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Mini review

Metabolic regulation of suppressive myeloid cells in cancer

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ABSTRACT

Cancer cells rewire their metabolism to promote growth, survival, proliferation and long-term maintenance. The common feature of this altered metabolism is the increased glucose uptake and fermentation of glucose to lactate, which is observed even in the presence of completely functioning mitochondria. This effect is known as the 'Warburg Effect' and its intensive investigation in the last decade has partially established either its causes or its functions. It is now emerging that a major side effect of the Warburg Effect is immunosuppression, which limits the immunogenicity of cancer cells and therefore restricts the therapeutic efficacy of anticancer immunotherapy. Here we discuss how the metabolic communication between cancer and infiltrating myeloid cells contributes to cancer immune evasion and how the understanding of these mechanisms may improve current immunotherapies.

Contents

Abbreviations: ADRP, adipose differentiation related protein; AMPK, adenosine monophosphate kinase; AP1, activator protein 1; Arg1, arginase 1; ATP, adenosine triphosphate; CARKL, carbohydrate kinase-like; Cat2, cationic amino acid transporter 2; C/EBP, CCAAT/enhancer-binding protein; ER, endoplasmic reticulum; FAO, fatty acid-oxidation; G-CSF, granulocyte-colony stimulating factor; G-CSFR, G-CSF receptor; GM-CSF, granulocyte macrophage-colony stimulating factor; FFA, free fatty acid; HIF-1α, hypoxia inducible factor-1α; IGFBP3, insulin-like growth factor-binding protein 3; iNOS, inducible nitric oxide synthase; IRF5, interferon regulatory factor 5; LAL, lysosomal acid lipase; M-CSF, macrophage-colony stimulating factor; MCT, monocarboxylate transporters; MDSC, myeloid-derived suppressor cells; M-MDSC, monocytic-MDSC; mTOR, mammalian target of rapamicin; NAD, nicotinamide adenine dinucleotide; GSH, glutathion; NADPH, nicotinamide adenine dinucleotide phosphate; NAMPT, nicotinamide phosphoribosyltransferase; NO, nitric oxide; OXPHOS, oxidative phosphorylation; PGC-1β, peroxisome proliferator-activated receptor γ coactivators-1β; PMN-MDSC, granulocytic-MDSC; PPARγ, peroxisome proliferator-activated receptor; SIRT, sirtuins; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophages.

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1. Introduction

Malignant transformation of cells leads to enhanced glucose uptake and the conversion of a larger fraction of pyruvate into lactate, even under normoxic conditions (aerobic glycolysis). This phenomenon is known as the Warburg effect and serves to generate biosynthetic precursors, thus facilitating the survival of rapidly proliferating malignant cells.

While glycolysis has been shown to be associated with activated oncogenes (*e.g.* RAS and MYC) and lack of function of tumour suppressors [1], recent evidences have disclosed a panel of additional metabolic pathways altered in cancer, which encompass deregulated uptake of glucose and amino acids, access to unconventional nutrient sources, altered biosynthesis and nicotinamide adenine dinucleotide phosphate (NADPH) production, increased demand for nitrogen, alterations in metabolite-driven gene regulation and metabolic interactions with the microenvironment [2].

Similar to cancer cells, immune cells engage metabolic reprogramming to drive their activation and differentiation [3–6]. As an example, stromal cells are another source of lactate production in the tumor microenvironment, whose role in both tumor growth and the antitumor immune response is the subject of intense research [7]. The altered metabolism of tumors produces a series of catabolic products that enhance the exposure of immune cells to increased levels of lactate, adenosine triphosphate (ATP) and adenosine, as well as to alterations of the amino acid and lipid metabolism. Such events, profoundly influence both differentiation and functions of immune cells, particularly myeloid cells [3,8] and impose a radical alteration of hematopoiesis, with expansion of suppressor myeloid populations [9]. Among these populations, myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM) represent specialized suppressor myeloid cells that establish immunotolerance and resistance to cancer therapies [10,11]. Finally, tumor and immune cells share similarities in the use of nutrients and in metabolic pathways that support their proliferation and survival. This “metabolic competition” within the tumor microenvironment may fine-tune the activation and anti-tumor immune responses.

2. Myeloid-suppressor cells

A pool of heterogeneous myeloid cells endowed with immune suppressive properties are generated during immunologic stress (emergency myelopoiesis), such as cancer, where their accumulation favors disease progression by inhibiting antitumor immunity [3]. Despite their clinical relevance, the molecular pathways and metabolic events guiding the expansion of these myeloid populations, mainly represented by MDSC and TAM [12], remain largely unknown. Solid tumors promote infiltration of leukocyte populations, among which TAM represent a paradigm for cancer promoting inflammation. TAM orchestrate various aspects of cancer, including diversion and skewing of adaptive responses, cell growth, angiogenesis, matrix deposition and remodeling, the construction of a metastatic niche and actual metastasis, response to hormones and chemotherapeutic agents. TAM infiltration is generally associated with poor prognosis, as shown in Hodgkin disease, glioma, cholangiocarcinoma, and breast carcinoma [13]. Several evidence indicate that TAM show a remarkable degree of plasticity and functional heterogeneity, suggesting that during tumor progression macrophages undergo a phenotypic ‘switch’, eventually exhibiting the alternatively activated, ‘M2’, phenotype, associated with immunosuppression, promotion of tumor angiogenesis and metastasis. While recent studies have attempted to address the role of microenvironmental signals on the TAM phenotype, their metabolic reprogramming is emerging as a crucial step of this event [8]. Similarly to TAM, MDSC display a certain degree of plasticity and may assume a classically activated (M1) or alternatively activated (M2) phenotype, with antitumor or tumor promoting functions respectively [14]. Myeloid-derived suppressor cells (MDSC) comprise heterogeneous population of early myeloid progenitors of monocytic (M-MDSC) and granulocytic (PMN-MDSC) populations, sharing an immature state and the ability to suppress adaptive immunity. Due to the phenotypic and functional heterogeneity of these cells, an updated nomenclature and characterization standards of MDSC was recently proposed [15] to avoid confusion in the field. In mice an initial characterization of M-MDSC and PMN-MDSC is respectively provided by the $CD11b^{+}Ly6C^{high}Ly6G^{-}$ and $CD11b^{+}Ly6G^{+}Ly6C^{low}$ cell surface markers. In human the equivalent M-MDSC and PMN-MDSC subsets are defined as $CD11b^{+}CD14^{+}HLA\text{-}DR^{-/low}CD15^{-}$ and $CD11b^{+}CD14^{-}CD15^{+}$, respectively. Similarly to TAM, newer studies suggest that MDSC maturation and function is under the control of metabolic and inflammatory parameters, which control their tumor-promoting and suppressive functions [9].`

3. Metabolic pathways of the tumor microenvironment

3.1. Lactate

It is estimated that the majority of tumor cells produce up to 40 times more lactic acid than normal cells [16]. In cancer cells characterized by increased aerobic glycolysis and excessive lactate formation (lactagenic tumors), oncogenes and tumor suppressor mutations orchestrate increased glucose utilization for lactate production, whose exchange, is promoted through the increased expression of the monocarboxylate transporter (MCT) 1 and MCT4 [17]. Lactate is a unique multitask metabolite which is involved in all main sequela of carcinogenesis, specifically: angiogenesis, immune escape, cell migration, metastasis and self-sufficient metabolism [17]. Its increased production results from a metabolic reprogramming of tumor cells that restructur the Krebs cycle and enhance glycolysis, eventually leading to production of high amounts of lactic acid [16]. Cancer-generated lactic acid has been shown to divert myeloid cell functions, including TAM [18], and to act as an immunosuppressive metabolite. Innate immune cells present in the tumor microenvironment also produce lactate at some point. Moreover, the few mitochondria present in neutrophils make these cells mostly dependent on glycolysis for ATP production [19].

Macrophages are defined as plastic cells that in response to different signals may acquire different polarization states, exemplified in the two M1 *vs* M2 functional extremes [20]. M1 and M2 macrophages differ in their metabolism and in their immune functions. While M1 (classically activated) macrophages act as a first line of defense against bacterial infections and obtain energy through glycolysis, M2 (alternatively activated) macrophages are involved in tissue repair and wound healing and use oxidative metabolism to fuel their longer-term functions [21]. Whereas resting macrophages preferentially metabolize the up-taken glucose by glycolysis rather than by oxidative phosphorylation (OXPHOS) [22], in M1 macrophages the reduced expression of carbohydrate kinase-like (CARKL) is associated with greater flux through glycolysis and the oxidative pentose phosphate pathway, to increase the overall redox potential ($NADH:NAD^{+}$, GSH:GSSG) and reduce the oxygen consumption rate [22,23]. In contrast, in M2 macrophages CARKL maintains sedoheptulose-7-phosphate levels, favoring oxidative phosphorylation [23]. The dynamic M1–M2 switch of macrophage polarization occurring during the transition from early to advanced stages of tumor development [24] appears