International Journal of Biochemistry and Cell Biology 89 (2017) 171–181

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review article

Cell biology-metabolic crosstalk in glioma

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ARTICLE INFO

Keywords:
Metabolism
Glioma
Eicosanoids
Prostaglandins
Migration

ABSTRACT

The renewed interest in cancer metabolism in recent years has been fuelled by the identification of the involvement of key oncogenes and tumour suppressor genes in the control of metabolic pathways. Many of these alterations lead to dramatic changes in bioenergetics, biosynthesis and redox balance within tumour cells. The complex relationship between tumour cell metabolism and the tumour microenvironment has turned this field of biochemistry and cell biology into a challenging and exciting area for study. In the case of gliomas the involvement of altered metabolic pathways including glycolysis, oxidative phosphorylation and glutaminolysis are pointing the way to new possibilities for treatment. The tumour-promoting effects of inflammation are an emerging hallmark of cancer and the role of the eicosanoids in gliomas is an area of active research to elucidate the importance of individual eicosanoids in glioma cell proliferation, migration and immune escape. In this review, the different aspects of metabolic reprogramming which occur in gliomas are highlighted and their relationship to glioma cell biology and the wider tumour microenvironment is described.

1. Introduction

In their highly cited paper from 2000, Hanahan and Weinberg proposed six hallmarks of cancer as an organizing principle for rationalizing the complexities of neoplastic disease (Hanahan and Weinberg, 2000). The main hallmarks addressed were the tumour cell's limitless ability to proliferate, self-sufficiency in growth stimulating signals, insensitivity to classic growth inhibitory signals, escape from cell death through altered apoptotic responses, capacity to stimulate angiogenesis and, lastly, migratory and invasive behaviour allowing the development of distant metastases. Over a decade later the authors revisited and revised their ideas with the inclusion of additional hallmarks (Hanahan and Weinberg, 2011). The emerging hallmarks of deregulated cellular energetics and evasion of immune destruction were accompanied by two characteristics thought to enable the acquisition of the hallmarks of cancer, these being genome instability with its resulting mutations and tumour-promoting inflammation.

Each of these hallmarks is found in most tumours and classic examples of how these properties are acquired exist for many common tumour types. The best known is probably self-sufficiency in growth stimulating signals which, through gene mutation, can cause the alteration of gene product quantity, e.g. receptor protein expression levels, or function, e.g. altered receptor tyrosine kinase activity (Lemmon and Schlessinger, 2010; Hanahan and Weinberg, 2011).

This review will highlight areas where alterations in tumour cell metabolism impact upon biological processes of cells contributing to the development and progression of tumours, with emphasis on the most common primary brain tumours, the diffuse gliomas. The emerging hallmark of deregulated energy metabolism and the enabling characteristic of tumour-promoting inflammation will be considered in detail in the context of gliomas.

2. General cancer metabolism

The capacity for aerobic glycolysis, accompanied by high rates of lactate formation both *in vitro* and *in vivo* is one of the best known

Abbreviations: AA, arachidonic acid; COX, cyclooxygenase; cPGES, cytoplasmic prostaglandin E synthase; CREB, carbohydrate response element binding protein; CYP450, CYP450 epoxygenase; DAG, diacylglycerol; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; EP, prostaglandin E receptor; ERBB2, receptor tyrosine-protein kinase erbB-2; FA, fatty acid; FABP, fatty acid binding protein; FASN, fatty acid synthase; GBM, glioblastoma; GLA, gamma-linolenic acid; GLS, glutaminase; GSC, glioma stem-like cell; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HIF-1α, hypoxia-inducible factor 1α; HODE, hydroxyoctadecadienoic acid; HpETE, hydroxyperoxyeicosatetraenoic acid; IDH, isocitrate dehydrogenase; LOX, lipoxygenase; MCT, monocarboxylate transporter; MDR, multiple drug resistance; MGMT, O6-methylguanine DNA methyltransferase; mPGES1, microsomal prostaglandin E synthase 1; mPGES2, microsomal prostaglandin E synthase 2; mTORC1, mammalian target of rapamycin complex 1; NDGA, nordihydroguaiaretic acid; NF1, neurofibromatosis 1; NSAID, non-steroidal anti-inflammatory drug; PDGFRA, platelet-derived growth factor receptor alpha; PG, prostaglandin; PGE2, prostaglandin E2; PGES, prostaglandin E synthase; PI3K, phosphoinositide-3-kinase; PIK3R1, phosphatidylinositol 3-kinase regulatory subunit alpha; PIP3, phosphatidylinositol-3,4,5-triphosphate; PKA, (cAMP-dependent) protein kinase A; PTEN, phosphatase and tensin homologue; PUFA, polyunsaturated fatty acid; R-2-HG, R-2-hydroxyglutarate; S-2-HG, S-2-hydroxyglutarate; SREBP, steroid response element binding protein; TAG, triacylglycerol; TGF β2, transforming growth factor β2; TMZ, temozolomide

