Deciphering the Hallmarks of Cancer; Deregulation of Cellular Energetics

Ioannis Ntanasis-Stathopoulos, Maria Gavriatopoulou & Meletios Dimopoulos, A.*

Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital, Athens, Greece

*Correspondence to:** Dr. Meletios Dimopoulos, A., Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Alexandra General Hospital, Athens, Greece.

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In 2011, Hanahan and Weinberg presented the next generation of hallmarks of cancer, by providing an update of their initial review [1,2]. Deregulation of cellular energetics and evasion of immune destruction were proposed as emerging cancer hallmarks [2]. Currently, accumulating data support the reprogramming of energy metabolism as a cardinal event in carcinogenesis and sustainable cancer cell survival.

Warburg was the first to describe the effect of metabolism reprogramming in cancer cells [3,4]. It was hypothesised that mitochondrial dysfunction in cancer cells resulted in a shift towards glycolysis, even in the presence of oxygen in the tumour microenvironment, the so-called "aerobic glycolysis". Throughout the years, aerobic glycolysis among cancer cells has been repeatedly confirmed; however the underlying pathophysiological mechanisms do not coincide with Warburg's beliefs [5]. It has to be noted, though, that Warburg provided the basis for investigating cancer metabolism and his contribution remains widely appreciated [6].

Cancer cells are no longer considered as carrying mitochondrial defects [5]. Mitochondrial function is being reprogrammed in favor of glycolysis in order to provide important glycolytic intermediates to biosynthetic pathways resulting in macromolecules production, which is vital for cancer cell survival and proliferation [7].

Interestingly, current evidence suggests that the activation of proto-oncogenes and the inactivation of tumor suppressor genes play a key role in deregulating cellular energetics [8]. The phosphatidylinositol-3-kinase

(PI3K)/Akt and the mammalian target of rapamycin (mTOR) pathway, which is upregulated in the majority of human carcinomas, promotes glucose uptake and glycolysis [5,9,10]. MYC activation is also implicated in mitochondrial function and glutamine utilisation as a carbon source [5]. Furthermore, loss of *p53* tumor suppressor gene may promote glycolysis [11].

Hypoxic conditions are common in the tumor microenvironment. Hypoxia mediates its effects primarily through the regulation of hypoxia-inducible factor-1 (HIF-1) [12], that in turn upregulates glucose transporters and glycolytic enzymes in order to maintain the redox homeostasis and sustain cancer cell survival [10,13]. α-ketoglutarate, an intermediate molecule in Krebs cycle, is one of the cosubstrates for HIF-α [14]. A deregulation of their interplay could skew the metabolic balance in favour of aerobic glycolysis and rapid cell proliferation, making it susceptible to both epigenetic alterations and genetic mutations that may promote carcinogenesis [15]. Mitochondrial autophagy is also important in this process, as it is mediated by HIF-1 and it may represent a switch between promoting or impeding cancer progression [16,17].

Furthermore, there is currently a vivid interest in the scientific community on the convergence of cancer metabolism with cancer immunology [18], which have been both described as emerging cancer hallmarks in 2011 [2]. It has been supported that metabolic disturbances favouring cell proliferation and acquisition of mutations in combination with deregulated immune surveillance are necessary for promoting carcinogenesis [18]. Tumour microenvironment plays a key role in this process [18]. Deregulation of several metabolic factors, such as prohibitin, mevalonate and tryptophan pathway, induces alterations in the immune responses and ultimately promotes cancer cell survival [19-21]. Such observations aim to provide the rationale for targeted therapies. Potential metabolic targets include lactic acid in cervical [22] and pancreatic cancer [23], arginine 1 in breast cancer [24] and Hodgkin lymphoma [25], nitric oxide synthetase (iNOS) in ovarian cancer [26] and the tryptophan pathway in glioblastoma [27-29].

From the bench to the bedside, the avid glucose uptake by cancer cells has provided the basis for positron emission tomography (PET) with a radiolabeled analogue of glucose (18F-fluorodeoxyglucose, FDG), that in combination with computed tomography (PET/CT scan) is currently a valuable technique for cancer diagnosis and disease monitoring [30].

In conclusion, deregulated cellular energetics is considered as an emerging cancer hallmark and metabolic reprogramming has been described in cancer cells. Beyond the mere alterations in metabolic indices, there is a vivid interplay between proto-oncogenes, tumour suppressor genes and metabolic effectors. Interestingly, the emerging field of cancer immunometabolism may provide a better understanding of the underlying pathophysiological mechanisms of carcinogenesis. Furthermore, the identification of novel metabolic immune checkpoints may provide the rationale for a new breakthrough in cancer therapeutics.

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