Natural Compounds as Metabolic Modulators

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The tumor microenvironment (TME) comprises a heterogenous assemblage of malignant and non-malignant cells, including infiltrating immune cells and other stromal cells, together with extracellular matrix and a variety of soluble factors. This complex and dynamic milieu strongly affects tumor differentiation, progression, immune evasion, and response to therapy, thus being an important therapeutic target. The phenotypic and functional features of the various cell types present in the TME are largely dependent on their ability to adopt different metabolic programs. Hence, modulating the metabolism of the cells in the TME, and their metabolic crosstalk, has emerged as a promising strategy in the context of anticancer therapies. Natural compounds offer an attractive tool in this respect as their multiple biological activities can potentially be harnessed to '(re)-educate' TME cells towards antitumoral roles.

Keywords: tumor microenvironment ; stromal cells ; metabolism ; metabolic modulation ; natural compounds ; phytochemicals ; cancer

1. Introduction

The tumor microenvironment (TME) can be defined as the complex and dynamic milieu where cancer cells are embedded. It comprises nonmalignant cells, such as infiltrating immune cells, fibroblasts, endothelial cells, and adipocytes, together with the extracellular matrix and a variety of cytokines, chemokines, and growth factors resulting from heterotypic signaling. All these components actively interact and contribute to an evolving balance between anti- and protumoral events [1]. For instance, immune cells recruited to the tumor site (e.g., monocytes/macrophages and lymphocytes) can either help to eliminate cancer cells, mainly in early stages of tumor development, or perform protumorigenic functions via multiple mechanisms. Nonimmune stromal cells are also key for cancer cells to thrive, as evidenced by the role of activated fibroblasts in ECM remodeling to favor cell invasion and migration or the involvement of endothelial cells in tumor vascularization needed to supply oxygen and nutrients to cancer cells, clear metabolic waste, and enable tissue invasion by metastatic cells. Besides supporting tumor growth and progression, the TME strongly determines the success of anticancer therapies, mainly by physically influencing drug access and inducing drug resistance through soluble factors, cell–cell interactions, and/or immune responses [2]. Hence, due to its well-established importance in cancer progression and response to treatment, the TME is currently considered a central paradigm in oncobiology and anticancer drug development.

Metabolic reprogramming is widely accepted as one of the major cancer hallmarks [3][4]. Tumor cells typically show altered uptake and metabolic processing of nutrients, mainly to sustain their enhanced energetic and biosynthetic needs, as well as to maintain a favorable balance between the production of reactive oxygen species (ROS) and antioxidant mechanisms [5]. Rewired metabolism of tumor cells stems from changes in signaling pathways, protein expression, and other molecular mechanisms but is also strictly linked to the interplay with other cells in the TME via paracrine signaling, competition for nutrients, and cooperative metabolic exchange [6]. For instance, lactate produced by glycolytic cancer cells and activated fibroblasts may serve as metabolic fuel for less glycolytic tumor cells. Moreover, lactate-induced acidification favors metastasis, angiogenesis, immune evasion, and immunosuppression [7]. On the other hand, the metabolic programs adopted by stromal cells, in response to tumor signals and the changing microenvironment, strongly determine the phenotypic and functional features of TME cells, hence their contribution to tumor development and progression [8]. Consequently, modulating the metabolism of the TME cells has emerged as an attractive strategy to hinder the protumoral roles of these cells or even to '(re)-educate' them towards antitumoral functions.

