Immunometabolism and Epithelial–Mesenchymal Transition

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Epithelial–mesenchymal transition (EMT) and metabolic reprogramming in cancer cells are the key hallmarks of tumor metastasis. Since the relationship between the two has been well studied, researchers have gained increasing interest in the interplay of cancer cell EMT and immune metabolic changes. Whether the mutual influences between them could provide novel explanations for immune surveillance during metastasis is worth understanding.

Keywords: immunometabolism ; epithelial–mesenchymal transition ; tumor microenvironment

1. Introduction

Metastasis is the primary cause of cancer-related mortality, which can occur early through parallel progression along with the primary tumor or late after linear tumor progression [1]. Being recognized as a major determinant of the metastatic event, epithelial-mesenchymal transition (EMT) is a reversible dynamic process in which stationary epithelial cancer cells lose their intercellular adherence, trans-differentiate into invasive mesenchymal-like cells, and initiate tumor metastasis [2][3]. During an EMT, specific changes are required by the cancer cells to migrate and colonize distant organs, including changes in intrinsic tumor cell properties and the tumor microenvironment (TME), as well as those affecting the crosstalk between the two compartments mentioned above. Amongst these changes, metabolic reprogramming has been suggested as a key hallmark of cancer progression [4][5]. Cancer cells undergo an alteration in their mode of energy metabolism to fulfill the bioenergetic and biosynthetic needs for rapid cell proliferation and adaptation to the tumor microenvironment. Apart from cancer cells, evolving studies have revealed that immune cells possess distinct metabolic characteristics that influence their immunological functions in response to cancer development [6].

Compared to the extensive understanding of metabolic alterations in cancer cells during metastasis, the role of metabolic reprogramming in tumor-associated immune cells and whether the process has mutual effects with EMT are the key questions that have not been investigated in depth. Because immunotherapy has emerged as a promising oncologic treatment, it has become increasingly vital to understand the metabolic interdependence of infiltrating immune cells and cancer as much as possible. In this review, we aim to discuss the following topics: (1) the regulatory loop between tumor-infiltrated immune cells and EMT; (2) how immune-metabolic reprogramming takes part in the loop; (3) the challenges and perspectives of targeting immunometabolism as a cancer treatment.

2. Epithelial-Mesenchymal Transition and Functional Change of Immune Cells in Tumor Metastasis: The Mutually Regulatory Loop

These EMT-associated changes in cancer mainly occur in the tumor microenvironment, consisting of a heterogeneous population of cancer cells and a variety of resident stroma, infiltrating immune cells, secreted factors, and extracellular matrix proteins [7]. As a tumor is generally described as “a wound that never heals”, it is not hard to speculate that it is a complex interaction network in the TME that helps generate a chronic, unresolved inflammatory reaction. During a chronic inflammatory condition, TGF-β1 and hypoxia activate EMT to generate activated mesenchymal cells, notably myofibroblasts associated with tissue regeneration and fibrosis [8]; however, within the context of cancer, when chronic inflammation proceeds beyond control, these EMT programs, in an unsuccessful attempt to repair the injured tissue, turn to a vicious role and destroy epithelial homeostasis through the accumulation of the extracellular matrix in fibrosis, leading to the progression of carcinomas towards the metastatic state [9]. Apart from affecting the migratory capability of cancer cells, the immunosuppressive effect of EMT enables continuous tumor growth. The mechanism by which EMT alters the functional roles of immune cells is further discussed below.

Similar to innate immune cells, immunosuppressive Tregs are induced or recruited during cancer cell EMT. Using Snail1 overexpression models of melanoma cells, it was suggested that TGF-β and thrombospondin-1 (TSP1) production apparently generated immunosuppressive Treg cells and non-responsive CD8+ T cells, resulting in enhanced tumor metastasis in various organs of the B16-F10 mouse model [10]. In HBV-positive hepatocellular carcinoma, an increase in TGF-β signaling suppresses the expression of miR-34a, resulting in enhanced production of the chemokine CCL22 and recruitment of Treg cells, promoting the development of intrahepatic venous metastasis [11]. Resistance of Cytotoxic T lymphocytes (CTLs) was also observed in the human mammary carcinoma model MCF7, which underwent EMT, following stable expression of SNAIL or after prolonged exposure to tumor necrosis factor-alpha (TNF-α) [12]. Another possible explanation for EMT-induced CTL dysfunction is the more abundant expression of PD-L1 in tumor cells. A previous study demonstrated that ZEB1, a well-known EMT activator, induces PD-L1 expression in tumor cells by relieving the miR-200 (a suppressor of EMT that targets PD-L1, a ligand for the CTL checkpoint receptor PD-1)–mediated suppression of PD-L1, resulting in the suppression of CTL function and promotion of metastasis [13]. Whether cancer cells undergoing EMT impact natural killer (NK) cells has rarely been studied, as multiple studies have shown that NK cells demonstrate little or no direct contact with cancer cells as they preferentially localize to the tumor stroma [14][15]. Consistent with this finding, emerging data suggest that circulating NK cells are potent killer cells of cancer cells compared with organ-specific or tumor-infiltrating NK cells [14]. Although there is little direct interaction between NK cells and cancer cells, an immunosuppressive TME regulated by EMT can render tumor-infiltrating NK cells with low cytotoxic activity [14].

