



REVIEW ARTICLE OPEN

Implications of metabolism-driven myeloid dysfunctions in cancer therapy

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Immune homeostasis is maintained by an adequate balance of myeloid and lymphoid responses. In chronic inflammatory states, including cancer, this balance is lost due to dramatic expansion of myeloid progenitors that fail to mature to functional inflammatory neutrophils, macrophages, and dendritic cells (DCs), thus giving rise to a decline in the antitumor effector lymphoid response. Cancer-related inflammation orchestrates the production of hematopoietic growth factors and cytokines that perpetuate recruitment and activation of myeloid precursors, resulting in unresolved and chronic inflammation. This pathologic inflammation creates profound alterations in the intrinsic cellular metabolism of the myeloid progenitor pool, which is amplified by competition for essential nutrients and by hypoxia-induced metabolic rewiring at the tumor site. Therefore, persistent myelopoiesis and metabolic dysfunctions contribute to the development of cancer, as well as to the severity of a broad range of diseases, including metabolic syndrome and autoimmune and infectious diseases. The aims of this review are to (1) define the metabolic networks implicated in aberrant myelopoiesis observed in cancer patients, (2) discuss the mechanisms underlying these clinical manifestations and the impact of metabolic perturbations on clinical outcomes, and (3) explore new biomarkers and therapeutic strategies to restore immunometabolism and differentiation of myeloid cells towards an effector phenotype to increase host antitumor immunity. We propose that the profound metabolic alterations and associated transcriptional changes triggered by chronic and overactivated immune responses in myeloid cells represent critical factors influencing the balance between therapeutic efficacy and immune-related adverse effects (irAEs) for current therapeutic strategies, including immune checkpoint inhibitor (ICI) therapy.

Keywords: Myelopoiesis; Tumor-associated macrophages; Myeloid-derived suppressor cells; Metabolism; Cancer therapy

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INTRODUCTION

Enhanced myelopoiesis is recognized as the primary factor that drives inflammatory disorders, including cancer, and is characterized by aberrant differentiation of myeloid progenitors, with an accumulation of dysfunctional myeloid cells endowed with suppressive functions, including myeloid-derived suppressor cells (MDSCs), tolerogenic dendritic cells (DCs), and tumor-associated macrophages (TAMs).¹

Hematopoietic stem cells (HSCs) activation in persistent low-grade inflammation in cancer or overactivation (i.e., in acute infections or sepsis) perpetuates and increases myelopoiesis at the expense of lymphopoiesis, leading to expansion of a pool of immature and dysfunctional myeloid cells¹ that besiege and exhaust antitumor immunity, thus resulting in local and systemic host immunosuppression.^{2,3} This pathologic myelopoiesis, leading to pro-disease phenotypes, provides us with an unresolved immunological paradox to date, since enhanced myeloid recruitment and function in tumors or infections should represent the front line of host defense and avoid disease progression.

Multiple inflammatory insults drive “pathological myelopoiesis”,⁴ including pathogen-associated molecular patterns and damage-associated molecular patterns,⁵ which are sensed by pattern-recognition receptors.⁶ Innate immune cells activated through PRRs provide the source for cytokines and myelopoietic growth factors acting on myeloid progenitors. Among these cytokines, the pleiotropic cytokines IL-1, tumor necrosis factor (TNF), and interleukin-6 (IL-6) serve as key promoters of emergency myelopoiesis by controlling the dynamics of transcription factors involved in myeloid lineage fate decisions and function.⁷ Growing evidence suggests that key transcription factors of emergency myelopoiesis, such as PU.1, interferon regulatory factors, CEBP/beta and RORC, in addition to driving myelopoiesis, are expressed in adipose tissue and have a central role in adipocyte differentiation, adipose inflammation, and insulin resistance (IR).^{8–10} This sharing of transcription networks between the adipose tissue and myeloid cells indicates that alterations in metabolic homeostasis may have a profound impact on myelopoiesis and therefore coordinate immune responses to environmental cues. Interestingly, studies show that low-grade

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inflammation in the adipose tissue and liver of elderly individuals or patients with metabolic dysfunction triggers transcriptional networks that reprogram steady-state hematopoiesis towards persistent and myeloid-biased hematopoiesis.^{7,11} Therapeutic targeting of PU.1 on adipocytes and adipose and liver macrophages improves glucose homeostasis and reduces liver steatosis, inflammation, and fibrosis in mouse models of steatohepatitis,¹² indicating that targeting regulators of emergency myelopoiesis in patients with metabolic inflammation may revert pathologic inflammation and restore tissue homeostasis. Evidencing a critical contribution of dysregulated transcriptional networks of myelopoiesis and immunometabolism to the outcome of immunotherapy, recent studies have shown that hyperglycemia and hypercholesterolemia induce long-lasting changes in the transcriptional landscape of HSCs and myeloid progenitors (MPs), which perturb myeloid lineage fate decisions and the functional polarization of myeloid cells,^{13,14} and these changes persist even after changing to a control diet and upon weight loss^{15,16}. Studies support this novel concept by showing that resistance to cancer immunotherapy correlates with host intrinsic metabolic dysfunctions such as hormone imbalance, IR, changes in glucose and lipid metabolism and enhanced inflammatory mediators.¹⁷

Extensive research published in medical and scientific journals has demonstrated that cancer cell-intrinsic metabolism hijacks the regulation of antitumor immune signaling, contributing to immunotherapy resistance.^{18,19} However, the role of aberrant immune cell-intrinsic metabolism in immunotherapy resistance remains poorly investigated to date.

As the majority of patients still show *de novo* or adaptive resistance to current immunotherapies, identifying immunometabolic checkpoints that coordinate myelopoiesis and effector lymphoid responses to oscillations in metabolites and inflammatory signals has become a hot research topic for improving cancer immunotherapy and preventing immune-related adverse events (iRAES). In accordance with this scenario, increasing evidence shows dysregulated cellular signaling and metabolism in myeloid cell subsets that infiltrate immunologically cold tumors resistant to immune checkpoint inhibitors (ICIs), chemotherapy (CT), and radiotherapy, with the infiltrates characterized by a lack of T and NK cell infiltrates, and accumulation of MDSCs, TAMs, and tolerogenic DC.^{3,20}

This review aims to highlight potential targets for myeloid therapy, with a specific focus on recent efforts combining myeloid-targeted immune therapy with strategies to restore metabolic homeostasis.

INTERCONNECTION BETWEEN METABOLIC SYNDROME AND INFLAMMATION

Metabolic syndrome is a collection of disturbances, including glucose intolerance, obesity, hypertension, and dyslipidemia,²¹ with increasing prevalence in developed countries. Chronic low-grade inflammatory conditions have been implicated as a major factor for metabolic syndrome,²² which is accompanied by metabolically triggered inflammation,²³ a condition that does not completely fit into the classical definition of acute or chronic inflammation. Systemic metabolic inflammation accelerates immune overactivation and dysregulation and can support profound immune deficiency. This dual role of metabolic inflammation suggests that the plasticity of immune responses is intricately linked to the intracellular metabolism of immune cells and is highly sensitive to systemic and local metabolic oscillations in tissues.