Several natural compounds produced by plants, microorganisms and marine organisms, which display strong cytotoxic activity against a variety of tumor cells, are under preclinical testing or used already as conventional chemotherapy drugs [9]. The enormous structural diversity, adequacy to chemical modification, and multitargeting activities of these compounds are some of the features that make them attractive as anticancer cytotoxic and/or cytostatic agents. Moreover, many of these molecules have great potential to sensitize cancer cells to different therapeutic approaches, including radiotherapy,

chemotherapy, and immunotherapy, as recently reviewed for flavonoids [10]. Notably, besides direct effects in cancer cells, some natural compounds exhibit other biological activities in noncancerous cells, such as antioxidant, anti-inflammatory, and immunomodulatory activities that empower the host immune system, enhance the efficacy of anticancer drugs, and/or protect normal cells from drug toxicity [11][12]. Consequently, a growing number of studies is now focusing on the effects of natural compounds beyond tumor cells, with special emphasis on the modulation of immune cells in the TME [13][14]. Here, we describe some illustrative examples of antitumoral metabolic reprogramming mediated by natural compounds. This knowledge, combined with our understanding on the direct effects of these compounds in the metabolism of tumor cells (recently reviewed in [15][16]), is expected to provide a more integrated picture of the biological impact and therapeutic potential of these compounds as anticancer metabolic modulators.

2. Metabolic Modulation of TME Cells by Natural Compounds

2.1. Curcumin

Curcumin (**Figure 1**a) is a hydroxycinnamic acid present in the rhizome of *Curcuma longa* (turmeric), which is used as a dietary spice. It has potent antiproliferative and proapoptotic effects in tumor cells of various origins, and it can alter their susceptibility to radio- or chemotherapy treatments [17], as well as to anticancer gene therapy [18]. Moreover, curcumin can inhibit the replication and/or reactivation of herpesvirus involved in the etiology of human cancers, such as Kaposi's sarcoma-associated herpesvirus (KSHV) and the Epstein–Barr virus (EBV) [19]. The activities of curcumin in tumor cells involve multiple signaling pathways and molecular targets, including inflammatory mediators, transcription factors, growth factors, and proteins orchestrating cell survival, proliferation, and death. In recent years, curcumin's antitumoral action has also been linked to its metabolic effects [20]. Subtoxic levels of curcumin inhibited glucose uptake and glycolytic conversion to lactate in several cancer cell lines by decreasing the expression of key glycolytic enzymes like hexokinase 2 (HK2) [21] and pyruvate kinase isoform M2 (PKM2) [22][23]. As many cancer cells strongly depend on the Warburg metabolism for rapid energy production and macromolecular synthesis, this effect may contribute to curcumin's antiproliferative activity. Importantly, glycolysis inhibition and reduced extracellular lactate levels were accompanied by the downregulation of lactate hydroxycarboxylic acid receptor-1 (HCAR-1/GPR81) in hepatic carcinoma cells. As HCAR-1 modulates the multidrug resistance (MDR) protein family involved in cytotoxic drug expelling, this could explain the curcumin-induced sensitization to chemotherapy drugs [24]. Moreover, the antitumoral effects of curcumin were related to inhibition of fatty acid synthase (FASN) [23][25][26], a key enzyme in *de novo* lipid synthesis, as well as to its ability to inhibit ATP synthase activity, resulting in impaired mitochondrial respiration, increased production of ROS, and apoptosis [27].

