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Cisplatin resistant NSCLC cells suffer a metabolic reprograming and can be targeted using Metformin

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Lung cancer is the most common cancer worldwide in terms of incidence and it is also the leading cause of cancer-related death. Platinum-based chemotherapy remains the standard of care for most cases, however chemoresistance is often developed during the treatment, limiting clinical utility of this drug. The mechanisms of cisplatin resistance are complex, involving diverse strategies and pathways. Over the last years, an increase of the oxidative metabolism has been suggested as common mechanism for various cancers and treatments.

In this study, we first described this mechanism for NSCLC in response to cisplatin treatment using 3 different cell lines (A549, H1299, and H460) and their cisplatin-resistant versions. Two out of three CDDP-resistant cell lines derived showed an stable increase in their mitochondrial inner membrane potential (MIMP) and PGC1-? expression. Interestingly, all of them showed a stable increase in ROS levels. Moreover, the early response to CDDP treatment of the six cell lines was similar to the stable changes observed.

Remarkably, this increase of the OXPHOS dependence can be exploited as a weakness of resistant cells, as demonstrated by their increased sensitivity to Metformin treatment. This results provide a new understanding into cisplatin resistance, that may lead to novel therapeutic approaches to improve drug efficacy