Targeting tumor metabolism: novel strategies against cancer stem cells? New aspects and changing paradigms

DEREK ZIEKER 1,2, INGMAR KOENIGSRAINER 1, RUSSELL S. TAICHMAN 3, MARKUS LOEFFLER 1,2

1Department of General, Visceral and Transplant Surgery, Comprehensive Cancer Center, University of Tuebingen, Hoppe-Seyler-Str.3, D-72076 Tuebingen, GERMANY
2Institute of Clinical and Experimental Transfusion Medicine, University of Tuebingen, Otfried-Mueller-Str. 4/1, D-72076 Tuebingen, GERMANY
3Department of Periodontics and Oral Medicine, University of Michigan, School of Dentistry, Ann Arbor, Michigan, 1101 N. University Ave, Ann Arbor, MI 48109-1078, USA.
Correspondence to: derek.zieker@med.uni-tuebingen

Abstract: - Novel evidence suggests there could be more to metabolism than meets the eye at first impression. A newly discovered link between metabolic changes and differentiation has intriguing connections to an old hypothesis advocated by Otto Warburg for tumor metabolism. As stem cells are predominantly reliant on glycolytic metabolism, which may be applicable to cancer stem cells, new metabolism findings could constitute a vantage point for cancer research. If these concepts and interconnections between metabolism and cellular differentiation can be further substantiated in solid malignancies and apply to cancer initiating cells, our view on cancer may significantly change, which may alter future therapeutic strategies.

Key-Words: - Cancer stem cells, cancer initiating cells tumor metabolism, differentiation, differentiation therapy, cancer treatment

1 Introduction

Recent progress in our comprehension of malignant disease suggests that neoplastic stem cells, contained within “side populations” of cancers, are the responsible source for disease progression and metastasis [1]. This notion has initially been evidenced in leukemic cells [2] and was later additionally substantiated in solid malignancies [3]. Tumors having their “seed” or origin in rare but immortal cells with the unlimited ability to self-renew and differentiate, creating heterogeneous progeny, hold these cells with stem-like abilities. Therefore the term cancer stem cells or cancer initiating cells has been established based upon analogies to normal somatic stem cells present in most adult tissues. A special characteristic of stem-like cells in cancers however and relevant to patient care, is their extraordinary resistance to conventional chemo- and radiotherapy, rendering these cells an important target for future therapeutic strategies aiming at cure for cancer [4]. A particularly relevant notion to this consideration might be, that stem cells intrinsically immortal adopt a mortal emergence upon differentiation [5], thus induction of differentiation in solid malignancies may imply novel tools for treating malignancies resistant to conventional therapeutical approaches [6].

Predictions made based upon a tumor stem cell paradigm hold important clues for a novel approach and treatment strategies in many solid malignancies. To overcome resistance to therapy, which constitutes a major problem in treatment of many solid malignancies, breaking new ground in our view on malignant disease and adopting new ideas, which are supported by novel evidence, might be invigorating to research. This view was already coincided by Hanahan and Weinberg in their seminal paper termed “The hallmarks of cancer”, which was published ten years ago [7], asking for a fundamental conceptual change in our view on cancer.

Malignant tumors are highly complex cellular compounds, that have to overcome the endogenous resources impeding their development, and they need to generate various features which enable them to become a fully fledged malignancy. Several of these features are recognized as established hallmarks of cancer [7]. Although these six traits are common to malignant development, only some of these contribute to their lethality and distinguish benign from malignant solid tumors [8]. The most critical of these are invasiveness and metastatic potential.
2 Problem Formulation

We therefore believe that some of the most critical components of malignant disease are novel and profound changes that occur, when the interactions between neoplastic cells and normal host tissues change their relationships, in which the new interactions are the major reason for cancer associated death. One could be immune evasion. Another is educating host-cells such as cancer associated fibroblasts and macrophages to produce growth factors and hormones that drive neoplastic selection and/or drive epithelial - mesenchymal transitions.

Although there is considerable complexity and heterogeneity among solid malignancies, another common feature is the shift in metabolism that occurs towards a greater use of glucose. This view has been evidenced since early studies on cancer have been performed [9]. In recent years a causal role for metabolic changes has been increasingly suggested and led to the proposal of a view including the metabolic shift towards augmenting glycolysis in the hallmarks of cancer [10]. A clear remark to this theory is also that interference with this metabolic shift is able to dampen tumor growth, prevent malignant onset and has been shown to provide relevant therapeutic potential [11-13]. Nevertheless evidence how metabolism accurately influences cancer ontogenesis is still in the early stages and many discoveries undoubtedly are to be discovered. The concept that carcinogenesis constitutes a multimodal process involving an irreversible block of terminal differentiation [14] may be critical to our understanding of cancer and may prove significant for targeting malignancies.