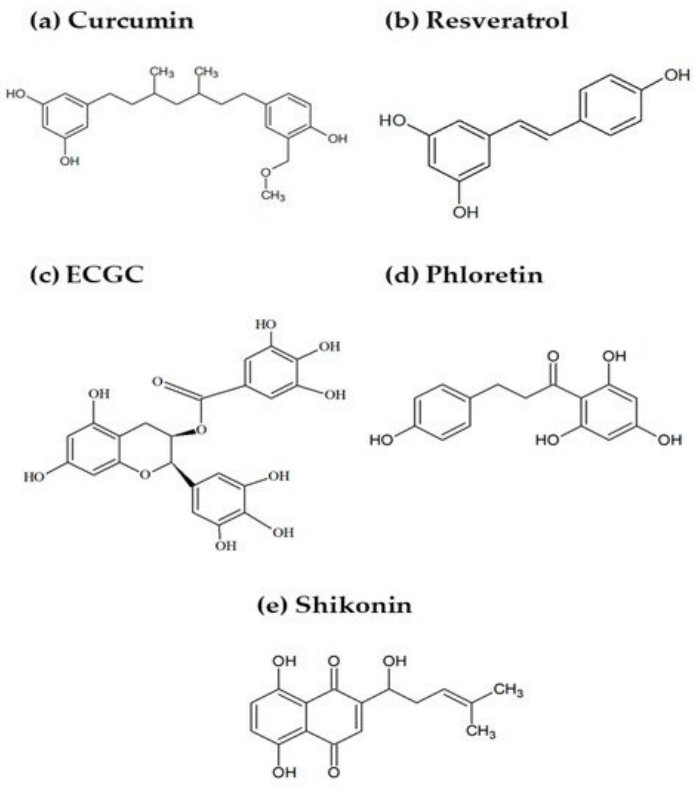

Figure 1. Chemical structures of some natural compounds reported to alter the metabolism of stromal cells in the TME: (**a**) curcumin, (**b**) resveratrol, (**c**) epigallocatechin gallate (EGCG), (**d**) phloretin, and (**e**) shikonin.

Curcumin has also been shown to target CSCs and cause their elimination through interference with several biological processes and pathways [28]. At the metabolic level, curcumin (40 μM, 48 h) was proposed to interfere with glutamine uptake in colon CSCs, possibly via direct coupling with CD44 at the cell surface [29]. In that study, purported CSCs were isolated from the HT29 colorectal cancer cell line through CD44-positive selection using magnetic beads. A 48h-treatment with 50 μM of curcumin induced apoptosis in $CD44^+$ cells but not in $CD44^-$ cancer cells, suggesting that curcumin preferentially targets the CSC subpopulation within colorectal cancer cells. Through mass spectrometry-based metabolic profiling, curcumin was also found to differentially affect the metabolism of $CD44^+$ and $CD44^-$ cells. The former showed significantly reduced intracellular levels of glutamine, an amino acid that typically serves as an anaplerotic substrate to sustain the increased energetic needs of cancer cells. Based on the unchanged ATP levels observed in curcumin-treated $CD44^+$ cells (which excluded intensified OXPHOS), it was hypothesized that glutamine uptake could be blocked due to direct interaction of curcumin with CD44 at the cell membrane and that this metabolic disruption could induce apoptosis of CSCs. On the other hand, corroborating this hypothesis, the glutamine levels were not affected in curcumin-treated $CD44^-$ cancer cells [29].

Regarding stromal TME cells, curcumin was found to modulate the lipid metabolism in THP-1-derived macrophages. In particular, it induced lipid accumulation by upregulating the expression of lipid transport genes, such as fatty-acid transporter (CD36/FAT) and fatty acid-binding protein-4 (FABP-4) [30][31]. The authors suggested that lipid accumulation in macrophages could be a mechanism through which curcumin helps lowering the lipid levels in the bloodstream. In the context of the TME, this may reduce the availability of the lipids for cancer cells, which, in turn, could contribute to impairing the tumor growth.

2.2. Resveratrol

Resveratrol (**Figure 1**b) is a stilbenoid produced by many plants in response to stress factors and is commonly found in the skin of grapes, berries, and peanuts. Among other biological activities (e.g., anti-inflammatory, antioxidant, and cardioprotective), the chemopreventive and anticancer effects of resveratrol have been widely reported and reviewed [32] [33]. Like curcumin, the antitumoral activity of resveratrol is multitargeted and comprises interference with the cell cycle and death mechanisms of tumor cells, together with the modulation of the processes involved in oncogenic signaling in the tumor microenvironment, such as hypoxia, oxidative stress, and inflammation.