Recent findings have highlighted the substantial impact that metabolic syndrome has on lymphoid tissue integrity, lymphocyte development, phenotypes and activity, and the coordination of innate and adaptive immune responses. Importantly, these changes are associated with an overall negative impact on

relapse-free survival in cancer patients.^{24,25} How exogenous and intrinsic metabolic signals affect the immune response in patients is poorly understood to date. Extensive clinical data and experimental models demonstrate the involvement of obesity and adipokines in the pathogenesis and treatment response of a broad variety of autoimmune diseases.²⁶ Hyper and persistent secretion of inflammatory cytokines can cause IR in the adipose tissue, skeletal muscle and liver by inhibiting insulin signal transduction. Myeloid cells, primarily resident in colon, liver, muscle, and adipose tissue, serve as a source of chronic inflammation, termed meta-inflammation, causing localized IR via autocrine/paracrine cytokine signaling and systemic IR via endocrine cytokine signaling.²⁷ In addition, meta-inflammation predisposes patients to overactivated immune responses, with co-occurring immune exhaustion and immunosuppression.²⁸

Finally, the level of inflammation has a direct implication in therapy, affecting the plasticity of the immune system. Indeed, cancer therapy-induced inflammation (i.e., inflammation induced by CT and radiotherapy) is considered an additional mechanism reinforcing aberrant myelopoiesis. In this respect, IL-6 was shown to activate emergency myelopoiesis after myeloablation consequent to cytotoxic treatments.^{29,30} Furthermore, the use of monoclonal antibodies (i.e., nivolumab) targeting checkpoint inhibitors (i.e., PD-1) in cancer immunotherapy is frequently associated with severe side effects, which are mitigated by anti-inflammatory treatments, including steroids or the anti-IL-6 antibody tocilizumab in steroid-refractory patients.³¹ Combination therapy with nivolumab + ipilimumab was recently approved for treating unresectable cases of malignant melanoma. Despite the high response rate, this therapy is associated with a high incidence of serious adverse events, including immune-related hemophagocytic syndrome/hemophagocytic lymphohistiocytosis (iRHS/HLH), macrophage activation syndrome, and secondary HLH, a cytokine storm syndrome associated with multiorgan system dysfunction and high mortality rates.^{32,33} Therefore, understanding the role of inflammatory mediators and their interconnection with patient metabolic status will be necessary to ensure proper immunological manipulation and the best personalized therapies.

The controversial role of metabolic syndrome-associated myeloid dysfunction in cancer

In response to immunologic stresses, including infection and cancer, hematopoietic stem and progenitor cells in the bone marrow (BM) sense peripheral inflammation and adapt through increased proliferation and skewing towards the myeloid lineage. Although these adaptations meet the need for more innate immune cells, this lymphoid-myeloid switch and the enhanced myelopoiesis might also perpetuate inflammatory and metabolic disorders by generating a feed-forward loop between inflammation-triggered MP cells and the inflamed tissue.⁴ Alterations in MPs, as well as the expansion of pro-inflammatory monocytes and MDSCs, also arise in high-fat diet (HFD)-induced obesity^{34–36} and are considered a biomarker for the risk of obesity-associated diseases, such as diabetes and atherosclerosis.^{37,38} Notably, it has been hypothesized that one of the mechanisms by which obesity promotes cancer mortality is through the induction of MDSCs.^{39–41} In accordance with this hypothesis, obese mice with renal cancer develop a robust immunosuppressive environment that is characterized by heightened local and systemic CCR2⁺ MDSC prevalence.⁴² In a pancreatic cancer mouse model of diet-induced obesity, cells expressing common neutrophil and MDSC markers (Gr1⁺CD11b⁺) were recruited to the pancreas by adipocytes and pancreatic stellate cells producing the pro-inflammatory mediator IL-1 β . Depletion of Gr1⁺CD11b⁺ cells, IL-1 β , or pancreatic stellate cells prevented the rapid growth of cancer in obesity.⁴³ Similarly, in BALB/c mice carrying 4T1 mammary carcinoma, MDSCs from HFD mice were more

immunosuppressive than MDSCs from low-fat diet (LFD) mice, correlating with higher tumor progression and reduced survival, and depletion of MDSCs in HFD mice restored activation of tumor-reactive CD8⁺ T cells, reducing tumor progression, and spontaneous metastasis to levels comparable to those seen in LFD mice.⁴⁴ In addition to dampening the host-specific antitumor T cell and DC immune responses, metabolic syndrome-associated myeloid cells can drive pathologic overactivation of the immune response. The increased risk of developing intra-abdominal obesity and metabolic syndrome in the elderly population⁴⁵ is associated with hyperactivated macrophages, persistent myelopoiesis, and MDSC expansion, which paradoxically can drive a deadly cytokine storm.⁴⁶ This increase in inflammatory sensitivity leads to a mixed immunophenotype of hyperactivated and exhausted and tolerogenic immune cells that may predispose individuals to infection or CAR-T cell cancer therapy-induced cytokine storm. The role of MDSCs in immune dysregulation in patients with metabolic syndrome remains controversial, as MDSCs can also have beneficial effects and protect mice against metabolic dysfunction and inflammation.^{47,48} Nevertheless, metabolic syndrome-associated myeloid dysfunction, including the expansion of MDSCs, has been associated with persistent and unresolved myelopoiesis, leading to immune-mediated tissue pathologies such as fibrosis, tumor angiogenesis, and metastases.⁴⁹ Therefore, therapeutic interventions that reprogram the metabolism of MPs and myeloid cells in tumor patients towards lineage fate decisions supporting myeloid effector and antigen-presenting functions may restore immune-mediated tissue homeostasis and decrease the risk of disease relapse.

Metabolic cues can inform pathogenic myelopoiesis

Mounting evidence demonstrates a role for hypercholesterolemia and hyperglycemia as factors that can independently regulate HSPC function and/or alter the BM niche, influencing HSPC proliferation and maturation.^{50–52} Hypercholesterolemia and hyperglycemia promote leukocytosis, particularly of neutrophils and monocytes.^{51,53,54} In addition, epigenetic mechanisms or metabolic memory may permanently alter the functionality and inflammatory status of HSPCs in diabetic patients, whose glucose levels are inadequately controlled.^{55–57}

The concordance of the changes in circulating progenitors and leukocyte populations in diabetic mice and humans with diabetes strongly suggests that BM myelopoiesis bridges the innate immune response to metabolite oscillations. Supporting this view, a newer study in a mouse model of obesity demonstrated that chronically inflamed visceral adipose tissue, through enhanced production of S100A8/A9, can signal to BM HSPCs to proliferate, expand, and increase the production of myeloid cells.⁵⁸ The authors showed that in adipose tissue macrophages (ATM), S100A8/A9 induces TLR4/MyD88- and NLRP3 inflammasome-dependent production of IL-1 β , which then travels to the BM to induce the proliferation of hematopoietic progenitor cells via IL-1R, ultimately resulting in monocytosis and neutrophilia.⁵⁸ These studies suggest that obesity may have life-long effects on inflammatory responses by altering HSPC function and are consistent with the observations that adipose tissue inflammation and fibrosis are not resolved even after returning to normal weight upon weight loss.^{15,16} Increasing evidence notes that a western diet and lifestyle, as well as aging, drive the pandemic of chronic noninfectious degenerative diseases, termed “civilization diseases” (i.e., metabolic syndrome, cancer, and autoimmune and neurodegenerative diseases), and dramatically increase the susceptibility to and severity of infectious pandemics, such as the current COVID-19 pandemic.⁵⁹ Therefore, a better understanding of the immunometabolic signaling networks that coordinate immune responses to environmental cues is warranted, with the ultimate goal of identifying new therapeutic strategies.

CANCER METABOLISM AND TRANSCRIPTIONAL CONTROL OF EMERGENCY MYELOPOIESIS

In stress/pathological conditions (e.g., infection and cancer), signals derived from the HSC niche modify the magnitude and composition of the hematopoietic output, a feature of immune regulation defined as “emergency” hematopoiesis, to guarantee a proper supply of both lymphoid and myeloid cells in response to increased demand.^{60,61} Most of the transcriptional mechanisms that guide dysfunctional myelopoiesis in cancer patients have been proven to be mechanistically linked to cancer-driven and/or preexisting metabolic reprogramming of the host. Acquisition of a tumor-supporting myeloid phenotype is the last event of a multistep process, encompassing initial immunometabolic reprogramming of MPs in the BM and later steps of terminal differentiation in the tumor microenvironment (TME), that occurs through modulation of selected transcriptional activities.⁶⁰

Role of orphan nuclear receptors (NRs) in metabolism-driven myelopoiesis

Significant advances have been made in elucidating the molecular mechanisms underlying the complex crosstalk between inflammation and metabolism and the emergent role of ligand-activated transcriptional regulators belonging to the NR superfamily,⁶² highlighting nutrient availability and intermediate metabolites as the main orchestrators of stem cell behavior. A number of studies have demonstrated a role of peroxisome proliferator-activated receptors (PPARs) in controlling HSC specification and functional polarization of myeloid cells through fine tuning of glucose and lipid metabolism,^{63,64} implicating a metabolism-centric regulation of lineage commitment.

