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Short Commentary

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Structural and Functional Remodelling of Mitochondria as an Adaptive Response to Energy deprivation

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Abstract

Cancer cells show high adaptation and plasticity. They are dependent on glycolytic energy production. It has been suggested that glycolysis inhibition may be beneficial in cancer treatment. In this study, 2-Deoxyglucose (DOG) was applied to inhibit glycolysis in several cell lines. In all cells used, DOG treatment resulted in about 50% ATP decrease, but cell viability remained normal. Unexpectedly, we found ~2-fold increase in mitochondrial respiratory activity, together with large morphological changes showing creation of mitochondrial networks. It has been demonstrated also an increase of mitochondrial fusion protein Mitofusin-2 and decrease of fission protein Drp1. These results show possible link between mitochondrial shape and their respiratory activity and that network can be more functional effective than fragmented organelles.

Keywords: *Cellular ATP; 2-Deoxy-D-glucose; Energy stress; Glucose metabolism; Mitochondria; Mitochondrial function; Mitochondrial dynamics/network; Mitochondrial membrane potential*

Abbreviations: *AMPK: AMP-activated protein kinase; 2-DG: 2-deoxy-D-glucose; Drp1: Dynamin-related protein 1; HUVEC: Human umbilical vein endothelial cells; Mfn1: Mitofisin 1; Mfn2: Mitofisin 2; SMC: Smooth muscle cells*

Commentary

It is well known that cancer cells are much more dependent on the glycolytic pathways and glycolysis-based energy metabolism ("Warburg Effect") [1-5]. This makes it possible that glycolysis abolishing using various substances/inhibitors may specifically influence cancer cells, expecting a new strategy for tumor therapies [6-17]. In this context, it can be stressed that the possible influences of glycolysis inhibition/inhibitors on the mitochondrial respiratory function, their morphology, and intracellular organization were not known. In addition, it has also been implied that glycolysis inhibition could help overcome chemoresistance problems [18,19] (e.g. frequently observed resistance to anticancer drugs doxorubicin or 5-fluorouracil). However, the study of Kuznetsov AV, et al., where they tried to check all these propositions, did not confirm them. Instead, the authors found significant and interesting changes in mitochondrial functional and morphological properties as an adaptation response to the glycolysis inhibition and ATP depletion. The authors investigated the comparative effects of 2-deoxy-D-glucose (2-DG, a glucose analog, which suppresses cellular glycolysis) on cellular bioenergetics in human colon cancer DLD-1 cells, smooth muscle cells (SMS), human umbilical vein endothelial cells (HUVEC), and HL-1 atrial cardiomyocytes. In all cells, 2-DG treatment resulted in significant ATP depletion; nevertheless, the cells' viability stayed unchanged. In addition, the authors did not notice any synergistic effects of glycolysis inhibition with anticancer drugs doxorubicin and 5-fluorouracil. Consequently, the author's findings were not consistent with the previous ideas that glycolysis inhibition may be beneficial in solving the chemoresistance problem. Interestingly, and rather unexpectedly, glycolysis inhibition and ATP depletion after 2-DG treatment significantly enhanced mitochondrial respiratory activity/capacity (both endogenous and uncoupled respiration at quite constant mitochondrial mass) in living cells, together with the substantial

increase in the mitochondrial inner membrane potential (Δψm).

Importantly, in some cells, the activation of mitochondrial functional state, due to glycolysis inhibition, was concurrent with the changes in mitochondrial morphology and intracellular organization, analyzed by confocal fluorescent imaging, in the direction of mitochondrial network creation.

Accordingly, the authors found that glycolysis inhibition induces a remarkable increase in mitochondrial fusion machinery proteins Mfn1 and Mfn2, in parallel with a decrease in a fission protein Drp1 and therefore leading to the shift between fusion and fission. These findings indicate that in cells it could be a strong association between mitochondrial intracellular organization/morphology with mitochondrial functionality (respiration and Δ□m). Besides, it is known that mitochondrial fragmentation can be an early apoptosis sign, probably also with decreased mitochondrial functional activity. It is thought that the study of Kuznetsov AV, et al. may represent one of the first analyses of the simultaneous changes in the main functional properties of mitochondria and the structure/organization of these organelles during energy stress and glycolytic ATP deprivation. The authors have proposed therefore that in some cells, the functional activity of the mitochondrial network can be higher than that in disconnected, fragmented mitochondria.

Using high-resolution respirometry of living cells, together with confocal fluorescent imaging analysis of the mitochondrial organization and expression of mitochondrial fusion-fission proteins (Mfn1, Mfn2, and Drp1) authors afford the evidence of tight-fitting associations between the mitochondrial structure and their main functions. This is in a line with previously published data, showing that ATP depletion by the inhibition of glycolysis may activate the mitochondrial function, suggesting also that this activation may compensate for the lack of ATP [20-24] and that mitochondrial fusion is predominantly essential in cells of high respiratory activities. This phenomenon may work also against the accumulation of mitochondrial mutations. Also, analysis of the effects of energy substrates and their availability (assessed in the human cancer cell line, HeLa) on mitochondrial function and structure has shown that they can regulate the balance between glycolysis and mitochondrially produced ATP [25-28]. These studies demonstrated a complex and cooperative response of mitochondria to energy substrates availability.

So, changes in the mitochondrial structure-function (remodelling of mitochondria) can be involved in the mechanisms of their adaptation to variable metabolic demands. This provides a link between mitochondrial dynamics and the balance of energy demand/supply, regulating cell metabolic efficiency and mitochondrial respiratory capacity [23,24]. Therefore, several studies imply the existence of a relationship between mitochondrial biogenesis, their function, and structure in various cells (muscles, beta cells, COS-7, etc., reviewed by Picard M, et al. [20]). Moreover, the study of Kuznetsov AV, et al. suggests that remodelling of highly dynamic mitochondria may take place in, and be a part of molecular mechanisms of various cellular processes, like energy stress, oxidative stress, calcium overload, etc. and involved in various pathologies and diseases.

In addition, the results of this study show that AMPK (a critically important cellular energy sensor) can be activated after energy depletion with increased levels of p-AMPK. Although the molecular basis of this phenomenon is not clear, some participation of mitochondrial dynamics fusion-fission proteins in the cellular AMPK activation may play a role, can be involved in these mechanisms, and require further investigation.

Conclusion

Summarizing, the work of Kuznetsov AV, et al. demonstrates that crosstalk exists between structural reorganization and functional remodelling of mitochondria in response to 2-DG treatment and glycolysis inhibition due to adaptation of cells to the energy deprivation. The main question remains unanswered: - whether the dynamic structure of the mitochondria is remodelled due to a higher mitochondrial activity, or rather a specific mitochondrial structure (networks) possesses a higher mitochondrial respiratory capacity. The authors mentioned that future studies are needed to establish cause-and-effect relationships between structural and functional remodelling of mitochondria.

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Conflicts of Interest

The authors declare no conflict of interest.

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