Resveratrol rewires glucose metabolism of tumor cells by inhibiting glycolysis and upregulating OXPHOS, in association with PKM2 downregulation and AMPK activation, as reviewed in reference [34]. Notably, this ability to shift the glycolytic-to-oxidative balance of tumor cells was recently shown to enhance the antitumor effect of silencing PD-L1 (programmed cell death protein ligand 1), a protein that hinders the cytotoxic activity of T cells [35]. In that study, resveratrol (10 μM) was co-delivered with PD-L1 siRNA, through copolymer-based polyplexes and found to stimulate mitochondrial OXPHOS while downregulating the glycolytic enzymes and lactate production in melanoma (B16F10) and colorectal (CT26) cancer cell lines. These effects were also observed *in vivo*, after the injection of resveratrol-containing polyplexes into tumor mouse models. The abrogation of glycolysis and consequent decrease in tissue lactic acidosis could, in itself, be expected to mitigate the immunosuppressive TME [7]. However, the accompanying upregulation of mitochondrial respiration was found key to enhance the immune responses [35], consisting of higher infiltration of $CD8^+$ and $CD4^+$ T cells, the inhibition of Tregs and myeloid derived suppressor cells (MDSCs), and increased secretion of interferon-gamma (IFN-γ), a cytokine that stimulates Th1 responses and macrophage activation and, thus, promotes antitumoral immunity.

The importance of resveratrol-mediated metabolic reprogramming in the TME was further demonstrated by its direct effects on T cells [36]. The exposure of human $CD4^+$ T cells (isolated from peripheral blood of healthy donors) to low-dose resveratrol (20 μM) downregulated the membrane glucose transporter 1 (GLUT1) and decreased the glucose uptake and glycolysis, as monitored by the production of lactate and extracellular acidification. Moreover, resveratrol induced a higher glutamine consumption by lymphocytes, as shown by increased glutamine transporter ASCT2, previously found to be critical for T-cell activation [37]. This was accompanied by an upregulation of glutaminase 2 (GLS2), an enzyme that catalyzes the conversion of glutamine into glutamate, and by an increased glutamine uptake, all data indicating the resveratrol-induced stimulation of glutaminolysis in T cells. Moreover, resveratrol-treated lymphocytes displayed an increased oxygen consumption rate (OCR), which indicates a shift to OXPHOS, corroborated by increased intracellular ATP levels and a higher production of mitochondrial ROS. These metabolic changes were linked to the activation of p53, which was mediated by a genotoxic stress response involving kinase ataxia telangiectasia-mutated and Rad3-related ATR. Most importantly, the enhancement of T-cell bioenergetic fitness by resveratrol was associated with increased IFN-γ secretion and, thus, an augmented effector function.

2.3. Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) (**Figure 1**c) is the most abundant and bioactive catechin in green tea, and its anticancer effects have been extensively studied. As recently reviewed [38], EGCG can hit a variety of molecular targets in different cancer cells and induce antiproliferative, antioxidant, anti-inflammatory, and antiangiogenic effects at all stages of carcinogenesis. A few studies have additionally shown that EGCG interferes with tumor cell metabolism [39][40]. In breast cancer cells, concomitantly with the induction of autophagy and apoptosis, EGCG (20–240 μM) downregulated the expression of the glycolytic regulators GLUT1 and hypoxia-inducible factor 1-α (HIF-1α) and inhibited several glycolytic enzymes, thus hampering the glucose metabolism [39]. Moreover, in colon cancer cells, this flavonoid (50 μg/mL) was shown by joint transcriptomics and metabolomics analyses to impact other metabolic pathways, namely glycerophospholipid metabolism and glutathione metabolism, likely related to antiproliferative and antioxidant actions, respectively [40].

The metabolic effects underlying the ability of a green tea extract (GTE) and EGCG (50 μM) to inhibit the proliferation of umbilical vein endothelial cells (HUVECs), thus avoiding neovascularization, have also been recently described [41]. GTE was found to downregulate the pathways related to the synthesis of cellular building blocks (nucleotides, nucleotide sugars, amino acids, and pantothenic acid); mitochondrial energy production; and inositol signaling, all postulated to explain GTE's antiproliferative actions. On the other hand, it triggered protective mechanisms by activating the pathways related to vitamin B6, glycerophospholipids, and antioxidants production, thus maintaining the cellular integrity. Interestingly, EGCG also exerted inhibitory and protective effects but through different pathways, as revealed by metabolic profiling. Growth inhibition was ascribed to prooxidant effects and the suppression of membrane signaling molecules, while cellular protection appeared to be promoted via the upregulated expression of vitamins B6 and B2, NAD, and putrescine. Comparatively to catechins, the antiangiogenic drug Bevacizumab, which blocks proliferation by specifically inhibiting the binding of vascular endothelial growth factor (VEGF) to its receptor, displayed a narrower spectrum of metabolic effects. It mainly suppressed the biosynthesis of amino acids and increased polyunsaturated fatty acids expression, which may alter the membrane properties and affect cellular proliferation. Altogether, the multitargeting activity of GTE and catechin mixtures in endothelial cells, which could be largely explained at the metabolic level, represents a valuable feature in antiangiogenic approaches.