3 Problem Solution

A recently published paper by Bracha et al. linking cellular differentiation to metabolism might thus shed new light on the interconnection of metabolism and cancer characteristics [15]. Particularly in the context of induction of differentiation in cancer stem cells. These findings could envision a novel basis for additional therapies in solid malignancies and spur further research [6]. The newly proven association between three metabolic enzymes namely phosphoglycerate kinase (Pgk1), hexose-6-phosphate dehydrogenase (H6pd) and ATP citrate lyase (Acl) and cellular differentiation highlights various aspects of malignancy, which may provide novel means to overcome radio- and chemo-resistance in many tumors.

The central assertion of the mentioned study by Bracha et al. is, that perturbations in the enzymes participating in carbon metabolism (in their study proven in a myofibroblast cell line and in rhabdomyosarcoma cells by mRNA knockdown with small hairpin RNA) can induce cellular differentiation [15]. One of the most interesting findings as reported was, that not only transcription factors but also enzymes of carbon metabolism and thus the cellular metabolite milieu are relevant factors inducing cell differentiation. These alterations are mediated by metabolic enzymes involved in glycolysis, regulation of NADPH production in the endoplasmatic reticulum lumen and in cholesterol biosynthesis. Interestingly, only Pgk1, H6pd and Acl were able to induce these striking changes out of 50 enzymes involved in carbon metabolism studied [15]. From studies in stem cells the predominant dependency on glycolytic metabolism and the interconnected resistance to hypoxia is well established [16,17]. Furthermore, novel findings indicate that hypoxia may be a factor influencing plasticity in malignant cells resulting in a phenotypic shift propagating selection of more stem like cells [18]. Thus by virtue of the fact that Pgk1 is involved in the glycolytic pathway and a downstream target of hypoxia inducible-factor [19], which has been additionally shown to mediate important transcriptional functions in cellular DNA repair and replication [20], this suggests it may play a critical if not a central role in the resistance to therapy of malignant cells.

Although the notion that aerobic glycolysis and shifts in cellular metabolism are intimately linked to malignancy have been evidenced for long time [9] and have been demonstrated in a wide variety of solid tumors, the concept promulgated first by Otto Warburg has always raised the question to which degree metabolic alterations contribute to a epiphenomenon of malignant transformation, rather than constituting a feature of malignancy per se [21]. Inhibition of glycolysis has frequently been suggested as a means to overcome drug resistance and to limit tumor spread [22,23]. Depletion of adenosine triphosphate by targeting glycolysis has been successfully shown in rodents for the treatment of advanced malignancies [13]. Furthermore hypoxia and upregulation of glycolysis has been shown to be accompanied by increased aggressiveness in tumors and is associated with a poor outcome [24]. Owing to the successful use of 18Fluor 2-deoxyglucose – positron emission tomography imaging a large scale body of clinical experience is available underscor ing the importance of glycolysis in malignancy in principal, adding an unprecedented functional level to tumor diagnostics increasing sensitivity and negative predictive value [25]. Thus this link between cellular metabolism influencing cellular differentiation and cancer stem cells as possible therapeutic targets in solid malignancies is very intriguing and may provoke to revisit our cancer paradigms.
4 Conclusion

One obvious conclusion that can be drawn from the aforementioned findings, may be the selection of cancer cells with more cancer stem cell properties [18], due to exogenous factors such as chemo- or radiotherapy or endogenous factors such as low oxygen levels, nutrient scarcity and accumulation of adverse cellular waste products in the tumor microenvironment. These factors together may propel tumors to select resistant glycolytic phenotypes with cancer stem cell features.

Warburg's pioneering work on the origin of cancer cells, suggested that a metabolic shift towards aerobic glycolysis is a distinctive feature of malignant cells [26]. Due to the recent findings introducing altered levels of Pgk1 and salient changes in downstream metabolites 3-phosphoglycerate and phosphoenol pyruvate during differentiation, cancer cells with cancer stem cell properties in particular, may contribute to the pool of cells with undifferentiated phenotype but highly resistant to conventional therapies which are specifically reliant on these changes [15]. If this concept proves correct and there was a therapeutical window for instance by targeting distinct metabolic enzymes or reducing Pgk1 levels, this may be a strategy that renders tumors and their cells of origin vulnerable to conventional treatment strategies [6]. Together these findings suggest that targeting key metabolic enzymes in tumors may open a new chapter in cancer treatment, which is well worth exploring. As a proof of principle acute promyelotic leukemia has been successfully targeted by such an approach [27], however past treatments in solid tumors were less efficacious. Perhaps these data suggest a new era is at hand to overcome resistance in solid malignancies targeting metabolism.

References:


