O2k-brief communicated by AC Bastos and L Tindle-Solomon
Oroboros Instruments

Cancer


High-resolution respirometry: cancer

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

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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. Representative HRR traces with permeabilized tissue. Red line (left Y-axis): wet mass-specific O2 flux. Blue line (right Y-axis): O2 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). (b) Respiratory capacity in benign (blue, N = 50) versus malignant (red, N = 50) tissue samples: OXPHOS-capacity (GM, N, and NS) and ET-capacity (NSE and S). (c) Effects of substrates GM, pyruvate, succinate, oxidative stress, uncoupler FCCP, and CI inhibitor rotenone on O2 flux in benign (blue, N = 50) and malignant (red, N = 50) tissue samples. (d) 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). (e) Effects of substrates oxidative stress, uncoupler, and CI inhibitor on O2 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.
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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; EPI156T, 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.


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