2.4. Phloretin

Phloretin (**Figure 1**d) is a hydroxylated dihydrochalcone present in the root bark and leaves of apple and other fruit trees. It was shown to inhibit glucose transporters in breast [42] and colon cancer cells [43], an effect that has been related to cell growth suppression. Recently, its potential role in modulating the TME metabolism, namely the tumor–fibroblasts metabolic crosstalk, has been highlighted [44]. To induce a CAF-like state, bone marrow-derived mesenchymal stem cells (MSCs), at 60–70% confluence, were incubated for up to 30 days in a medium conditioned by MDA-MB-231 breast cancer cells. The CAFs were shown to oxidize lactate into pyruvate, which, in turn, supported the biosynthetic, energetic, and antioxidant needs of cancer cells. This lactate–pyruvate metabolic loop was disrupted by phloretin (100 μM), which significantly attenuated glycolysis and ROS accumulation in cancer cells, while disrupting the lactate uptake in CAFs. In addition, phloretin enhanced the cytotoxicity of doxorubicin (a conventional chemotherapy drug) in the presence of a CAF-conditioned medium, but it did not contribute to drug cytotoxicity in the complete medium. Overall, phloretin was demonstrated to be a powerful adjuvant to potentiate the effects of anticancer drugs, due to its efficacy in downregulating the glucose uptake and monocarboxylate exchange, which are key metabolic dependencies of tumors [44].

2.5. Shikonin

Shikonin (**Figure 1**e) is a naturally occurring naphthoquinone found in the root of plants from the Boraginaceae family and the first compound to be obtained from large-scale plant cell cultures [45]. It has been used in traditional Chinese medicine for centuries and shown to possess several therapeutic properties, including antimicrobial, wound healing, anti-inflammatory, antioxidant, and anticancer activities [46]. The potential of shikonin and its derivatives in cancer treatment has received increasing attention in recent years, mainly due to its wide spectrum antitumor effects [47]. Repression of glycolysis through specific inhibition of PKM2, the enzyme catalyzing the conversion of phosphoenolpyruvate to pyruvate, is a key mechanism in shikonin's antitumor activity, as demonstrated in a variety of tumor cells [48][49][50].

Recent data clearly showed that shikonin-mediated metabolic effects impacted the TME by repolarizing TAM and synergizing with PD-1 blockage (mediated by JQ1), thus enhancing the immune response [51]. In that work, mannosylated lactoferrin nanoparticles were loaded with shikonin (1 μM) and JQ1 (3 μM), for targeted codelivery to colon cancer cells (CT26) and TAM. The bioactive NPs reduced lactate production in cancer cells (in association with PKM2-mediated glycolytic inhibition), and skewed macrophages towards a pro- inflammatory phenotype, characterized by higher production of TNF-α and lower secretion of TGF-β. Furthermore, treatment of CT26-tumor-bearing mice with the shikonin/JQ1-loaded nanosystem efficiently decreased tumor growth, suppressed glucose metabolism (as seen by

reduced levels of lactate, PKM2 and HIF-1α in the tumor tissue), downregulated intratumoral PD-L1 expression, and remodeled the TME's immune configuration (e.g., promotion of dendritic cell maturation and CD8+ T cell infiltration, as well as suppression of Treg). Overall, the synergism between metabolic reprogramming and regulation of immune responses was shown to improve antitumor treatment efficacy.

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