Not only does cancer cell EMT lead to immune evasion, emerging evidence suggest that immune cells can also regulate the process of EMT owing to their ability to produce a diverse array of EMT inducers and mediators [16][17][18].

In comparison with innate immune cells, there is less evidence stating that adaptive immune cells modulate the process of EMT, with Treg being the only relatively well-studied EMT modulator to date. Treg cells produce cytokines such as TGF-β, IL-6, IL-10, and TNF-α to mediate EMT. A recent study found that infiltrating Treg cells could activate Smad2/3 by secreting TGF-β1, greatly triggering EMT in hepatocellular carcinoma (HCC) [19]. The induction of EMT by TNF-α synergizing with TGF-β or other inflammatory factors has been described in human cancer cell lines in vitro [20][21]. In colorectal cancer cell lines, TNF-α and TGF-β induce EMT-like changes in an NLRP3/Snail1 axis-dependent manner, with Snail being stabilized and protected from degradation in response to TNF-α signaling, helping complete EMT and promote cancer cell migration and metastasis [22][23].

3. Interplay of Metabolic Reprogramming of Immune Cells and EMT

Apart from mTOR1, transcriptional factor c-Myc, which is controlled by the availability of glutamine and other amino acids, also acts as an essential metabolic regulator in NK cells; c-Myc controls the expression of glucose transporters and glycolytic enzymes required to support increased metabolism during NK cell activation [24]. As important nutrients, whether fatty acids (FAs) can fuel NK cells remains unclear. In fact, a study showed that FA administration could suppress NK cell effector functions and metabolism [25]; thus, NK cells preferentially utilize glucose metabolized by glycolysis and CMS to power effector functions.

As is the case for T cells, even though NK cells are present in the tumors, there is little evidence showing their capability to promote tumor progression, including induction of EMT. In fact, tumor infiltration of NK cells is primarily associated with better patient prognosis or has barely any influence. As NK cells preferentially localize to the tumor stroma, they become a major obstacle for them to mediate immunosurveillance due to limited access to cancer cells in the tumor bed [14][15][26][27]. In agreement with this finding, emerging data suggest that circulating NK cells are potent killer cells of cancer cells compared with organ-specific or tumor-infiltrating NK cells [14][28].

Unlike macrophages, there is relatively limited evidence suggesting that T cells modulate tumor cell phenotype directly, including induction of EMT, despite contributing to the overall tumor progression. In contrast, similar to innate immune cells, activated T cells are induced to immunosuppressive Tregs during cancer cell EMT. Using Snail1 overexpression models of melanoma cells, it was suggested that production of TGF-β and thrombospondin-1 (TSP1) appears to generate immunosuppressive CD4 + Foxp3+ T cells (Tregs) and non-responsiveness of CD8+ T cells, resulting in enhanced tumor metastasis in various organs of the B16-F10 mouse model [10]. Several studies have highlighted that a switch to the Treg phenotype indicates the preference of T cells relying on FAO and TCA cycle, which supports OXPHOS through multiple pathways [29][30][31][32][33]. Several studies have shown that when tumor cells undergo EMT, Foxp3 reprograms T cell metabolism by suppressing glycolysis, enhancing OXPHOS, and increasing nicotinamide adenine dinucleotide (NAD) oxidation [34][35]. These adaptations allow Tregs to have a metabolic advantage in a low glucose-high lactate environment (which is normally observed in the TME) through by the ability of Tregs to convert lactate into pyruvate and support OXPHOS effectively. To be more precise, as lactate accumulation has been reported to impair effector T cell function, decreasing lactate concentrations may help Treg cells resist lactate-mediated suppression of cell function and proliferation

