# *Quiescence-like metabolism to push cancer out of the race*

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**Biological features acquired or lost during the tumorigenic process are a source for the discovery of molecular cues relevant to cancer. The latest study led by the Weinberg lab (Keckesova et al., 2017) focuses on the transcriptional program underlying quiescence to uncover a novel metabolic tumor suppressor, LACTB.**

Technological advances have allowed us to reduce the need of milligrams of tissue for molecular research down to a single cell, and to move from monitoring a few molecules to OMICs approaches. We have at hand thousands of well-annotated cancer genomes and transcriptomes. Yet, all this information rarely provides clues about key events that sustain or oppose malignant transformation, unless we ask the right question.

The Weinberg lab focused on a well-accepted clinical evidence: the susceptibility to malignant transformation differs among mammalian tissues. Cells in our body specialize and can enter a terminal differentiation stage that, in general, precludes them from re-entering the cell cycle. This stage is defined as quiescence. Interestingly, quiescent cells succumb less frequently to malignant transformation, perhaps associated with a reduced cumulative stem cell divisions and probability of mutations (Tomasetti et al., 2017). The nature of this cellular state drove the authors to hypothesize that there is a molecular link between quiescence and cancer resistance. The authors asked: *can the transcriptional program of quiescence unravel novel cancer genes?* To this end, they interrogated the transcriptome of cellular systems in which differentiation and quiescence can be experimentally induced. This analysis provided a list of upregulated genes in post-mitotic muscle cells, that they considered potential tumor suppressors. The authors pursued the study of the mitochondrial protein Lactamase Beta (LACTB), based on its capacity to reduce cancer cell proliferation. This gene has been associated to alterations in cellular and systemic metabolism, in turn suggesting that quiescent cells present a tumor suppressive metabolic program. Due to the fact that metabolism is a hallmark of cancer that can be pharmacologically exploited, the possibility of manipulating it to drive a quiescence-like tumor suppressive state is attractive. The Weinberg lab identified a subset of cancer cell lines that presented reduced levels of LACTB and elaborated on the biological consequences of enforcing expression of this gene. Ectopic expression of *LACTB* resulted in a tumor suppressive response that consisted on reduced proliferation, increased epithelial phenotype and a decrease in mesenchymal and cancer-stem cell markers.

Cancer pathogenesis and progression is frequently associated to changes in mitochondrial metabolism (Vyas et al., 2016), to the extent that the loss of mitochondrial enzymes observed in certain cancers is a key contributing factor to the aggressiveness of the disease (Sciacovelli et al., 2016). In agreement with the reported association of LACTB to metabolism, the authors observed changes in mitochondrial function in cells expressing the protease, including reduced mitochondrial membrane potential and ATP levels, and increased production of reactive oxygen species. Metabolomics analysis upon LACTB expression revealed early alterations in phospholipid composition, with a predominant decrease of ethanolamine-based species (both in phospholipid and lysophospholipids, PE and LPE, respectively). The causal contribution of these lipids to the tumor suppressive activity was demonstrated by the partial abrogation of the anti-proliferative activity of LACTB upon supplementation with LPE. The reduction in PE/LPE abundance suggested that the enzyme responsible for its production from phosphatidylserine (Phosphatidylserine Decarboxylase, PISD) could be under the regulation of LACTB. Indeed, Keckesova and colleagues demonstrated that LACTB expression resulted in reduced PISD protein levels (through a mechanism yet to be determined) in cells sensitive to the expression of the protease. The regulation of PISD by LACTB provides a feasible explanation to its impact on mitochondrial function since the enzyme and its lipidic products (PE/LPE) have been associated to mitochondrial activity, cell proliferation and aging (Di Bartolomeo et al., 2017).

This study rises interesting aspects that could pave the way for future research in oncology. The authors establish a link between quiescence and tumor suppression. Interestingly, this data is mirrored by the relevance of tumor suppressors as guardians of a quiescence state in non-transformed cells, including PTEN and LKB1 (Gan et al., 2010; Yue et al., 2017). It will be interesting to decipher to which extent the role of these cancer genes in quiescence is dependent on their ability to impact on mitochondrial function (Gan et al., 2010; Garcia-Cao et al., 2012). Furthermore, it is plausible that an “optimal” mitochondrial state is required for quiescence and tumor suppression. Conversely, excessive (e.g. defective autophagic clearance of mitochondria) or defective mitochondria levels and activity (loss of mitochondrial function

activators; e.g. LKB1) could result in exit from quiescence, and, in turn, malignant transformation or aging.

LACTB is a protease that requires a functional connection to PISD in order to elicit its tumor suppressive activity. The authors identify non-transformed and cancer cell lines that are refractory to LACTB expression, and this resistance correlates with the lack of PISD down-regulation. In turn, evasion of a quiescence-like metabolic state could be supported by either down-regulating LACTB or disconnecting PISD from the negative control of the protease (Figure 1). On the basis of this study, PISD inhibition rises as an attractive therapeutic strategy to hamper tumor growth and progression.

LACTB modulates mitochondrial function and suppresses cancer cell proliferation. However, it is important to note that tumors are heterogeneous within and between individuals, and their aggressiveness, envisioned as the time and capacity to metastasize, might vary. The study of slow metastasizing cancers has led to the concept of dormant tumor cells. The molecular cues underlying this phenomenon, and the ultimate escape from a dormant state, is an emerging question in the field. Dormancy and quiescence share phenotypic and conceptual aspects. Since dormant (or latent) cancer cells have common transcriptional programs with stem cells (that often enter a quiescent state) (Malladi et al., 2016), it is tempting to speculate that common molecular and metabolic cues will emerge. In this regard, a functional LACTB-PISD axis in these cells could be relevant to characterize the dormant mitochondrial program that prevents metastatic reactivation, hence stressing the need for additional work in this interesting field.

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## Figure legends

**Figure 1. Schematic representation of the main findings of the study.** Quiescent cells exhibit resistance to transformation, which led the authors to identify the putative tumor suppressor LACTB. This protease reduces PISD protein abundance and PE/LPE production, resulting in a mitochondrial state compatible with tumor suppression, decreased proliferation and enhanced differentiation. Three scenarios can be observed in cancer with regards to LACTB function: low LACTB, high mutant LACTB expression, or a molecular context were high LACTB is unable to negatively regulate PISD. In all instances, PISD and PE/LPE abundance is increased. In turn, these cells present a mitochondrial state compatible with tumor growth, proliferation and loss of differentiation markers. LACTB, Lactamase Beta; PISD, Phosphatidylserine Decarboxylase; PE, Phosphatidylethanolamine; LPE, Lysophosphatidylethanolamine; PS, Phosphatidylserine; LPS, Lysophosphatidylserine. Dotted lines represent non-operative molecular regulations. Dashed lines depict a potentially indirect effects. $LACTB^{mut}$ refers generally to mutations that could impact on its activity or function, as represented in the study with $LACTB^{R469K}$.

***Torrano and Carracedo, Figure 1***