O03 Mitochondrial complex I gene mutations drive metabolic reprogramming in prostate cancer

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Introduction & Objectives: Remodeling of energy metabolism is a hallmark of tumors, including prostate cancer. A major player are the mitochondria, which provide energy and metabolites for malignant growth. Several studies highlighted the occurrence of mutations in the mitochondrial DNA (mtDNA) and liked these events to higher malignancy and worse survival of patients. In our study, we identified mtDNA mutations and linked them to mitochondrial respiratory function and mitochondrial complex I.

Materials & Methods: Paired benign/cancer fresh tissue biopsies were isolated from prostate specimens of patients undergoing radical prostatectomy for first-line treatment of prostate cancer to measure mitochondrial respiratory capacity by high-resolution respirometry and determine DNA sequence alterations by NGS deep-sequencing of mtDNA. Grouping mtDNA mutations into different categories, e.g. control region or coding genes, silent or amino acid-changing mutations, we analyzed a possible association with respiratory function. Furthermore, we assessed the impact of mutations on the 3D structure of proteins of the mitochondrial megacomplex I.

Results: High-Resolution respirometry uncovered a reduced respiratory capacity with NADH-pathway substrates glutamate and malate in malignant tissue, with most severe alterations in high-grade tumors (Gleason score ≥8). Reduced NADH-pathway capacity was fully compensated by an increase of the S-(succinate)-pathway capacity, which provided the vast portion of total respiratory capacity. The number and heteroplasmy level of mtDNA mutations was significantly increased in tumors compared to the benign tissue samples, for example, 38 potentially deleterious mutations in protein-encoding mt-genes in malignant versus 10 in benign samples. High levels of potentially deleterious mutations in mitochondrial Complex I-encoding genes were associated with up to 70% reduction of NADH-pathway capacity. Structural Analysis of these mutations suggests that specific amino acid alterations could lead to potentially deleterious effects on the Complex I molecular structure, thus supporting a causal relationship.

Conclusions: We provide evidence of a crucial role of mutations in mitochondrial Complex I encoding genes in prostate cancer, with an impact on mitochondrial megacomplex I-dependent NADH pathway capacity, which is compensated by increased metabolization of succinate.