Multiplatinum resistance and metabolic plasticity in metastatic castration resistant prostate cancer (CRPC) and colorectal cancer (CRC)

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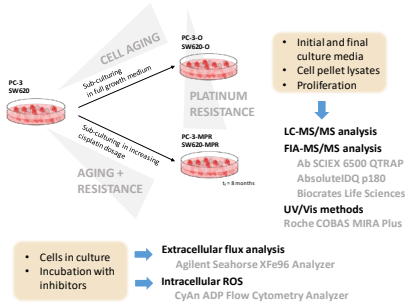
Abstract

Platinum chemotherapy is of capital importance for cancer therapy. Still, many tumors circumvent the multitarget antineoplastic effect of platinum drugs by increasing drug efflux, DNA damage repair rates, drug detoxification mechanisms, and suppressing apoptotic stimuli. All these processes are necessarily associated to a significant reprogramming of metabolic pathways that enables an increased synthesis of nucleotides for DNA damage repair, alters active transport and redox balance, or nurtures the synthesis of drug-metabolizing and antioxidant machinery.

For this, in this work, we aimed to investigate the metabolic reprogramming that arises in metastatic solid tumors as a response to long term treatment with platinum compounds. We generated multiplatinum resistant CRPC and CRC models along with their age-matched controls, allowing us to uncouple the effects of aging from acquired platinum resistance, and revealing the metabolic alterations that can be genuinely ascribed to each variable. Even if our CRPC and CRC models are in origin radically opposed in metabolic terms, we attempted to match the metabolic profiling performed for each of them, seeking to unveil a common metabolic signature of platinum resistance across radically different types of metastatic tumors.

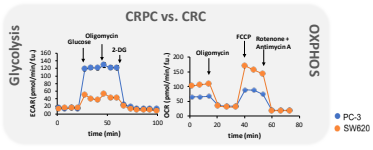
Methods



CRPC

Castration-resistant Prostate cancer

Glycolysis ▶ OXPHOS

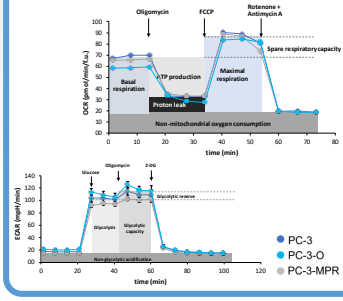


OXPHOS ◀ Glycolysis

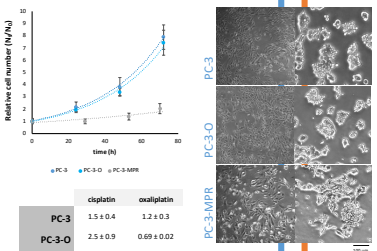
CRC

Colorectal cancer

Glycolysis and oxidative phosphorylation



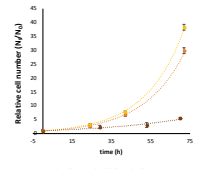
Cell proliferation and phenotype



	cisplatin	oxaliplatin
PC-3	1.5 ± 0.4	1.2 ± 0.3
PC-3-O	2.5 ± 0.9	0.69 ± 0.02
PC-3-MPR	23 ± 9	51 ± 12

IC_{50} values (72h of treatment) (µM)

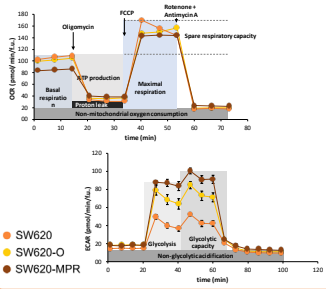
Cell proliferation and phenotype



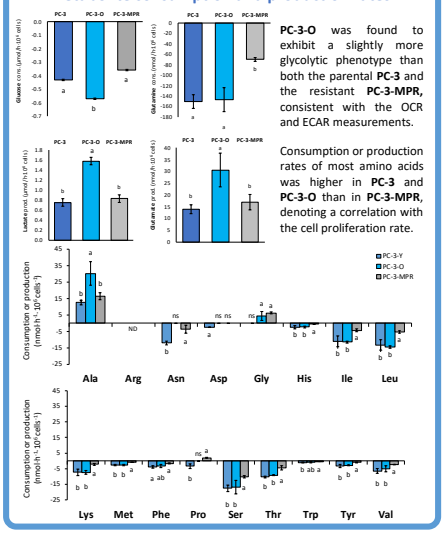
	cisplatin	oxaliplatin
SW620	1.4 ± 0.5	0.32 ± 0.10
SW620-O	1.1 ± 0.9	0.3 ± 0.2
SW620-MPR	21 ± 4	3.2 ± 1.1