We have demonstrated for the first time that myeloid-specific expression of the retinoic acid-related orphan NR (RORC1/ROR γ) marks advanced cancer inflammation and that expansion of circulating ROR γ ⁺ myeloid cells is associated with an increased number of both immature suppressive cells (MDSCs) and TAMs.⁶⁵ Ablation of ROR γ in myeloid cells reprograms cancer myelopoiesis in favor of effector APCs capable of inducing potent antitumor CD4⁺ and CD8⁺ T cell responses and tumor regression.⁶⁵ Interestingly, cholesterol precursors (i.e., desmosterol) and oxysterols are known to be potent endogenous ROR γ agonists,^{66,67} and ROR γ has been shown to be an important player in the circadian regulation of lipid and cholesterol metabolism.⁶⁸ In addition, ROR γ has a key role in adipocyte differentiation and mediating insulin sensitivity¹⁰ and is upregulated in patients with severe obesity.⁶⁹ Altogether, these studies suggest that myelopoiesis and myeloid lineage fate are tightly regulated by circadian oscillations in metabolites. Therefore, profound changes in dietary lipid composition and insulin sensitivity may contribute to pathologic dysregulation of myelopoiesis and are one plausible mechanistic link between cancer and obesity.

Role of myeloid transcription factors in metabolism-driven myelopoiesis

Additional transcriptional mechanisms contribute to the metabolic plasticity of myelopoiesis. CCAAT enhancer-binding protein- α (C/EBP α) is a major regulator of “steady state” granulopoiesis⁷⁰ that interacts with the p50 NF- κ B subunit to stimulate neutrophil production during acute inflammation.⁷¹ Of note, the role of p50 NF- κ B in the functional diversity of myeloid cells has been delineated, demonstrating that its nuclear accumulation, in response to tumor-derived prostaglandin E2 (PGE2), promotes the suppressive phenotype of MDSCs and limits the antitumor efficacy of ICIs.⁷² A recent study demonstrated that inhibition of the NF- κ B family member c-Rel transforms tumor-promoting MDSCs into effector APCs, resulting in inhibition of CD4⁺CD25⁺ Treg cell expansion and consequent activation of potent antitumor T cell responses, through metabolic reprogramming via C/EBP β .⁷³ In contrast with C/EBP α , C/EBP β ⁷⁴, and signal

Pro-tumor reprogramming of myeloid cells

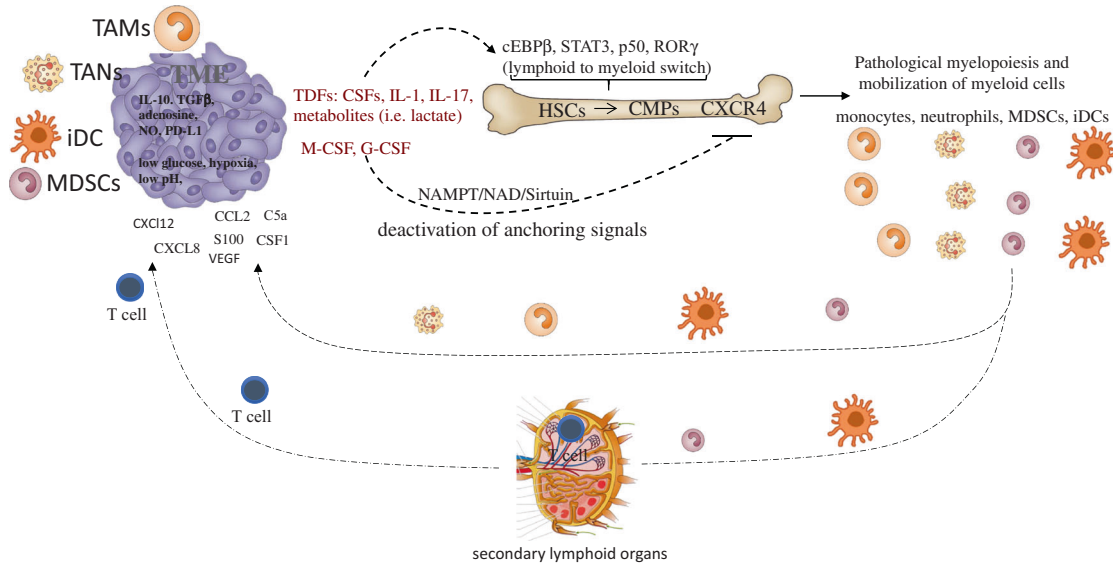


Fig. 1 Protumor reprogramming of myeloid cells. Tumor-derived factors (TDFs), including cytokines, myeloid growth factors and metabolites, induce transcriptional activities (i.e., expression of cEBPβ, STAT3, p50, and RORC1/RORγ) guiding the enhanced proliferation and lymphoid to myeloid switch of HSCs. In parallel, activation of CSF-dependent induction of iNAMPT provides enhanced NAD-dependent activation of the sirtuin 1 deacetylase, which inhibits the HIF-1α-dependent and p65 NF-κB-dependent transcription of CXCR4. Deactivation of the anchoring signal CXCR4 mobilizes myeloid cells from the bone marrow, allowing peripheral expansion of myeloid populations (monocytes, neutrophils, MDSCs, and DCs). These cells reach the tumor site through the circulation and infiltrate the tumor tissue in response to tumor-derived chemotactic signals (TDFs) (i.e., CXCL2, CXCL8, CCL2, S100, VEGF, C5a, and CSF1). In particular, DCs and MDSCs enter the secondary lymphoid organs (lymph nodes and spleen), eliciting inhibitory signals to T cells. Once in the tumor, myeloid cells undergo a further step of reprogramming in response to inhibitory molecules (IL-10, TGFβ, adenosine, NO, and PD-L1) and microenvironmental conditions (low glucose levels, hypoxia, and low pH), terminally differentiating into myeloid suppressor cells (TAMs, TANs, MDSCs, and immature DCs). Overall, the tumor-dependent reprogramming of myeloid populations has to be considered a multistep program, which comprises induction of emergency myeloopoiesis (enhanced proliferation and the “lymphoid to myeloid” switch), mobilization to the periphery and final intratumor reprogramming. Common myeloid precursors (CMPs), hematopoietic stem cells (HSCs), tumor-derived factors (TDFs), immature DCs (iDCs)

transducer and activator of transcription 3 (STAT3)⁷⁵ play major roles in emergency conditions, contributing to MDSC accumulation.⁷⁶ Importantly, C/EBPβ accumulation contributes to β cell failure and IR in mice by enhancing susceptibility to ER stress⁷⁷ and is crucial in regulating diet-induced inflammation and hyperlipidemia in hematopoietic cells and macrophages.⁷⁸ Of relevance, C/EBPβ expression is controlled by RORγ in cancer-associated myeloid cells,⁶⁵ thus indicating a RORγ-C/EBPβ axis as a novel integrator of cancer myeloopoiesis and lipid homeostasis. These pioneering studies suggest that the myeloid transcriptome and coordination of immune responses by myeloid cells are fine-tuned to stress and environmental cues through metabolic reprogramming.

