Streszczenie rozprawy doktorskiej mgr Jessici Catapano pt. „Wpływ nabytej lekooporności na wrażliwość komórek raka prostaty na działanie blokerów metabolicznych"

Abstract

Drug resistance of cancer cells is a significant challenge for the contemporary oncology and remains a leading cause of cancer treatment failures. Combined therapies are commonly used to overcome this problem, as they can potentially enhance the effectiveness of the treatment while reducing its side effects. This is especially important for the patients with prostate cancer, who are typically elderly men burdened with comorbidities. Metabolic blockers, which interfere with cancer cell metabolism, are promising drugs for the combined cancer therapies. Amongst them, metformin, which is commonly used in the treatment of type II diabetes, is considered as a potential anti-cancer drug. Its mechanism of action is based on the inhibition of the complex I of the mitochondrial respiratory chain. However, the side effects of the application of metabolic blockers, including metformin, and their ability to trigger phenotypic microevolution of cancer cells remain unaddressed.

This dissertation was aimed at verifying the hypothesis claiming that the acquired drug resistance of prostate cancer cells affects their sensitivity to the simultaneous administration of a cytostatic and metformin as a metabolic blocker. Sensitivity of prostate cancer model cells (PC-3 WT and DU145 WT) and their drug-resistant lineages (PC-3_DCX20 and DU145_DCX20) to the simultaneous administration of docetaxel and metformin was compared along with the assessments of adaptive cell responses and cell invasiveness in response to the combined chemotherapeutic/metabolic stress. Metabolic background of the cells' responses to metformin and the microevolutionary consequences of the application of this metabolic blocker were considered. Alongside, the reactivity of the cells to metformin and fenofibrate (which is anti-hyperlipidemic PPARα activator and a metabolic blocker) were compared in prostate cancer model.

The obtained data confirmed metformin's potential in supporting prostate cancer treatment. Metabolic decoupling was observed in docetaxel-sensitive prostate cancer cell lineages (PC-3 WT and DU145 WT) upon metformin administration. It was manifested by the augmentation of cytostatic/cytotoxic effects induced by docetaxel, the accumulation of energy carriers (NAD(P)H and ATP) and the impairment of the drug-efflux systems. Independently, docetaxel impaired the pathways of energy transfer from their carriers to membrane ABC transporters, complementing its classic mechanism of action. However, studies on docetaxel-resistant cells (PC-3_DCX20 and DU145_DCX20) showed that the "acquired" drug resistance of prostate cancer cells interferes with their sensitivity to metformin and (to lesser extend) to fenofibrate. Apparently, their ability to finely tune the profile and intensity of metabolism according to the current needs underlies their metabolic flexibility and the ability to adapt to chemotherapeutic and metabolic stress. Furthermore, an increase of the invasive potential of these cells was observed in response to metformin and docetaxel, confirming the links between the drug resistance, epithelial-mesenchymal transition, and the metabolic flexibility of prostate cancer cells. These links may be crucial for the course of tumor recurrence after chemotherapy.

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Collectively, the studies performed within the frames of this dissertation allowed for the determination of the potential of metformin in prostate cancer treatment, but also pointed to the potential side effects induced by this drug. They confirm a limited usefulness of metformin in supporting the treatment strategies of prostate cancer based on cytostatic drugs. In particular, the study shows that the acquired drug resistance can affect the susceptibility of prostate cancer cells to metabolic blockers. Metabolic flexibility impairs cellular susceptibility to the combined chemotherapeutic and metabolic stress, thus creating circumstances suitable for the invasive front formation. These data point to the need for a careful reconsideration of the use of metabolic blockers as the supplements in prostate cancer treatment.

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