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"Oncometabolism: The switchboard of cancer – An editorial"

In the 1920's, Otto Warburg, one of the greatest biochemists of all time, uncovered an intriguing bioenergetic phenotype shared by most tumor cells: a higher than normal reliance on lactic acid fermentation for energy generation [1]. Warburg's seminal finding gave rise to a new field of cancer research that came to be known as oncometabolism. Research in this fascinating field, which has since expanded its scope well beyond the metabolic processes of energy generation, has already translated into one of the most successful imaging techniques for the diagnosis and staging of tumors, ^{18}F-deoxyglucose positron emission tomography (FDG-PET). Targeting the metabolic peculiarities of tumor cells for cancer treatment, on the other hand, has only yielded modest results. Recently, the Food and Drug Administration (FDA) granted approval to two inhibitors of mutated forms of isocitrate dehydrogenase (IDH)—IDHIFA® (enasidenib) and Tibsovo® (ivosidenib)—but only for certain forms of acute myeloid leukemia (AML). In this context, it must be stressed that drugs targeting nucleotide metabolism, which have been in the clinic for many decades, target proliferating cells in general, not tumor cells specifically. Nonetheless, it is still believed that a more detailed and comprehensive understanding of the metabolic rewiring that accompanies neoplastic transformation will ultimately translate into highly effective metabolic anticancer agents.

While oncometabolism is now very popular among researchers in the life and health sciences, this has not always been the case. In truth, for a great part of the twentieth century, the majority of cancer researchers scorned the proposal that alterations in the energy metabolism, traditionally viewed as an autonomous and self-regulated network of reactions, disconnected from cellular signalling, are a driving force for uncontrolled cell proliferation. More recently, the discovery of unsuspected links between the energy metabolism and cellular proliferation, differentiation and death led to a reappraisal of the role played by bioenergetic deregulation in carcinogenesis. In 2011, the classification, by Hanahan and Weinberg, of tumor metabolism as an emerging cancer hallmark confirmed oncometabolism's full maturity as a research field [2].

Warburg's seminal discovery of tumor cell bioenergetic rewiring was made during the so-called Golden Age of intermediary metabolism, the large branch of biochemistry devoted to the study of the metabolic networks that provide cells with usable forms of energy and precursors for biosynthesis. Once a striving field, as attested by the many Nobel Prizes awarded for work conducted in this field between the late 1910s and the 1950s, it was gradually superseded by the field of molecular biology and, with time, became equated with little more than a very large number of metabolites, reactions and enzymes that students in the life and health sciences are made to memorize, to put aside straight after their examinations. In the first paper of this special issue, Ferreira et al. readdress intermediary metabolism, presenting selected critical links, often reciprocal, that it establishes with most, if not all, aspects of cellular function and fate [3].

As is often the case in all areas of research, the present wave of oncometabolism researchers has shown little interest in the history of the field, let alone in consulting the original papers, written in German. Thus, current literature is flooded with inaccuracies and misconceptions regarding Warburg's true findings and views, which might retard further progress in oncometabolism research. The very expression "Warburg effect", employed in hundreds of research papers almost as a synonym of neoplastic transformation, needs qualification. In the second paper of this special issue, Urbano revisits Warburg's original papers, providing a more accurate acquaintanceship with his findings and his metabolic theory for the origin of tumors. In addition, the paper outlines aspects of Warburg's personal and early research life that, in retrospect, might be viewed as a preparation for his successful attack on the cancer problem [4].

The metabolic characterization of tumor cells is still a work in progress. This does not come as a surprise, considering the complexity of the intracellular milieu, containing thousands of metabolites and proteins in notoriously low levels. Nonetheless, advances in analytical techniques, most notably magnetic resonance spectroscopy (MRS)- and mass spectrometry (MS)-based metabolomics and proteomics, have led to increasingly detailed metabolic profiles of tumor cells, opening up novel clinical applications. Three reviews in this special issue deal with some of these advances: Araújo et al. provide a compilation of metabolomic studies of breast cancer in murine models [5], Torresano et al. overview current knowledge on the major changes in steady-state levels of metabolic proteins in primary carcinomas, highlighting those proteins whose changes correlate with patients' survival [6], and Kowalczyk et al. discuss how information gathered through MS-based proteomics and metabolomics can further advance personalized oncology, providing also background on technical aspects [7].