NAD metabolism in myeloid cell mobilization and differentiation
Cancer cells display an atypical metabolic balance featuring increased glucose uptake and fermentation of glucose to lactate, even in the presence of oxygen and functioning mitochondria.⁷⁹ This metabolic setting influences the crosstalk between tumor cells and tumor-infiltrating immune cells, creating competition for essential nutrients (glucose, in particular) and immunosuppression, which consequently hinder the therapeutic efficacy of anticancer immunotherapy.⁸⁰ TME metabolism requires the cofactor nicotinamide adenine dinucleotide (NAD), which functions in many critical redox processes necessary for cancer cells and immune cells.⁸¹ Based on this, inhibitors of intracellular nicotinamide phosphoribosyltransferase (iNAMPT), the rate-limiting enzyme of NAD production in its salvage pathway, have entered clinical trials for solid and nonsolid tumors due to their ability to lower NAD and ATP levels and interfere with malignant

cell growth.⁸² We recently reported that M-CSF, in addition to inducing PU.1-driven myeloid differentiation, has a direct role in controlling iNAMPT activity. Elevated iNAMPT in MPs causes negative regulation of the CXCR4 retention axis of hematopoietic cells in the BM,⁸³ thus disengaging these cells and allowing the mobilization of suppressor myeloid cells to the periphery. In agreement, iNAMPT inhibition prevents MDSC mobilization, reactivates specific antitumor immunity, and enhances the antitumor activity of ICIs⁸³ (Fig. 1).

The system composed of iNAMPT and the NAD-dependent protein deacetylase sirtuin 1 (SIRT1) plays a key role both in maintaining correct energy metabolism and in enhancing the robustness of physiological processes that control the resolution of the inflammatory response.^{83,84} In this regard, emerging evidence shows an age-related loss of iNAMPT/NAD⁺/SIRT1 activity that undermines antioxidant, metabolic and anti-inflammatory systems.^{85,86} Furthermore, iNAMPT activity is necessary for the differentiation of anti-inflammatory myeloid cells under stress conditions.⁸³ NAMPT converts nicotinamide into nicotinamide mononucleotide (NMN), a precursor of NAD,⁸⁷ which is actively consumed by NAD-dependent enzymes (e.g., sirtuins, mono-, and poly-(ADP-ribose) polymerases/ARTs and CD38/CD157)⁸⁴ that control a variety of metabolic and stress responses through modulation of distinct transcriptional activities. In particular, the deacetylase SIRT1 acts homeostatically by repressing the transcription of HIF-1α⁸⁸ and p65 NF-κB-dependent genes.⁸⁹ Of relevance, SIRT1 was shown to promote alternative/M2 macrophage polarization^{83,90} and suppressive activity of MDSCs.⁹¹ Of note, C/EBPα and C/EBPβ are controlled by NAD metabolism,⁹² indicating that in addition to insulin, glucose and

lipids, regulators of cellular redox reactions may play a key role in myeloid homeostasis.

NAMPT expression is increased in various diseases, including chronic inflammatory conditions (e.g., rheumatoid arthritis), metabolic diseases (e.g., diabetes), and cancer.⁹¹ The robustness of the NAMPT/NAD⁺/SIRT1 system is controlled by the nutritional supply of tryptophan, and tryptophan and vitamin B3 (niacin) enable the primary and rescue pathways for the synthesis of NAD, respectively.⁸⁷ Furthermore, administration of vitamin D3 to tumor-bearing mice (bearing metastatic Lewis lung carcinoma) reduces tumor-induced suppressor myeloid cells and enhances T cell functions⁹³ and the differentiation of CD34⁺ immature myeloid cells.⁹⁴ Importantly, recent studies have associated increased levels of extracellular NAMPT/visfatin with overweight/obesity, type 2 diabetes mellitus, IR, metabolic syndrome, and cardiovascular disease.⁹⁵ Therefore, a better understanding of obesity-induced alterations in redox homeostasis and oxidative stress may provide us with important novel immunotherapeutic targets to reprogram pathogenic myelopoiesis in favor of effector APCs capable of coordinating potent antitumor responses.

INTERACTIONS BETWEEN METABOLISM AND MYELOID CELL ACTIVATION STATE

Of relevance, myeloid cells, macrophages in particular, express different functional programs in response to microenvironmental signals, a property defined as plasticity. The extremes of this functional spectrum are generally defined as classical (M1) and alternative (M2) activation states, which identify a cytotoxic and inflammatory phenotype as opposed to an anti-inflammatory and immunosuppressive phenotype, respectively.⁹⁶ The shift between these antithetical activation states plays a distinct role in disease and has inspired new anticancer strategies aimed at the functional reprogramming of myeloid cells.⁹⁶ Notably, evidence indicates that selected metabolic pathways can alter immune cell differentiation and direct effector functions.⁹⁷ In response to M1-polarizing signals (i.e., LPS and IFN γ), macrophages fuel their energy requirements by enhanced glycolysis, associated with high flux through the pentose phosphate pathway, FA synthesis and a truncated tricarboxylic acid cycle, leading to accumulation of succinate and citrate.⁹⁸ This metabolic profile induces the activation of transcriptional factors (i.e., NF- κ B and STAT1) supporting the expression of a pro-inflammatory and antimicrobial program.⁹⁶ Conversely, in response to IL-4, M2-polarized macrophages obtain energy through oxidative phosphorylation (OXPHOS)⁹⁹ and fatty acid oxidation (FAO). In agreement, STAT6-dependent upregulation of the transcription factors peroxisome PPAR γ -coactivator-1 β , PPAR γ , and PPAR δ drives the expression of genes that are crucial promoters of both oxidative metabolism and anti-inflammatory activities.^{100–102}

In addition to macrophages, DCs and neutrophils are strongly affected by metabolic cues. DCs are the most potent antigen-presenting cells (APCs) of the immune system, and their phenotype is influenced by inflammatory and metabolic disorders.¹⁰³ Tumors alter host hematopoiesis and induce an immature DC phenotype with immune-suppressive properties. In particular, cancer cell-derived immune-suppressive factors (VEGF, IL-10, and PGE2) disable DC differentiation, maturation, migration, and functions.¹⁰⁴ Furthermore, lipid and amino acid metabolism modulate DC functions. Of relevance, while 27 hydroxycholesterol acts on HSCs via estrogen receptor α to increase their proliferation and mobilization,¹⁰⁵ oxysterols, which are produced through enzymatic and nonenzymatic oxidation of cholesterol,¹⁰⁶ interact with liver X receptors exerting an anti-inflammatory role on DCs.¹⁰⁷ In agreement, oxysterols produced by tumor cells impair antigen presentation by inhibiting CCR7 expression on DCs.¹⁰⁸ DC functionality can also be compromised by the uptake of lipids enriched within the TME, which lead to DC dysfunctions.¹⁰⁹

Furthermore, DC immunogenicity is hampered by both TAMs and MDSCs through the production of copious amounts of indoleamine 2,3-dioxygenase 1 (IDO1), which converts tryptophan into kynurenines (Kyns).¹¹⁰ The metabolic plasticity of DCs is particularly evident during their progression from an immature to a mature state. Immature DCs generate ATP through OXPHOS, a process primarily driven by FAO.¹¹¹ In response to maturation signals, DCs undergo a metabolic shift towards glycolysis.¹¹² DC commitment to glycolysis correlates with activation of HIF-1, which is necessary to enhance the expression of glycolytic enzymes.¹¹³ Nevertheless, several tumors actively inhibit glycolysis and lipid synthesis in these cells, exacerbating impaired metabolic and immunologic functions of DC.¹¹⁴

The disrupted metabolic flux of cancer cells, characterized by aerobic glycolysis (Warburg effect), results in the preferential conversion of pyruvate to lactate, which in turn impairs the maturation of DCs¹¹⁵ and M2 polarization of TAMs.¹¹⁶ Adenosine production by tumors is an additional mechanism that impairs DC antitumor activities.¹¹⁷ Mechanistically, adenosine promotes the accumulation of cAMP in DCs and the consequent activation of the PKA and Epac pathways that polarize these cells to a tumor-promoting phenotype (IL-10^{high}/IL-12^{low}).¹¹⁸ Notably, the antitumor activity of CT has also been attributed to the induction of “immunogenic cancer-cell death”, which favors the processing and presentation of dead cell-associated antigens by DCs.¹¹⁹

