PGC-1α induction may also confer chemoresistance by promoting a metabolic shift to overcome ATP requirements, as described for cells treated with BRAF inhibitors (Haq *et al*.[136] 2013). This is also the case for 5FU resistance, which enhanced PGC-1α expression and consequently altered cellular metabolism to mitigate the energetic stress induced by treatment[58,102,131].

Finally, it is important to highlight the regulatory role of PGC-1α and mitochondrial mass for CSCs[18,135,137], the main subpopulation responsible for chemoresistance. For instance, PGC-1α silencing sensitized chemoresistant stem-like cells to chemotherapy[127].

These reports suggest that PGC-1α targeting could help to overcome therapeutic resistance. Although no specific inhibitors of PGC-1α are available to date, indirect inhibition through upstream modulators may be possible. In fact, MAPK inhibitor-resistant melanoma cells were sensitized to therapy when treated with mTORC inhibitors, which decreased PGC-1α expression and reversed metabolic changes[128].

CONCLUSION

Contrary to the traditional view, mitochondria are now considered the "Achilles heel" of cancer due to the heavy dependency of cancer cells (especially CSCs) on both mitochondrial metabolism and ability to cope with stress. In fact, these mitochondrial properties allow cancer cells to develop resistance to various therapies [Figure 1], suggesting that multimodal therapies targeting mitochondria would constitute promising therapeutic strategies[33,138,139].

However, much research is still needed to unveil the role of mitochondria in cancer. In fact, tumor metabolism may not only change with disease progression and course of treatment: due to intrinsic heterogeneity, mitochondrial function may be variable across tumors and cell subpopulations within a tumor. In fact, it is well known that the activity of mitochondria is largely dependent on various factors, including physical location, nutrient and oxygen availability and the microenvironment. Indeed, cancer-associated cells also exhibit different metabolic phenotypes and directly affect cancer cells metabolism, adding an extra layer of variability. Therefore, carefully designed therapies targeting diverse populations and considering the tumor microenvironment will be crucial in order to develop successful treatment strategies.

DECLARATIONS

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Authors' contributions

Wrote the main draft and designed the figure: Bokil A
Developed the study concept, obtained funding and wrote the final version of the manuscript: Sancho P
Contributed to the conception and design of the manuscript, wrote sections, revised, read and approved the submitted version: Both authors

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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