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http://dx.doi.org/10.1016/j.biocel.2017.05.022
Received 2 March 2017; Received in revised form 15 May 2017; Accepted 17 May 2017
Available online 24 May 2017
1357-2725/

alterations in tumour cell metabolism and was first described by Otto Warburg and by Cori and Cori in the 1920's (Cori and Cori, 1925; Warburg, 1928). The ability of cancer cells to produce lactic acid from glucose even under normoxic conditions became known as the Warburg effect. Initially, Warburg believed that damaged respiration was the reason for the metabolic alterations found in tumour cells and he defended this idea for decades (Warburg, 1956). With the improved methods for the study of metabolism available nowadays, the ideas of Warburg have been corrected and refined and it is clear that instead of increased aerobic glycolysis being caused by damaged respiration, it is more readily attributed to the many alterations found in the control of the glycolytic pathway itself. For a detailed review of Warburg's contributions to metabolism see (Koppenol et al., 2011).

Studies in the 1950's by Eagle determined the amino acid requirements of mammalian cells in *in vitro* culture and found that glutamine was required in higher concentrations than most other amino acids (Eagle, 1955; Eagle et al., 1956). Glutamine metabolism has long been proposed to contribute building blocks to anabolic processes both in normal proliferating cells such as thymocytes and lymphocytes (Brand, 1985; Newsholme et al., 1985) and in tumour cells (Moreadith and Lehninger, 1984; Mares-Perlman and Shrago, 1988). In the absence of glutamine, certain tumour cells can produce glutamine through an increase in glutamine synthetase activity (Colquhoun and Newsholme, 1997; Tardito et al., 2015). This increase in activity allows the cells to provide precursors for the biosynthetic processes necessary to support sustained cell proliferation. Together, glucose and glutamine are the main energy and biosynthetic sources in the majority of tumour cells, with lipids third in terms of contribution to energetic and biosynthetic processes (Board et al., 1990; DeBerardinis et al., 2007; Moreno-Sánchez et al., 2007; DeBerardinis and Chandel, 2016). The increased glucose metabolism in cancer cells can provide multiple intermediates for biosynthesis, as well as the production of ATP, including glucose-6-phosphate for glycogen synthesis, dihydroxyacetone phosphate for lipid synthesis, citrate from the tricarboxylic acid cycle for fatty acid, cholesterol and isoprenoid synthesis, ribose-5-phosphate from the pentose phosphate pathway for nucleotide synthesis, and NADPH for both fatty acid synthesis and redox balance (Board et al., 1990; Kroemer and Pouyssegur, 2008). The increased glutamine metabolism seen in cancer cells also provides both ATP, through glutaminolysis, and biosynthetic intermediates including glutamate for amino acid and glutathione (GSH) synthesis, malate for pyruvate and NADPH synthesis and glutamine itself for hexosamine and nucleotide biosynthesis (Board et al., 1990; Board and Newsholme, 1996; DeBerardinis et al., 2008; DeBerardinis and Cheng, 2010) [Fig. 1].

The identification of the involvement of oncogenes and tumour suppressor genes in the metabolic reprogramming which takes place in tumour cells has revitalized the study of metabolism and has led to the development of new avenues of research in metabolic intervention for the treatment of cancer (Pedersen, 2007; Tennant et al., 2010). The major metabolic changes are the result of gene mutations which can activate signalling pathways such as Ras, phosphoinositide-3-kinase (PI3K), Akt and mammalian target of rapamycin complex 1 (mTORC1) and the transcription factors Myc, hypoxia-inducible factor 1α (HIF-1α) and steroid response element binding protein 1 (SREBP-1). The alterations tend to funnel into the main functions of biosynthesis, energy provision and redox balance, all of which are essential to enable sustained growth (Kroemer and Pouyssegur, 2008; Obre and Rossignol, 2015; DeBerardinis and Chandel, 2016; Vander Heiden and DeBerardinis, 2017).