Neutrophils have a short half-life of 7–10 h in both humans and mice.¹²⁰ In accordance with their high turnover rates and rapid adaptability to diverse conditions of the tissue microenvironment, a number of studies have demonstrated their functional plasticity and capacity to extend their life in response to cytokines (i.e., IL-1 β , IL-6, and TNF) and granulocyte colony-stimulating factor (G-CSF).^{121,122} Tumor-associated neutrophils (TANs) can elicit cytotoxic activity against tumor cells and promote inhibition of metastasis.¹²³ However, contrasting evidence suggests that TANs can support tumor angiogenesis, cancer cell migration and invasion and immunosuppression.¹²⁰ According to these results, IL-1 β -driven IL-17 expression by $\gamma\delta$ T cells promoted TAN expansion in mammary cancer-bearing mice, which eventually suppressed cytotoxic CD8⁺ T cell functions.¹²⁴ Furthermore, PD-L1⁺ neutrophils from patients with hepatocellular carcinoma effectively suppressed the proliferation and activation of CD4⁺ and CD8⁺ T cells via PD-1/PD-L1 interactions.¹²⁵ Of relevance, a high neutrophil-to-lymphocyte ratio (NLR) correlates with poor clinical outcome in patients with advanced-stage cancers,¹²⁶ and a recent meta-analysis on 39 different malignancies identified tumor-infiltrating neutrophils as the immune population associated with the worst prognosis.¹²⁷ In line with these contrasting observations, a recent paradigm has highlighted the phenotypic plasticity of TANs, which in response to microenvironmental signals can either display an inflammatory (N1) or an alternative (N2), tumor-promoting activation state. Transforming growth factor- β (TGF β) was demonstrated to promote the N2 phenotype, whereas interferon- β leads to an antitumor (or N1) phenotype.¹²⁸ Neutrophils are highly dependent on HIF-1 regulation, and in general, hypoxic conditions increase neutrophil inflammatory functions,^{129,130} promoting tissue infiltration, survival, activation, and cytokine release. In agreement, evidence indicates that neutrophils can suppress CTLs via HIF-1 α -dependent¹³¹ iNOS-mediated nitric oxide (NO) production and reactive oxygen species (ROS).¹²⁴

Amino acid metabolism and suppressor myeloid cells

Consumption of essential amino acids is a classic example of how tumors exploit metabolic pathways to generate molecules endowed with immunomodulatory activities and deplete nutrients essential for T cells. In particular, TAMs and MDSCs express high levels of IDO1, an enzyme that converts tryptophan into its immunosuppressive catabolite Kyn, which is capable of inducing

the expansion of regulatory T (Treg) cells,⁸⁰ depriving T cells of an essential nutrient¹³² and hindering the immunogenicity of DCs.¹¹⁰ L-arginine depletion is one of the main mechanisms by which MDSCs inhibit antitumoral T cell activity; however, granulocytic (PMN-MDSCs) and monocytic (M-MDSCs) subsets of MDSCs use distinct enzymes or arginine metabolism to generate immunosuppression. In particular, L-arginine depletion by ARG1 predominantly occurs in PMN-MDSCs and leads to downregulation of T cell receptor (TCR)- ζ chain expression and inhibition of the cyclin-dependent kinase pathway regulating the cell cycle,¹³³ as well as downregulation of the ornithine and polyamine generation that supports tumor cell proliferation.¹³⁴ In contrast, M-MDSCs utilize the nitric oxide synthase (iNOS) enzyme to produce NO and promote tyrosine nitration and S-cysteine nitrosation of various proteins.^{135,136} Several lines of evidence also indicate that both enzymes can contribute to the immunosuppressive activities of human MDSCs.¹

Cysteine represents an additional essential nutrient for T cells that is introduced from the extracellular space. In contrast with APCs that import extracellular oxidized cystine and export the cysteine used by T cells, MDSCs only uptake cystine (using the AA antiporter xc), thus limiting the extracellular pool of cysteine required for T cell activation.¹³⁷

HOST INSULIN METABOLISM AND CANCER PROGRESSION

In the early 1990s, the role of TNF- α as a pro-inflammatory cytokine linked to IR was demonstrated in the adipose tissue of obese mice.¹³⁸ Later, studies in healthy and obese subjects confirmed that pro-inflammatory cytokines and immune cell infiltration were involved in glucose homeostasis.¹³⁹ These findings raised interest in the potential role of IR in obesity-induced chronic inflammation, which is now known to be associated with cancer development and aggressiveness.¹⁴⁰ The relationship between insulin, insulin sensitivity, the insulin growth factor (IGF) receptor family and cancer is now well established. Insulin and insulin-like growth factor 1 (IGF-1) activate insulin receptor and IGF-1 receptor, respectively, which are expressed at higher levels in malignant cells and support their proliferation.¹⁴¹ In addition, both insulin and IGF-1 increase sex hormone synthesis and reduce sex hormone-binding globulin levels, leading to elevated levels of estrogens and other endocrine tumor promoters.¹⁴¹ Moreover, obesity itself has been hypothesized to adversely impact the response to CT, not only through metabolic perturbations and underlying IR, adipokine production, and the IGF-1 axis but also by affecting drug delivery, pharmacokinetics, and transport.¹⁴² Of relevance, the obesity-driven transition of the macrophage activation state from "M2-like" to "M1-like" promotes inflammation and potentially contributes to IR.¹⁴³ Macrophages are very prominent in adipose tissue, where they can reach proportions of up to 50% of all cells.¹⁴⁴ Within breast adipose tissue, obesity leads to chronic, macrophage-driven inflammation, suggesting that obese breast cancer patients may benefit from metabolic targeting.¹⁴⁵ In general, the inflammatory state induced by neoplastic processes might increase the cancer cell proliferation and paracrine-related effects mediated by inflammatory cytokines, such as increased angiogenesis¹⁴⁶ and myeloid cell accumulation (TAMs and MDSCs), which orchestrate the creation of an immunosuppressive environment.¹⁴⁷

Epidemiological observations have provided evidence that higher circulating insulin levels are associated with an adverse outcome in early BC patients.^{148,149} From this perspective, the insulin pathway may represent a therapeutic target, especially in patients with high plasma insulin levels. Hyperinsulinemia may reflect an altered level of insulin sensitivity and be associated with chronic inflammation, characterized by high levels of IL-6, C-reactive protein, tumor necrosis factor- α , fibrinogen, and the cell adhesion molecules ICAM-1 and VCAM-1.¹⁵⁰ Moreover,

hyperinsulinemia induces proliferative tissue abnormalities due to strong anabolic effects, resulting in the enhancement of DNA synthesis and cell proliferation. In women with early BC without diabetes, it has been observed that hyperinsulinemia is associated with the presence of IR.¹⁵¹ In our recent publication, we hypothesized that insulin might exert its influence on tumor aggressiveness by modulating gene expression at the level of breast cancer cells. In particular, by using publicly available gene datasets, we recently identified a gene signature based on the differential expression of 15 genes related to the insulin (27%), chronic inflammation (30%), and IGF pathways (40%) that was strongly associated with disease-free survival in early breast cancer.¹⁵² These data suggest that it is possible to identify a subset of BC patients whose prognosis is modulated by a set of genes related to the insulin pathway.

