Clinical response to chemotherapy in oesophageal adenocarcinoma patients is linked to defects in mitochondria.

Abstract:
Chemotherapeutic drugs kill cancer cells, but it is unclear why this happens in responding patients but not in non-responders. Proteomic profiles of patients with oesophageal adenocarcinoma may be helpful in predicting response and selecting more effective treatment strategies. In this study, pretherapeutic oesophageal adenocarcinoma biopsies were analysed for proteomic changes associated with response to chemotherapy by MALDI imaging mass spectrometry. Resulting candidate proteins were identified by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and investigated for functional relevance in vitro. Clinical impact was validated in pretherapeutic biopsies from an independent patient cohort. Studies on the incidence of these defects in other solid tumours were included. We discovered that clinical response to cisplatin correlated with pre-existing defects in the mitochondrial respiratory chain complexes of cancer cells, caused by loss of specific cytochrome c oxidase (COX) subunits. Knockdown of a COX protein altered chemosensitivity in vitro, increasing the propensity of cancer cells to undergo cell death following cisplatin treatment. In an independent
validation, patients with reduced COX protein expression prior to treatment exhibited favourable clinical outcomes to chemotherapy, whereas tumours with unchanged COX expression were chemoresistant. In conclusion, previously undiscovered pre-existing defects in mitochondrial respiratory complexes cause cancer cells to become chemosensitive: mitochondrial defects lower the cells’ threshold for undergoing cell death in response to cisplatin. By contrast, cancer cells with intact mitochondrial respiratory complexes are chemoresistant and have a high threshold for cisplatin-induced cell death. This connection between mitochondrial respiration and chemosensitivity is relevant to anticancer therapeutics that target the mitochondrial electron transport chain. Copyright © 2013 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.