[36]. Glucose uptake and GLUT1 expression are downregulated in Treg cells compared to Teff cells in vitro. Deprivation of glucose and glutamine in media during in vitro skewing experiments has also been shown to alter CD4 differentiation and promote the development of Treg cells [37][38]; however, it is interesting that for Treg cells to exist as a highly active and long-lived phenotype, upregulation of glycolysis can optimize their function as the uptake of glucose might fuel oxidative metabolism in a manner that confers a metabolic benefit and relative advantage on Tregs in the TME [39]. Intrinsically, to allow themselves to adapt to the harsh and heterogeneous conditions in the TME, it is not surprising that Treg cells appear to have such metabolic flexibility.

In addition to cell-intrinsic metabolic regulators such as PD-L1 and CTLA4, extracellular nutrients or metabolites can also alter T cell function. Human mammary cells treated with TGF-β or undergoing EMT have been shown to upregulate CD73 cell-surface expression [40]. CD73 functions as a 5′-nucleotidase, which converts extracellular AMP to adenosine (eADO). There is now a general consensus that accumulation of eADO in TME has an immunosuppressive effect that is largely mediated by excessive stimulation of Gs-protein-coupled A2A receptors (A2AR) on immune cells, including CTLs, NK cells, macrophages, and DCs [41][42].

4. Targeting Immunometabolism: Challenges and Perspectives

Since the emergence of ICI drugs, novel discoveries have highlighted the roles of checkpoint receptors and their ligands in regulating cellular metabolism, both in immune and cancer cells. CTLA-4 and PD-1 receptors interfere with the signaling of CD28 co-stimulation, which acts through PI3K and Akt to increase the glycolytic rate in response to the activation required for T cells [43]. Emerging studies link checkpoint molecules with reprogramming cellular metabolism, thereby altering the function of immune cells to attenuate their antitumor ability. While PD-1 reduces glycolytic metabolism and FAS, PD-L1 expression in cancer cells promotes glycolysis via an Akt/mTOR/HIF-1α axis, while in the case of cancer harboring RAS family mutation (the mutation frequency of the Ras family in cancer is common and reaches approximately 19% [44]), the axis may be further tuned on since it was reported that RAS signaling could stabilize the expression of PD-L1 [45]. These facts suggest the synergetic effect brought about by the inhibition of both PD-1 and PD-L1 [46][47][48]. By reducing the glycolytic metabolism in cancer cells and potentially freeing up glucose in the TME, it is possible that glucose can be utilized by immune cells such as TILs, supporting the antitumor function. CTLA-4 also blocks glycolytic metabolism by inhibiting PI3K [49]. LAG-3, another negative checkpoint molecule, downregulates glycolytic and mitochondrial metabolism, potentially via elevated PTEN signaling [50]. As glycolysis is a crucial process in T cell activation, these checkpoint molecules maintain quiescence in T cells by blocking the glycolytic-related pathways, leading to an immunosuppressive TME. In addition to these inhibitory checkpoint molecules, stimulatory checkpoint molecules, such as GITR, have been shown to increase glycolysis and mitochondrial metabolism to support CD8+ T cell proliferation and effector function in vivo [51]; thus, by antagonizing stimulatory checkpoints or blocking inhibitory checkpoints is likely to restore T cell effector function by modulating cellular metabolism. Under the circumstances of understanding the limitations of simply targeting metabolism and discovering ICIs having a role in metabolic regulation, several clinical trials are underway to investigate the potential of combining metabolic interventions with conventional ICIs (**Table 1**).

Targeting the folate pathway using pemetrexed may strengthen the anti-tumor effects by disrupting nucleotide synthesis in cancer cells. Moreover, it has been demonstrated that pemetrexed augments antitumor immunity in combination with anti-PD-L1 in mouse models, in part by enhancing effector function of CD8+ T cell through stimulating mitochondrial biogenesis with subsequent increased T cell infiltration and activation [52].

Table 1. Ongoing clinical trials targeting immunometabolism in combination with ICIs. Bladder Urothelial Cancer (BLCA), Clear Cell Renal Cell Carcinoma (ccRCC), Colorectal Cancer (CRC), Esophagus Carcinoma (ESCA), Gastric Carcinoma (GC), Hepatocellular Carcinoma (HCC), Head and Neck Squamous Cell Carcinoma (HNSCC), Metastatic Castration Resistant Prostate Cancer (mCRPC), Microsatellite Instability/Microsatellite Stable-Colorectal Cancer (MSI/MSS-CRC), Renal Cell Carcinoma (RCC), Pancreatic Ductal Adenocarcinoma (PDAC), Triple Negative Breast Cancer (TNBC).