From this perspective, the potential antitumor effect of the antidiabetic drug metformin has been extensively studied due to its antiproliferative activity *in vitro*.^{153,154} In cancer patients, however, metabolic targeting does not translate into a measurable clinical benefit, probably due to the complexity of the IGF-1R/insulin receptor system and the presence of parallel pathways of growth and survival, as well as the lack of appropriate patient selection markers.^{154,155} Moreover, a number of clinical studies evaluating anti-IGF drugs (either monoclonal antibodies or TKIs) reported inconsistent results or were complicated by excessive metabolic toxicity (hyperglycemia). We recently performed a translational study to evaluate the potential role of IGF-1R expression on circulating tumor cells (CTCs) of patients enrolled in the MYME trial, which compares first-line CT with first-line CT plus metformin in HER2-negative, metastatic BC patients without diabetes. Our data demonstrate that patients with loss of IGF-1R on CTCs have a significantly worse outcome than patients with IGF-1R expression on CTCs, providing a possible clue for improved patient stratification strategies aimed at metabolic targeting in advanced BC.¹⁵² Overall, the relationship between IR, metabolic impairment, the underlying chronic inflammatory status and cancer needs to be extensively evaluated to better develop a strategy for "metabolic targeting".

Additional studies addressing the impact of obesity and IR on the outcome of ICI therapy have provided controversial data to date. ICIs have been reported to cause immune-mediated damage to islet cells, leading to ICI-induced type 1 diabetes mellitus (T1DM).¹⁵⁶ On the other hand, there are a number of reports supporting an "obesity paradox," in which patients with higher body mass index, i.e., patients with overweight or obesity, have an improved outcome if treated with immunotherapy for advanced tumors,¹⁵⁷ indicating a close connection between the immune system and patient metabolic status. Stratifying a cohort of patients with metastatic melanoma into groups based on receipt of first-line immunotherapy revealed a moderate but insignificant association between overweight or obesity and better progression-free survival in patients who received first-line immunotherapy. Conversely, an association with worse progression-free survival was observed in patients who received non-first-line ICIs.¹⁵⁸ Therefore, studies that better depict the contribution of IR and obesity to the outcome of ICI therapy are needed to adapt patient care to metabolic status.

Tumors alter the glycolysis vs. OXPHOS balance of myeloid cells to control their activation state

Recent studies indicate that impaired OXPHOS accompanied by increased glycolysis may be a significant contributor to increased myelopoiesis and heightened myeloid cell activation under acute and chronic settings.^{159,160} Enhanced tumor glycolytic flux converts a major fraction of pyruvate into lactate, even under normoxic conditions (Warburg effect). The conversion of pyruvate into lactate is mediated by lactate dehydrogenase A, a hypoxia-inducible factor 1 α (HIF-1 α) target.^{161,162} Lactate-mediated

inhibition of DC maturation¹¹⁵ is paralleled by the generation of MDSCs.¹⁶² Moreover, a recent study suggests that lactate operates as an endogenous inhibitor of histone deacetylases,¹⁶³ transcriptionally regulating a number of genes that not only are involved in metabolism and transcriptional control but also participate in immune response fate. Furthermore, increased tumor glycolysis enhances GM-CSF, G-CSF, C/EBP β ¹⁶⁴, and NF- κ B expression,¹⁶⁵ which represent major immune signaling pathways that support MDSC differentiation.

In addition to the competition for glucose and essential metabolites in inflamed tissue, intracellular metabolic aberrations may reprogram immune cell fate, survival and function. A new study shows that tumor MDSCs suppress glycolysis-mediated T cell effector functions by transferring methylglyoxal to CD8⁺ T cells via direct cell contact. The acquisition of methylglyoxal by T cells coincides with a reduction in free L-arginine and a concomitant increase in the products of glycation reactions between methylglyoxal and L-arginine, suggesting that depletion of L-arginine in the cytosol paralyzes T cell functions.¹⁶⁶ Under homeostatic conditions, cells are protected against methylglyoxal toxicity by different mechanisms, particularly the glyoxalase system, which represents the most important pathway for the detoxification of methylglyoxal.¹⁶⁷ Methylglyoxal is formed as a byproduct of glycolysis and is a major cell-permeant precursor of advanced glycation end-products (AGEs), while engagement of RAGE, the receptor for AGEs, is shown to activate downstream signaling and evoke oxidative stress and inflammation in diabetes.¹⁶⁸ Changes in the intracellular levels of glycolytic metabolites are linked to the inflammatory phenotype of immune cells implicated in autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and diabetes. Notably, targeting metabolic effectors, such as targeting of mTOR by rapamycin, hexokinase by 2-deoxy-D-glucose, and adenosine monophosphate (AMP)-activated protein kinase by metformin, may be used to ameliorate autoimmune inflammation.^{169,170} Preliminary studies suggest that extrinsic and intrinsic increases in glycolysis and uncoupling from OXPHOS may lead to aberrant myeloid cell differentiation, expansion, and activation in a broad range of inflammatory diseases.

INTERPLAY BETWEEN CANCER THERAPY, METABOLISM, AND MYELOID SUPPRESSOR CELLS

Deregulated myelopoiesis sustains malignant transformation and progression by shaping the TME via interactions with tumor cells, stroma, and other infiltrating immune cells, ultimately promoting cell growth, angiogenesis, and diversion and skewing of the adaptive immune response. The generation of suppressor myeloid cells is a driving force for tumor progression and therefore a promising therapeutic target. In addition, available anticancer strategies feature myeloid-specific activities as part of their antitumor actions. In particular, modulation of MDSCs is now accredited as a key therapeutic strategy due to the tumor-promoting phenotype of MDSCs and their capacity to affect the efficacy of CT, radiotherapy, and immunotherapy.

Metabolic effects of cancer therapy

Newer studies have shown that cancer treatment-induced metabolic syndrome (CTIMetS) is an especially prevalent and harmful side effect of CT. Long-term survivors of childhood, breast, colorectal and testicular cancer, and of several hematological malignancies face an increased risk of treatment-induced cardiovascular disease¹⁷¹ and metabolic syndrome.¹⁷² Metabolic comorbidities may adversely affect patient survival and quality of life and might be an important link between cancer treatment cardiovascular toxicity and accelerated atherosclerosis in cancer survivors.¹⁷³ Obesity is a contributing factor to the higher occurrence of metabolic syndrome and cardiovascular morbidity

in cancer survivors.¹⁷⁴ In addition, IR may be driven by CT. Alkylators, anthracyclines, camptothecins (e.g., irinotecan), epipodophyllotoxins (e.g., etoposide), and platinum-based treatments may drive IR due to mitochondrial dysfunction through increased production of ROS.¹⁷⁵ Antimetabolites such as capecitabine can decrease hepatic lipid export, causing steatosis, which is associated with decreased insulin sensitivity.¹⁷⁶ Furthermore, anemia, which is a common side effect of anticancer treatments, may cause adipose tissue hypoxia, leading to macrophage activation and inflammatory cytokine release.¹⁷⁵ Therefore, CT contributes to the development of CTIMetS mostly through weight gain but may also indirectly affect other metabolic syndrome components, such as dyslipidemia or IR.

Although the etiology of metabolic syndrome in noncancer patients probably differs from the etiology in cancer patients treated with conventional cancer therapy,¹⁷² the same treatment strategies to restore metabolic homeostasis may have similar positive effects on the prevention and treatment of the different components of metabolic syndrome and improvement of life quality and life expectancy.

Interestingly, in premenopausal and postmenopausal early breast cancer patients with no preexisting metabolic syndrome, adjuvant, or neoadjuvant CT was associated with an increased prevalence of metabolic syndrome and related anthropometrics, biomarkers of glucose metabolism, and inflammation.¹⁷⁷ Identifying markers able to capture the complex interplay among host metabolism, myelopoiesis, CT, and the TME might contribute to integrating preclinical and clinical research.

