibitor on O_2 flux in low-grade (light red, $N = 40$) and high-grade (dark red, $N = 10$) tissue samples. Data in (c-f) are presented as mean values ± SD.

O2k-brief communicated by AC Bastos and L Tindle-Solomon
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Supported by project NextGen-O2k which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 859770

Respiratory capacities in prostate cell lines

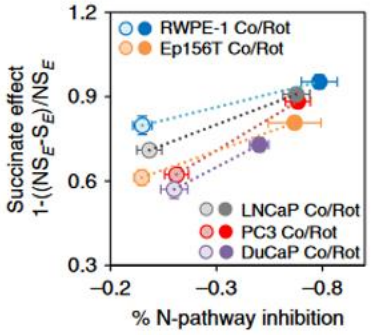

Figure 2. S-pathway OXPHOS capacity upregulation by partial inhibition of N-pathway oxidative flux in benign (RWPE1, *N* = 3; EP156T, *N* = 3) and malignant (PC3, *N* = 6; LNCaP, *N* = 4; DuCaP, *N* = 3) prostate cell lines. Relative S-pathway OXPHOS capacity (normalized to total respiratory capacity, NS_E) with different degrees of N-pathway inhibition is shown for all the cell lines as Control *versus* treatment with Rotenone (Co/Rot). Values represent mean ± SD.

Respiration of malignant biopsies carrying variant mutations of CI

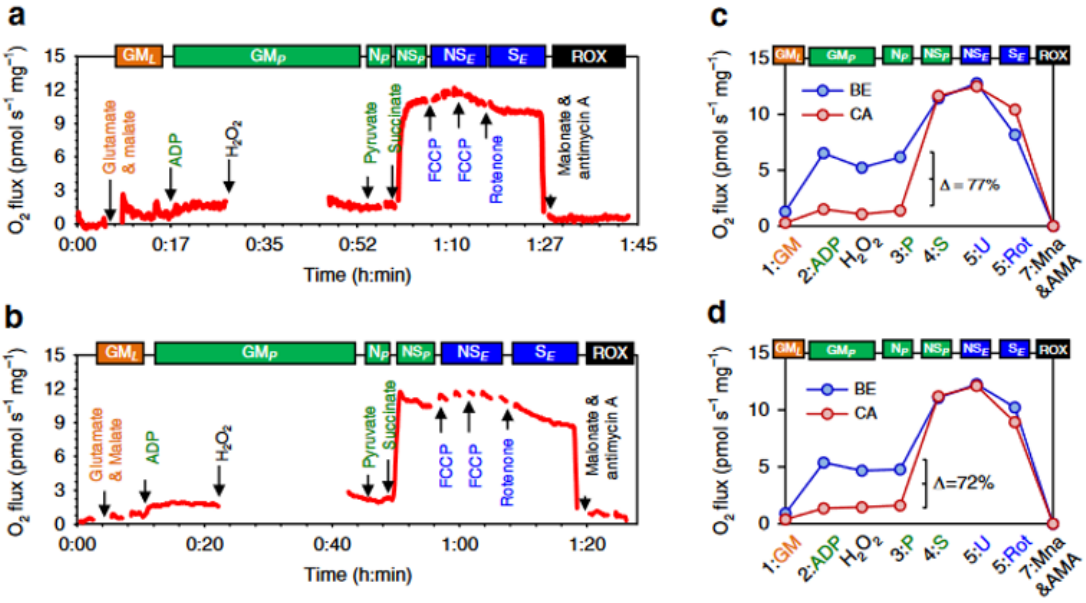

Figure 3. (a-b) HRR traces of the malignant biopsies carrying the F411S **(a)** or the T387A mutation **(b)**, respectively. **(c–d)** Respiratory capacities of malignant samples (red) carrying either the F411S mutation **(c)** or the T387A mutation **(d)**, compared to the corresponding benign tissue (blue). Values represent mean ± SD of the two separate measurements for each tissue sample.

Decreased N-pathway capacity associated with potentially deleterious, high-level mtDNA heteroplasmies in mt-CI genes, higher mtDNA load and increased mt-mass are distinct characteristics of high-grade tumors, highlighting the diagnostic and prognostic potential of metabolic rewiring.

Reference: Schöpf Bernd, Weissensteiner Hansi, Schäfer Georg, Fazzini Federica, Charoentong Pornpimol, Naschberger Andreas, Rupp Bernhard, Fendt Liane, Bukur Valesca, Giese Irina, Sorn Patrick, Sant'Anna-Silva Ana Carolina, Iglesias-Gonzalez Javier, Sahin Ugur, Kronenberg Florian, Gnaiger Erich, Klocker Helmut (2020) OXPHOS remodeling in high-grade prostate cancer involves mtDNA mutations and increased succinate oxidation. Nat Commun 11:1487.

Text slightly modified based on the recommendations of the COST Action MitoEAGLE CA15203. Doi:10.26124/mitofit:190001.v6

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