



Commentary

Oxidized ATM protein kinase is a new signal transduction player that regulates glycolysis in CAFs as well as tumor growth and metastasis



Álvaro Marín-Hernández, Sara Rodríguez-Enríquez, Rafael Moreno-Sánchez *

Departamento de Bioquímica, Instituto Nacional de Cardiología, Mexico

It has become clear that cancer associated fibroblasts (CAFs), the most abundant stromal cells in the tumor microenvironment, through the secretion of cytokines and other growth factors, and by increasing the estradiol levels, interact with cancer cells to help promoting tumor progression, metastasis and therapeutic resistances [1]. Like tumor cells, CAFs also undergo energy metabolism reprogramming in a process induced by hypoxia and adjacent tumor cells [2,3]. Due to their enhanced glycolysis, CAFs release large amounts of lactate to the extracellular milieu. This metabolite is rapidly internalized and transformed by adjacent tumor cells to pyruvate, which is then presumably taken up and fully oxidized by mitochondria for ATP generation via oxidative phosphorylation (OxPhos) to support the accelerated cellular proliferation and other ATP-demanding processes [4]. This metabolic interaction between cancer cells and CAFs has been called “Reverse Warburg Effect” [2], which requires functional mitochondria in cancer cells [5].

Thus, the identification of the activation mechanisms of glycolysis in CAFs is needed. Although it has been demonstrated that hypoxia and oxidative stress through HIF1- α [3] potently activate the glycolytic flux in CAFs, other factors may also regulate CAFs glycolysis under hypoxia or normoxia. Recently, in this article of *EBioMedicine*, Sun et al. [6] found a strong relationship between the levels of an oxidized ATM (ataxia-telangiectasia mutated) protein kinase and the glycolytic activity in CAFs. Oxidation of ATM protein kinase was triggered by hypoxia-induced oxidative stress. There are not well-defined markers that may allow distinguishing between CAFs and non-cancer associated fibroblasts (NAFs). The Sun et al. study clearly demonstrates that oxidized ATM may be used as a specific CAFs marker.

Two strengths of the Sun et al. study have to be mentioned. First, the integral analysis of the CAFs energy metabolism by assessing the transcription, protein contents and pathway fluxes of both glycolysis and OxPhos. Such an approach avoids mechanistic explanations of the observed phenotype based solely on transcriptomic and proteomic data, as the actual biological function (*i.e.*, pathway activities) is also assessed. One should be aware that strict correlations between either mRNA levels with protein levels, protein levels with enzyme activities, or

mRNA/protein levels with pathway fluxes and phenotypes, are not always attained [7]. Therefore, to have accurate mechanistic interpretations, the biological function has to be directly determined since the transcriptomic and proteomic data provide no information on the actual enzyme/transporter physiological activities and covalent (phosphorylation, acetylation) and metabolic (allosteric) regulation.

The second strength relies on a rigorous determination of the glycolytic and OxPhos fluxes, carried out by using specific inhibitors to correct for non-glycolytic (glutaminolysis) H⁺ production (which is stoichiometrically equivalent to lactate production) and oxygen consumption not associated to ATP synthesis, respectively. This is not a common feature in most energy metabolism studies, which use total lactate production and total O₂ uptake as equivalent to glycolytic and OxPhos fluxes, respectively. As glutaminolysis and extramitochondrial O₂ uptake are significantly enhanced in cancer cells, corrections to total fluxes are fundamental.

Sun et al. demonstrate that oxidized ATM kinase directly phosphorylates GLUT1, which prompts its translocation to the plasma membrane. Glucose consumption and lactate production are concomitantly stimulated because GLUT1 is a major controlling step of tumor glycolysis [8]. Although GLUT1 activity was not directly evaluated in Sun's study, it has been shown that GLUT1 phosphorylation significantly increases glucose uptake in rat fibroblasts and *Xenopus* oocytes over-expressing GLUT1 [9], suggesting that oxidized ATM did increase GLUT1 activity in CAFs. Enhanced glucose uptake/consumption is certainly a consequence of increased glucose transport activity, but also of increased activity of the ensuing enzymes, particularly hexokinase (HK). Then, glucose uptake/consumption is not a straightforward indicator of GLUT activity. Akt was also phosphorylated by oxidized ATM kinase thus activating the PI3K-Akt signaling pathway and promoting increased levels of its target PyK-M2, which contributed to the enhanced CAFs glycolysis. Other glycolytic enzymes regulated by phosphorylation such as PGAM, HK and LDH might also be targets of oxidized ATM kinase, but this issue will require further studies.

Glycolytic stimulation by oxidized ATM kinase was accompanied by a moderate decrease in OxPhos, which makes glycolysis the

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* Corresponding author.

E-mail address: rafael.moreno@cardiologia.org.mx (R. Moreno-Sánchez).

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predominant ATP provider in CAFs. In addition, Sun et al. show that secreted L-lactate, produced by the oxidized ATM-stimulated CAFs glycolysis, stimulates migration and invasion of metastatic cancer cells by activating both their TGF β 1/p38/MAPK/MMP2/9 signaling and mitochondrial function.

High L-lactate in serum and biopsies derived from cancer patients has been associated to poor prognosis and high metastasis risk in cervix, breast, and head and neck cancers [10]. Therefore, derived from Sun's study, it seems that inhibition of CAFs glycolysis may contribute to deter tumor growth and metastasis. To decrease CAFs glycolysis, the use of specific oxidized ATM inhibitors such as KU60019 and the inhibition of the controlling steps in CAFs glycolysis could be suitable strategies. A complete understanding of the mechanisms involved in the interaction between tumors and CAFs, at the transcriptional, translational and functional levels, should allow the identification of more specific and effective therapeutic anti-cancer targets.

Author contributions

AM-H, SR-E and RM-S equally contributed to conceive and elaborate this commentary.

Conflict of interest

The authors declare no conflicts of interest.

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