Cranial and abdominal radiotherapy are major risk factors for obesity, dyslipidemia, and IR in childhood cancer survivors.^{178,179} The pancreas has always been considered relatively insensitive to radiation.¹⁸⁰ However, recent evidence suggests that radiation may induce apoptosis of pancreatic beta cells and consequently decrease insulin production, leading to hyperglycemia, elevated FFA levels, hypertriglyceridemia, and IR.^{179,181} Deficiency of growth hormone is the most common endocrine dysfunction in patients treated with cranial radiotherapy and is associated with obesity, dyslipidemia, and IR.¹⁸² Growth hormone contributes to lipolysis and has an insulin-like influence because of its relationship with the production of IGF-1, which results in glucose uptake.¹⁷² Preliminary data suggest that assessment of metabolic fitness and myeloid function may be critical to avoid iRAEs and to increase the efficacy of conventional cancer therapy. MDSC levels may be used as a novel biomarker for metabolic syndrome and related immune dysfunction, as MDSCs are the end product of profound cellular metabolic changes.

Chemotherapy (CT) and MDSCs

CT is a long-standing inclusion in the therapeutic armamentarium against cancer. Mounting evidence from preclinical studies has revealed the contribution of the host immune system to the efficacy of several anticancer drugs. Most preclinical studies support CT-induced inflammation as a mechanism to reinforce aberrant myelopoiesis, which serves as a counterregulatory adaptation to prevent unnecessary damage from chemical insult.¹⁸³ Enhancement of MDSC suppressive activity is described with doxorubicin and with high-dose cyclophosphamide, among other treatments.¹⁸⁴ In contrast, other preclinical data have shown that a number of cytotoxic agents, including docetaxel, 5-fluorouracil, and gemcitabine, can induce MDSC apoptosis.^{185–187} Treatment with cyclophosphamide can be considered a prime example of the complexity of the interplay between CT and the immune system, since both immunostimulating effects and the induction of immunosuppressive cells have been described with this agent.^{188–192}

In breast cancer, data from clinical studies prospectively evaluating the effects of CT on MDSCs are scant, and the results are somewhat conflicting.^{193–195} However, these data are far from

conclusive, considering the limited sample sizes, the heterogeneity of the patient populations (in terms of breast cancer phenotype classified according to hormone receptor and HER2 expression), as well as differences in G-CSF use, which is one of the key drivers of aberrant expansion of myeloid cells.

In patients with advanced pancreatic cancer, MDSCs are significantly elevated compared to the numbers in healthy controls.¹⁹⁶ In a pilot nonrandomized trial, MDSCs were significantly decreased in patients treated with the combination of gemcitabine and omega 3 fatty acid, while no significant change was observed in patients treated with gemcitabine alone. Intriguingly, better progression-free survival was reported for patients treated with the combination. However, these findings should be interpreted with caution due to the nonrandomized nature of the study.¹⁹⁷

In patients with nonmetastatic urothelial cancer of the bladder undergoing radical cystectomy, the percentages of total MDSCs and PMN-MDSCs in PBMCs were significantly lower in patients achieving a pathologic complete response than patients showing no response. Higher levels of MDSCs before surgery were also associated with worse overall survival.¹⁹⁸

In patients with non-small-cell lung cancer receiving first-line platinum-based CT, a significantly worse outcome was reported for patients with higher M-MDSCs than for those with lower M-MDSCs. However, dynamic changes in MDSCs during CT were not evaluated.¹⁹⁹ Overall, these data suggest that CT can impact the TME by promoting an antitumor immune response or by inducing MDSCs that counterregulate the immune response.

Myeloid immunometabolism and immunotherapy

CT and radiotherapy still represent fundamental strategies in anticancer treatment. Nevertheless, in the past few years, restoring the immune response with ICIs has emerged as an effective strategy across different cancer types. Interestingly, though apparently counterproductive from a theoretical standpoint, the combination of these two strategies has resulted in clinically meaningful results.^{200–203} However, the magnitude of clinical benefit with immunotherapy is heterogeneous, since a significant proportion of patients do not respond or even experience hyperprogression.²⁰⁴ In this context, circulating immune-related biomarkers are particularly attractive. Cancer mortality is almost doubled in patients with elevated MDSCs.²⁰⁵ It has been reported that the presence of circulating MDSCs predicts higher stage and worse survival rates²⁰⁶ and increases the risk of resistance to ICIs.²⁰⁷ Measuring MDSCs is a novel and yet-to-be-exploited strategy for treating cancer. MDSCs are difficult to detect and quantify because their phenotypic signature includes multiple surface markers studied by flow cytometry or immunohistochemistry, and those markers can detect immature myeloid cells but cannot predict suppressor function. A consensus phenotype of human MDSCs has recently emerged^{208,209} and can predict dysregulated myelopoiesis when evaluated together with clinical parameters.

The importance of MDSCs in promoting resistance to immunotherapy was not recognized until the first studies demonstrated that MDSCs have potent utility in inhibiting T cell and NK cell activity, contributing to resistance to immunotherapy and predicting resistance to ICIs.²¹⁰ To date, the majority of the clinical data are available for melanoma patients treated with ipilimumab, in which a potential role of the frequency of monocytic MDSCs as a predictive marker of response has been suggested.²¹¹ In another study assessing the frequencies of MDSCs and Treg cells in 209 melanoma patients treated with ipilimumab, MDSC frequencies and CD4⁺CD25⁺FoxP3⁺ Treg cell frequencies were significantly associated with survival.²⁰⁷ In prostate cancer patients treated with ipilimumab combined with a cancer vaccine, a lower frequency of circulating MDSCs was found to correlate with an increased overall survival.²¹² Several ongoing trials of chemioimmunotherapy are prospectively evaluating MDSCs and TAMs, with

the aim of elucidating the mechanisms underlying different patterns of response and different outcomes upon treatment. In line with these studies, the field of cancer immunotherapy has focused on developing therapeutic strategies to eliminate MDSCs.

Tumor-infiltrating lymphocytes (TILs) are critical for inducing tumor regression; however, TILs in patients with “cold” myeloid-driven tumors are not sufficient to overcome tumor-associated immunosuppression. It is becoming clear that eliminating inflammation-driven emergency myelopoiesis is critical for enabling improved T effector-APC crosstalk, recruitment of antitumor immune responses, and inhibition of tumor-promoting angiogenesis. Emerging studies support the view that targeting tumor metabolism in combination with immunotherapy enhances the efficacy of immunotherapy.

In mice, inhibition of FAO significantly decreases FA uptake and inhibits the immunosuppressive function of MDSCs at the tumor site in Lewis lung carcinoma (3LL).⁴⁰ All-trans retinoic acid (ATRA), a metabolite of vitamin A, induces MDSCs to differentiate into APCs as well as myeloid maturation, which correlate with an improvement of the antitumor effector T cell response²¹³ and reduced MDSC levels in tumor-bearing mice and tumor patients.^{214,215} ATRA affects MDSCs by upregulating the expression of glutathione through ERK1/2 activation to neutralize a large amount of ROS in MDSCs and promote MDSC differentiation.²¹⁶

Inhibition of glucose uptake by a Glut1 inhibitor to inhibit exacerbated glycolysis in stroma cells, MPs and myeloid cells may provide a novel therapeutic approach to prevent myelopoiesis-driven inflammatory diseases.²¹⁷ AMP-activated protein kinase (AMPK) activation can inhibit several major immune signaling pathways, e.g., the JAK-STAT, NF- κ B, C/EBP β , CHOP, and HIF-1 α pathways. Activation of these pathways regulates cellular immunity in cooperation with pathways controlling energy metabolism, which favor the expansion and activation of MDSCs.¹⁶⁵ Furthermore, a recent study by Strauss et al. showed that immune checkpoints such as PD-1 suppress the differentiation of MPs to effector APCs and promote the expansion of MDSCs through metabolic reprogramming of myeloid precursors.²¹⁸ Metformin, a widely used drug in treating and curing type II diabetes, has been proven to reduce the incidence of cancers, reduce mortality, increase the response to radiotherapy and CT, optimize tumor cell migration, and reduce the likelihood of relapse.²¹⁹ Metformin inhibits mTOR activity by activating ATM (ataxia telangiectasia mutated) and LKB1 (liver kinase B1) and AMP-activated kinase (AMPK), thus preventing protein synthesis and cell growth,²¹⁹ as well as MDSC expansion.^{220,221} Taken together, these findings provide a rationale for combining strategies reprogramming the metabolism of MDSCs with immunotherapeutic strategies in cancer treatment and prevention.