Pathway	Drug	Function	Combined ICI	Cancer Type	Status
Adenosine pathway	Sym024	CD73 antibody	Sym021	Solid tumors	Phase I (NCT03835949)
	AK119		AK104	Solid tumors	Phase I (NCT04572152)
	TJ004309		Atezolizumab	Solid tumors	Phase I (NCT03835949)
	NZV930		PDR001	NSCLC, TNBC, PDAC, MSS-CRC, RCC, mCRPC, Ovarian cancer	Phase I (NCT03549000)
	CPI-006		Pembrolizumab	Solid tumors, Non-Hodgkin lymphoma	Phase I (NCT0345445)
	MED19447		Duvalumab	Ovarian cancer	Phase I (NCT03267589)
	BMS-986179		Nivolumab	Solid tumors	Phase I/II (NCT02754141)
	Ciforadenant	Adenosine Receptor (A2A) antibody	Atezolizumab	RCC, Mcrpc	Phase I (NCT02655822)
	NIR178		PDR001	Solid tumors, Non-Hodgkin lymphoma	Phase II (NCT03207847)
Arginine metabolism	INCB001158	Arginase inhibitor	Pembrolizumab	NSCLC, BLCA, MSI/MSS-CRC, GC, HNSCC, Melanoma, Mesothelioma	Phase II (NCT02903914)
Folate pathway	Pemetrexed	Pyrimidine and purine synthesis inhibitor	Nivolumab	HNSCC	Phase II (NCT04107103)
	5-fluorouracil			Biliary Tract Cancer	Phase Ib/II (NCT03785873)
				Melanoma	Phase I (NCT03311308)
Glucose metabolism	Metformin	Gluconeogenesis inhibitor	Pembrolizumab	NSCLC, BLCA, MSI/NSS-CRC, GC, HNSCC, RCC, HCC, ESCA, Melanoma	Phase II (NCT04414540) (NCT04114136)
			Nivolumab	NSCLC, BLCA, MSI/NSS-CRC, GC, HNSCC, RCC, HCC, ESCA, Melanoma	Phase II (NCT03048500) (NCT03800602) (NCT04114136)
			Sintilimab	SCLC	Phase II (NCT03994744)
			Durvalumab	HNSCC	Phase I (NCT03618654)
Glutamine metabolism	CB-839	Glutaminase inhibitor	Nivolumab	NSCLC, ccRCC, Melanoma	Phase II (NCT02771626)

Pathway	Drug	Function	Combined ICI	Cancer Type	Status
IDO pathway	PD-L1/IDO peptite vaccine	IDO inhibitor	Nivolumab	Melanoma	Phase II (NCT03047928)
	BMS-986205			HCC	Phase II (NCT03695250)
	Indoximod		Ipilimumab/Pembrolizumab/Nivolumab	Melanoma	Phase I/II (NCT02073123)
	KHK2455		Avelumab	BLCA	Phase I (NCT03915405)
	Epacadostat		Ipilimumab/Pembrolizumab/Nivolumab/Lirilumab	Solid tumors	Phase II (NCT03291054) (NCT03414229) (NCT03347123)

Blocking glutamine uptake is another way to starve cancer cells, meaning it is possible that less uptake would free up extracellular glutamine and in turn, reactivate the immune response. Although it remains unclear whether the blocking effect can merely be restricted in cancer cells and whether it affects immune cells, trials are still ongoing evaluating nivolumab in conjunction with CB-839, a glutaminase inhibitor, in several cancer types listed in **Table 1** .

Above all, although targeting immunometabolism during immunotherapy sheds light on the fight against malignancy, it still appears to be challenging, as tumor cells and activated immune cells share similar utilization of metabolic pathways, meaning targeting a given pathway may concurrently disrupt the antitumor function of immune cells. Additionally, the complexity of metabolism in the changeable and heterogeneous TME makes the prediction of therapeutic efficacy even more difficult; therefore, subtle differences between the utilization of nutrients by cancer cells and immune cells should be investigated as alternate strategies to optimize the synergistic effects of the combined therapies. Likewise, understanding the interplay between different metabolic pathways may also pave the way for discovering new therapeutic targets and opportunities for modulation.

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