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Review

Metabolic reprogramming in cancer cells, consequences on pH and tumour progression: Integrated therapeutic perspectives with dietary lipids as adjuvant to anticancer treatment

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ABSTRACT

While tumours arise from acquired mutations in oncogenes or tumour-suppressor genes, it is clearly established that cancers are metabolic diseases characterized by metabolic alterations in tumour cells, and also non-tumour cells of the host organism resulting in tumour cachexia and patient weakness. In this review, we aimed at delineating details by which metabolic alterations in cancer cells, characterized by mitochondrial bioenergetics deregulations and the preference for aerobic glycolysis, are critical parameters controlling the aggressive progression of tumours. In particular, metabolic alteration in cancer cells are coupled to the modulation of intracellular and extracellular pH, epithelial-to-mesenchymal transition and associated increased invasiveness, autophagy, and the development of anticancer treatment resistance. Finally, based on mechanistic, pre-clinical and clinical studies, we proposed the adjuvant supplementation of dietary n-3 polyunsaturated fatty acids for a complementary holistic treatment of the cancer disease.

Contents

Abbreviations: α-SMA, α-smooth muscle actin; AMPK, AMP-activated protein kinase; bHLH, basic Helix-Loop-Helix; DHA, docosahexaenoic acid (22:6n-3); Drp1, dynamin-related protein 1; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; EPA, eicosapentaenoic acid (20 5n-3); ERK1/2, extracellular signal-regulated kinase; ^{18}FdG, 18-fluorodeoxyglucose; 5-FU, 5-fluorouracile; HIF, Hypoxia-Inducible Factor; IFP, interstitial fluid pressure; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinase; mCAT, mitochondrial catalase; MCT, monocarboxylate-H^+ co-transporter; MDR, multidrug resistance; MMP, matrix metalloproteinases; n-3 PUFA, n-3 polyunsaturated fatty acid; Na_V, voltage-gated sodium channels; NHE, sodium-proton exchanger; NMU, N-nitroso-N-methylurea; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PET, positron emission tomography; P-gp, P-glycoprotein; PPAR, peroxisome proliferator activated receptor; PPI, proton pump inhibitor; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; TMZ, temozolomide; UCP-2, mitochondrial uncoupling protein 2.

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1. Introduction

Cancer is a leading cause of death, and it was estimated in 2012 that 14.1 million new cancer cases and 8.2 million cancer deaths occurred in the world [1]. These numbers are expected to increase rapidly in the next few years because of the growth and aging of populations, the changes in lifestyle and dietary behaviours, and/or the exposure to environmental conditions that are known or supposed to increase cancer risk. Sometimes, cancer is considered as merely being a genetic disease. The tumour mainly takes its origin in the occurrence of sporadic mutations leading to the amplification, or activation, of various oncogenes (such as *SRC*, *AKT*) [2,3], the increased expression (or gain-of-function mutations) of proto-oncogenes (such a *RAS*, *MYC*, *WNT*) [4–6], or the acquisition of loss-of-function mutations in tumour-suppressor genes (such a *RB1*, *TP53*, *PTEN*, *APC*) [7–9]. A small proportion of cancers (5–15% of cases depending on cancer types) are hereditary, *i.e.* due to the transmission of germline mutations in tumour-suppressor genes, such as the breast-ovarian hereditary cancers associated with mutations in *BRCA1/2* genes encoding for DNA repair enzymes [10]. These mutations, along with the stochastic accumulation of multiple others with undefined role(s), lead to the selection of some cancer cell clones [11]. The growth of the primary tumour and its progression towards an aggressive phenotype result from mutual interactions between cancer cells and their microenvironment in the host organism. This microenvironment comprises stromal, endothelial and immune cells, extracellular matrices, as well as soluble factors, such as cytokines, growth factors, and can be submitted to fluctuations in ionic composition, nutrients availability and oxygen tension.

1.1. Cancer progression

At the cellular level, the acquisition of extensive migration and extracellular matrix invasion potencies by cancer cells are critical steps in cancer progression, in the metastatic cascade [12,13] and eventually in patient death [14]. It is generally accepted, that the acquisition of pro-invasive capacities is associated with the epithelial-to-mesenchymal transition (EMT), which is a reversible phenotypical and functional programme, reminiscent of physiological mechanisms involved in embryonic development or tissue repairing [15]. During the EMT, cancer cells of epithelial origin dedifferentiate: they lose their apico-basal polarity to the profit of a rear-to-front cell polarity, lose intercellular junctions (especially tight and adherens junctions), remodel their intracellular cytoskeleton, and gain mobility and resistance to apoptosis (Fig. 1). They also overexpress and secrete ECM-degrading proteases, and express mesenchymal markers (such as vimentin, N-cadherin, α-smooth muscle actin (α-SMA)) [16]. The EMT is proposed to favour the acquisition of stemness characteristics in cancer cells [17,18], to support their survival in the bloodstream and their extravasation in metastatic sites [19,20]. Increasing evidence suggests that the EMT, and the reverse process called mesenchymal-to-epithelial transition (MET), may be better described as a spectrum of intermediate states that might depend on the physical and chemical nature of the microenvironment. The initiation of the EMT programme is driven by several signalling pathways including those mediated by transforming growth factor β (TGF-β) [21], bone morphogenetic protein (BMP) [22] or integrin signalling [23], that stimulate EMT-inducing transcription factors (Snail1/2, Zeb1/2, Twist) which bind to the promoter region of critical genes such as those regulating cell–cell adhesions [24–27]. In a primary tumour, the induction of EMT is generally visualized in areas of hypoxia [28]. In fact, low oxygen tension induces transcriptional, metabolic and phenotypic changes that directly induce, or synergize with, signalling pathways inducing EMT (see paragraph 2.1–"Aerobic glycolysis, pH regulation and consequences on cancer cell invasiveness and resistance to treatments"), hence linking this phenotypical switch to metabolic parameters.

Over the last decade, important knowledge on cancer cell migration and invasiveness has emerged, leading to the classification of different types of migrations, individual *versus* collective, and different migrating cell phenotypes, mesenchymal *versus* amoeboid [29,30]. These specific phenotypes are not mutually exclusives and can be combined depending on the nature of the microenvironment. In the mesenchymal mode of invasion, cancer cells harbour an elongated fibroblast-like morphology, with a rear-to-front lamellopodial cell polarity. Their motility is dependent on the interaction of integrins, at focal sites, with components of the substratum. In this mode of invasion, cancer cells self-generate a path through the participation of invadosomal structures that perform the proteolytic remodelling of the ECM by both membrane-associated and extracellularly-released soluble proteases, such as MMP2, MMP9 or cysteine cathepsins, for which extracellular release and activation are promoted by extracellular acidification [31–34].

In the "amoeboid" mode of invasion, cancer cells generally present a rounded morphology, but their shape changes in order to move through small gaps of the ECM, with no need to degrade it, and they display a high speed of migration due to strong actomyosin contractions [35]. While different cancer cell types may preferentially engage into one mode or the other, the most aggressive cancer cells show high plasticity, with transitions called MAT, for mesenchymal-to-amoeboid transition, and AMT for amoeboid-to-mesenchymal transition [35]. These transitions, orchestrated by RhoGTPases family members (such as Rac1/2, RhoA/B, cdc42) [36–38], offer selective advantages and complementary mechanisms to invading cancer cells, by counteracting and adapting to changes in the microenvironment (matrix composition and stiffness, accessibility to oxygen and nutrients), and are also proposed to abrogate the efficacy of some anticancer treatments [39–41].

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