Recent data have highlighted the crucial connection between metabolism and cancer immunotherapy. In particular, a new experimental glutamine antagonist has been shown to induce tumor regression not only through cancer cell starvation but also by activating effector T cells, thus dismantling the immunosuppressive TME. Indeed, T cells respond to glutamine antagonism by markedly upregulating oxidative metabolism and adopting a long-lived, highly activated phenotype. Exploiting different metabolic states of the components of the TME might contribute to improving the therapeutic armamentarium against cancer.²²²

CONCLUDING REMARKS

The ability of the immune system as well as adipose tissue to expand and contract in response to fluctuations in nutrient availability is essential for the maintenance of whole-body homeostasis. Given the shortages of nutrients that mammals have faced for millions of years, the current programs involved in immune and adipose plasticity likely evolved to be highly efficient in promoting metabolic strategies to adapt to nutrient stress. Therefore, it is not

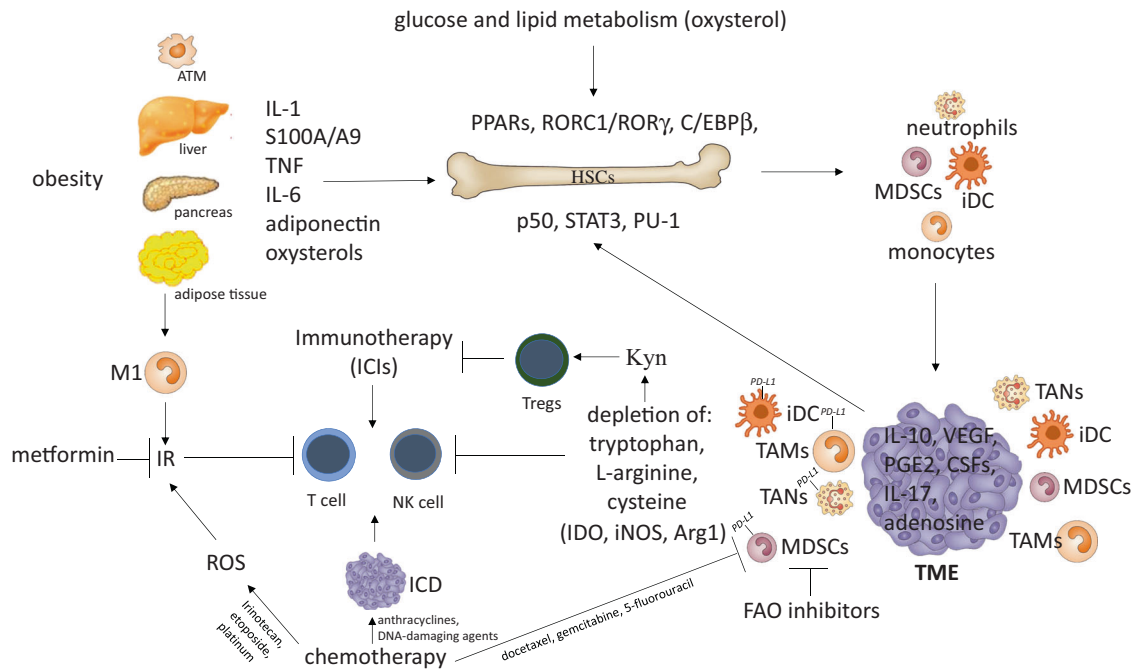


Fig. 2 Interconnections between metabolism, cancer-related inflammation, myelopoiesis, and cancer therapy. Obesity and adipose tissue macrophages (ATMs) promote myeloid cell expansion by releasing various inflammatory cytokines and adipokines that activate selected transcriptional activities (PARs, RORC1/ROR γ , and C/EBP β) affecting HSC proliferation and differentiation. This myelopoietic boost is amplified by cancer cells that release additional myelopoietic factors, including CSFs, IL-1, IL-17, and PGE2. These factors induce myelopoiesis through the upregulation of specialized transcription factors (i.e., p50 NF- κ B, STAT3, and PU-1). The production of adenosine, VEGF, and IL-10 by cancer cells induces the tumor-promoting phenotype (IL-10^{high}/IL-12^{low}) of iDCs. The emerging myeloid populations are then recruited to the tumor site, where they acquire suppressor phenotypes (TAMs, TANs, MDSCs, and iDCs) and establish an immunosuppressed tumor microenvironment (TME). The tumor site actively hinders the activation of T lymphocytes through the depletion of amino acids, orchestrated by both infiltrating myeloid suppressor cells and cancer cells that express immunosuppressive enzymes (IDO, iNOS, and Arg1). IDO activity, in particular, results in the production of the immunosuppressive catabolite kynurenine (Kyn), which is capable of inducing the expansion of regulatory T (Treg) cells. Further expression of immune checkpoint ligands (i.e., PD-L1) by myeloid suppressor cells contributes to the inhibition of antitumor immunity. The metabolic consequences of obesity also drive the transition of macrophages from “M2-like” to “M1-like” activation, contributing to inflammation-driven insulin resistance (IR). Of note, both obesity and select chemotherapeutics (i.e., irinotecan, etoposide, and platinum) can induce IR, interfere with the energetic balance and affect T cell activation. However, chemotherapy can also enhance antitumor immunity by promoting the immunogenic cell death (ICD) of cancer cells (i.e., anthracyclines, DNA-damaging agents) and by depleting MDSCs (i.e., docetaxel, gemcitabine, and 5-fluorouracil). In line with this, the inhibition of FAO significantly decreases FA uptake and inhibits the immunosuppressive function of MDSCs. Globally, the intersection of the host’s metabolic status, tumor metabolism, cancer inflammation and the quality of myelopoietic output strongly influences the response to therapy. ICD immunogenic cell death, IR insulin resistance, FAO fatty acid oxidation, FA fatty acid

surprising that many transcription networks critical for innate and adaptive immune cell functions are shared by adipose tissue and have a role in insulin signaling. Myelopoiesis, as the host first line of defense, requires very high plasticity and therefore shares many transcription and cytokine networks with adipocytes, and these networks provide MPs and myeloid cells with extra metabolites in response to environmental cues. Tumors perturb these adaptive networks by consuming oxygen and critical metabolites for immune and stromal cell function. In addition, these previously advantageous features may now represent a metabolic risk factor given the caloric excess of modern society. Acquisition of a tumor-promoting phenotype by myeloid cells as well as stress-triggered adipogenesis and IR are the results of a multistep process encompassing initial events originating in the BM and later steps operating in the TME.⁶⁰ The interplay between inflammation and metabolism dictates transcriptional programs supporting the differentiation of myeloid suppressor cells (MDSCs, iDCs, and TAMs). These cells are being recognized as novel biomarkers for metabolism-compromised dysregulation of central tissue homeostasis, which leads to systemic immune dysfunction and persistent inflammation in cancer and metabolic syndrome-related inflammatory diseases (Fig. 2). Recent research highlights the potential therapeutic impact of targeting specific metabolic pathways and/or modifying the quantity and

quality of myeloid output to stimulate anticancer immunosurveillance and prevent disease relapse. New studies are now required to carefully evaluate the myelopoietic and immunomodulatory impact of anticancer therapies, as well as their interplay with host immunometabolism. Immunometabolic characterization of the population of interest, cancer patients in particular, should therefore be sponsored, as it might establish new criteria for stratification of patients and therapeutic interventions. A lack of proactive and preventive efforts could lead to worldwide permeation of such immunometabolic dysfunctions, with an increased risk of developing resistance to and irAEs with immunotherapy and a consequent reduction in therapeutic options.

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ADDITIONAL INFORMATION

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