IC_{50} values (72h of treatment) (µM)

Glycolysis and oxidative phosphorylation



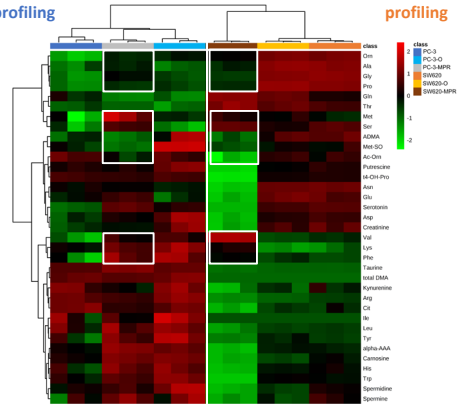
Metabolite consumption and production rates



PC-3-O was found to exhibit a slightly more glycolytic phenotype than both the parental **PC-3** and the resistant **PC-3-MPR,** consistent with the OCR and ECAR measurements.

Consumption or production rates of most amino acids was higher in **PC-3** and **PC-3-O** than in **PC-3-MPR**, denoting a correlation with the cell proliferation rate.

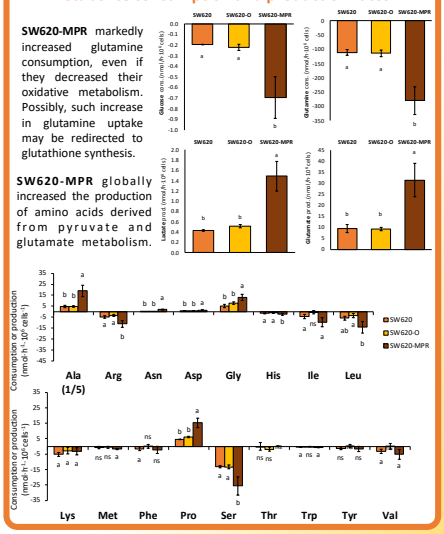
Intracellular metabolite profiling



In CRPC, we encountered most significant differences between **PC-3** vs. **PC-3-O** and **PC-3-MPR**, indicating that many metabolic changes arise from cell aging. In CRC, intracellular metabolic profile of **SW620-MPR** is significantly different from **SW620** and **SW620-O**, indicating that most metabolic alterations in **SW620** can solely be ascribed to acquired platinum resistance.

Intracellular metabolite profiling

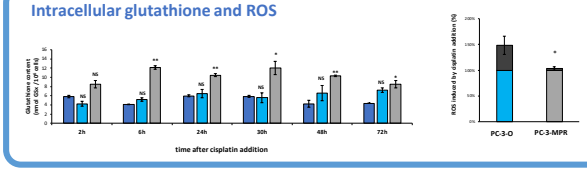
Metabolite consumption and production rates



SW620-MPR markedly increased glutamine consumption, even if they decreased their oxidative metabolism. Possibly, such increase in glutamine uptake may be redirected to glutathione synthesis.

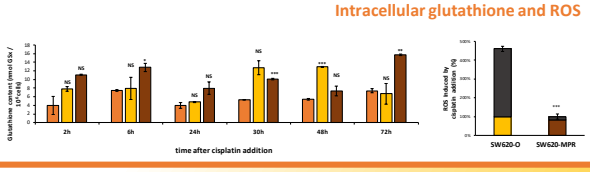
SW620-MPR globally increased the production of amino acids derived from pyruvate and glutamate metabolism.

Intracellular glutathione and ROS



Both **MPR** cell lines enhanced intracellular glutathione after 72 h incubation with cisplatin, which was encompassed by a reduced generation of ROS.

Intracellular glutathione and ROS



Conclusions

- Cell aging and multiplatinum resistance are two encompassed phenomena that give rise to metabolic adaptations that can be independently ascribed to one or the other.
- Metastatic solid tumors with originally opposed metabolic profiles can lead to different metabolic adaptations as they acquire platinum resistance.
- CRPC, mainly glycolytic, does not undergo a substantial metabolic reprogramming as platinum resistance is acquired. On the contrary, largely oxidative CRC undergoes a shift to a more glycolytic metabolic profile.
- Our results point out that a predominantly glycolytic metabolism aids the acquisition of platinum resistance. However, in cancer types in which the parental phenotype is already essentially glycolytic (e.g. CRPC), platinum resistance is acquired to a similar extent with fewer metabolic alterations.

Acknowledgements

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