The huge success of PET in the diagnosis and staging of cancer might be further increased through the use of novel radiopharmaceuticals that, similar to FDG, target the metabolic peculiarities of tumors. In their review, Abrantes et al. provide an overview of different radiopharmaceuticals developed for PET use in oncology. While most of these compounds are still only used in pre-clinical studies, there is hope that same of them might prove useful tools in personalized oncology, namely in the staging/restaging, characterization and stratification of different types of cancer, as well as in therapeutic response assessment [8].

Further advances are also being made regarding the reciprocal links that exist between intermediary metabolism rewiring and uncontrolled cell proliferation, as can be appreciated in the reviews by Boukalova

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et al., who discuss the role of dihydroorotate dehydrogenase (DHODH), an enzyme of the *de novo* pyrimidine synthesis pathway, in the oxidative phosphorylation system and in the initiation and progression of cancer [9], and by Leal-Estaban and Fajas, who describe recent data pointing to non-canonical roles of cell cycle regulators in metabolic control, with an emphasis on studies performed in cancer models [10]. These authors also discuss progresses made in targeting, respectively, DHODH and cell cycle regulators for cancer therapy, using specific inhibitors.

Renewed interest in oncometabolism paralleled, to a significant extent, the discovery that, far from mere power stations, mitochondria are central hubs in cellular metabolism, as hinted in the first paper of this special edition [11]. Multiple aspects of mitochondrial biology are now being investigated in relation to carcinogenesis. Selected examples can be found in three reviews and one original paper of this special issue. Oliveira et al. present a detailed overview of the metabolic and genetic drivers of mitochondrial adaptations in cancer, also focusing on the use of mitochondria-targeted interventions in the context of oncotherapy [12]. Simões et al. describe critical aspects of the biology, composition and function of mitochondria-associated membranes (MAM) and discuss how the tumor suppressors and oncogenes present in mitochondria-endoplasmic reticulum contact sites might be involved in carcinogenesis [13]. The review by Reinhardt et al., on the other hand, addresses the role that the apoptosis-inducing factor (AIF) has in regulating mitochondrial oxidative phosphorylation. Recent works suggested that AIF fulfils its mitochondrial pro-survival function by interacting physically and functionally with CHCHD4, a redox-regulated operating import machinery. These systems are potential therapeutic targets in a variety of human disorders including cancer [14]. The study by Roche et al. adds yet another layer to the complex involvement of mitochondria in cancer. Specifically, it provides evidence for the participation of translocase of the outer mitochondrial membrane complex subunit 20 (TOMM20) in the resistance to radiation and chemotherapy treatments typically exhibited by human chondrosarcoma tumors [15].

In his metabolic theory for the origin of tumors, Warburg assumed the existence, within healthy tissues, of a subpopulation of cells responsible for tissue renewal, proposing that these cells shared the increased fermentative capacity of tumor cells [1]. It is noteworthy that Warburg's proposal fits well within the concept of stem cell, introduced many decades later, as can be appreciated in the reviews by Rodrigues et al., who highlight the metabolic similarities between cancer cells and stem cells [16]. Along the same lines, the study by Sousa et al. suggests that metabolic rewiring, specifically the upregulation of the pentose phosphate pathway (PPP), might mediate the induction of anoikis-resistance in matrix-detached breast cancer cells by P-cadherin, a cell adhesion protein associated with poor prognosis in this type of cancer [17].

Another fascinating and rather recent area of research within the field of oncometabolism explores the interplay between intermediary metabolism and epigenetics and, ultimately, cellular phenotype. In their review, Li and Ye discuss the possible involvement of serine metabolism in epigenetic modifications typical of tumor cells [18].

As a result of their increased reliance on lactic acid fermentation, tumor cells generate large amounts of lactate. The study reported by Pereira-Nunes et al. investigated the impact of inhibiting lactate production/extrusion on prostate cancer cell survival and aggressiveness [19].

Last, but by no means least, Mboge and Bissell discuss how the use of conventional (two-dimensional) cell culture, which does not mimic contributions of the extracellular microenvironment, might influence the outcome of studies on tumor carbohydrate metabolism. Their paper highlights the relationship between 3D tumor architecture, glucose uptake and oncogenic signalling [20].

This special issue should be a reference for both the experienced oncometabolism researchers and for all of those willing to enter this fascinating field, which will yield so many impactful results in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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