3. Gliomas

The gliomas are primary tumours of the central nervous system derived from the glial cell lineage. They are traditionally subdivided into four groups dependent on the degree of aggressive, malignant behaviour (Louis et al., 2007). The most recent WHO classification of brain tumours released in 2016 has taken a step further in the classification of diffuse gliomas, with a more integrated approach including both phenotypic and genotypic parameters, in an attempt to add further objectivity to diagnosis. The diffuse gliomas of adults include the WHO grade II and III astrocytic tumours, the grade II and III oligodendrogliomas and the grade IV glioblastomas (GBMs). The high grade gliomas have an aggressive growth pattern and are extremely invasive but, for poorly understood reasons, are rarely metastatic (Lun et al., 2011; Franceschi et al., 2016). The overwhelming majority of GBMs develop *de novo* as primary GBMs without previous evidence of disease but a small proportion (5–10%) can develop from recurring lower grade gliomas and are known as secondary GBMs (Louis et al., 2016).

The GBMs are the most common primary malignant brain tumours in adults (46.6% of all cases), with an incidence of between 1.48-3.45 cases per 100,000 (dependent on ethnicity) in the USA (Ostrom et al., 2016). The average age at diagnosis is 64 years in both the USA and Europe (Vartanian et al., 2014; Ostrom et al., 2016). Despite considerable advances in surgical techniques, improved radiotherapy approaches and the arrival of the chemotherapeutic drug temozolomide, the overall survival rates for patients diagnosed with GBM continues to be dismal. For the most commonly affected age groups, 55–64 and 65–74, the 1 year survival rates are 45.6% and 28.7% respectively, dropping to only 4.6% and 2.4% at 5 years after diagnosis (Ostrom et al., 2016). The poor prognosis is due to several factors which combine to make GBM so difficult to treat.

The first problem is the location of the tumour, often in eloquent areas of the brain, which in many cases precludes its complete surgical resection. Secondly, the tumour cells which remain after surgical resection have the ability to both migrate and invade into the surrounding brain and most tumours recur within a 2 cm margin of the original resection site (Giese et al., 2003). The additional problem exists that the inflammation and reparative activity after surgery may be stimuli for the proliferation, migration and invasion of the remaining tumour cells (Okolie et al., 2016). Similarly, radiotherapy causes inflammatory responses in the brain which may also serve to stimulate the remaining tumour cells. Finally, the majority of the diffuse gliomas have a poor response to chemotherapy. GBMs are prone to develop multiple drug resistance (MDR) through increased expression of members of the ABC transporter family which, by transporting drugs out of the tumour cell, contribute to reduced treatment efficacy (Trog et al., 2005; Perazzoli et al., 2015; Stavrovskaya et al., 2016).

4. Glioma mutations and metabolism

Genomic and proteomic studies have allowed the division of diffuse gliomas into groups based on both phenotypic and genotypic profiles including the WHO grade II and III astrocytic tumours, the grade II and III oligodendrogliomas and the grade IV glioblastomas (Verhaak et al., 2010; Noushmehr et al., 2010; Louis et al., 2016). In the case of the GBMs four distinct subtypes have been identified as the mesenchymal, proneural, neural and classical groups, each with their own gene mutation/expression profile (Verhaak et al., 2010; Noushmehr et al., 2010). In these studies the mesenchymal GBMs were frequently mutated for the epidermal growth factor receptor (EGFR) and neurofibromatosis 1 (NF1) genes, while the classical GBMs were frequently mutated for the EGFR and EGFR variant III (EGFRvIII) genes. The proneural GBMs had mutations for platelet-derived growth factor receptor alpha (PDGFRA), phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1) and isocitrate dehydrogenase 1 (IDH1), while the neural GBMs had mutations for EGFR and receptor tyrosine-protein kinase erbB-2 (ERBB2) genes. Mutations common to the four subtypes included phosphatase and tensin homologue (PTEN) and tumour protein 53 (TP53) (except in classical GBMs) (Verhaak et al., 2010).

Mutation of p53 increases glycolytic flux in cancer cells and balances oxidative phosphorylation, allowing cells to adapt to and survive mild metabolic stresses (Kruiswijk et al., 2015). Glioma cells have a